Zebrafish larvae as a model system for systematic characterization of drugs and genes in dyslipidemia and atherosclerosis

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Short title: zebrafish for translation in atherosclerosis

Word count: 4396

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Abstract

Background: Hundreds of loci have been robustly associated with circulating lipids, atherosclerosis and coronary artery disease; but for most loci the causal genes and mechanisms remain uncharacterized.

Methods: We developed a semi-automated experimental pipeline for systematic, quantitative, large-scale characterization of mechanisms, drugs and genes associated with dyslipidemia and atherosclerosis in a zebrafish model system. We validated our pipeline using a dietary (n>2000), drug treatment (n>1000), and genetic intervention (n=384), and used it to characterize three candidate genes in a GWAS-identified pleiotropic locus on chr 19p13.11 (n>500).

Results: Our results show that five days of overfeeding and cholesterol supplementation had independent pro-atherogenic effects, which could be diminished by concomitant treatment with atorvastatin and ezetimibe. CRISPR-Cas9-induced mutations in orthologues of proof-of-concept genes resulted in higher LDL cholesterol levels (*apoea*), and more early stage atherosclerosis (*apobb.1*). Finally, our pipeline helped identify putative causal genes for circulating lipids and early-stage atherosclerosis (*LPAR2* and *GATAD2A*).

Conclusions: In summary, our pipeline facilitates systematic, *in vivo* characterization of drugs and candidate genes to increase our understanding of disease etiology, and can likely help identify novel targets for therapeutic intervention.

Introduction

Coronary artery disease (CAD) is the main cause of death worldwide, and results from the progression of atherosclerosis in the coronary arteries[1]. The response-to-injury theory suggests that chronic inflammation and dysfunction of the vascular endothelial cell layer are the initial causes of atherosclerosis[2,3]. Early-stage atherosclerosis manifests itself when circulating LDL cholesterol (LDLc) infiltrates endothelial cell junctions, accumulates in the vessel wall and becomes minimally oxidized[2]. Minimally oxidized LDL (oxLDL) subsequently induces pro-inflammatory changes in the endothelium, by activating platelets and neutrophils[4] and by recruiting monocytes from the circulation to the vascular intima[5]. These monocytes differentiate into macrophages, which internalize the oxLDL once it becomes highly oxidized. Apoptosis and necrosis of these so-called foam cells, together with local accumulation of extracellular lipids, calcium and other debris can lead to fatty streak formation, which in turn triggers the recruitment of smooth muscle cells to form a fibrous cap over the necrotic core[6]. Over time, intimal calcification, neovascularization of growing plaques and degradation of the fibrous cap by proteases can increase the influx of inflammatory cells into atherosclerotic plaques, thereby making them unstable. Rupturing of such unstable plaques can ultimately lead to thrombosis and myocardial infarction.

Many major risk factors of CAD have been known since the 1960s[7], and cholesterol levels and smoking have since been targeted successfully in the population. The pharmaceutical industry developed antithrombotic agents (antiplatelet and anticoagulant drugs), which together with early revascularization resulted in improved and standardized cardiac care and reduced CAD morbidity and mortality[8–10]. However, the incidence of CAD has since remained relatively stable in higher income countries, and is now increasing rapidly in lower- and middle-income countries, as a result of increasingly unhealthy lifestyles[11]. This worrying trend has not been met by the

development of conceptually new medication for CAD prevention in the last few decades. Hence, along with efforts to implement lifestyle-related changes in the population, new drugs are urgently needed for the primary and secondary prevention of CAD. In addition, the molecular causes of early-stage atherosclerosis remain poorly understood.

Since 2006, increasingly large genome-wide association studies (GWAS) have identified hundreds of genetic loci that are robustly associated with circulating lipid levels and CAD susceptibility[12–14]. Some of these loci harbor genes with well-known roles in cholesterol metabolism – e.g. *APOE*[15], *APOB*[16] and *LDLR*[17] – and some encode the targets of lipid-lowering drugs, i.e. *HMGCR* (statins)[18], *NPC1L1* (ezetimibe)[19] and *PCSK9* (evolocumab)[20,21]. It thus seems plausible that identifying and characterizing causal genes in the remaining loci would further increase our understanding of cholesterol metabolism, atherosclerosis and CAD pathophysiology, and yield new targets for prevention and treatment of CAD[21,22].

Murine model systems have traditionally been used to characterize genes that play a role in familial hypercholesterolemia and atherosclerosis[23,24]. However, such screens are too time consuming and costly to facilitate systematic screens across hundreds of candidate genes. In addition, mice differ in cholesterol ester and triglyceride transport between lipoprotein particles due to lack of *CETP*[25], and only develop atherosclerosis in an *LDLR* or *APOE* knockout background. Alternative *in vivo* model systems that are suitable for high-throughput characterization of disease-related traits are thus desirable. In this context, zebrafish (*Danio rerio*) provide a promising opportunity.

Thanks to their high reproductive rate, rapid early development, optical transparency during early life and low maintenance costs, the zebrafish has become a popular model system for human disease[26]. Importantly, in the context of gene characterization, the zebrafish has a well-characterized genome with orthologues of at least 71.4% of human genes[27]. These genes can now

be efficiently targeted in high-throughput using Clustered, Regulatory Interspaced, Short Palindromic Repeats (CRISPR) and CRISPR-associated systems (Cas)[28]. A range of fluorescent dyes[29–31] and transgenes[32–35] have been developed that allow visualization of atherogenic processes at a cellular level in live zebrafish larvae. In recent years, several small-scale studies have reported that zebrafish larvae fed on a cholesterol-supplemented diet are characterized by sub-endothelial deposition of lipids in macrophages and other cell types[36], disorganized vascular endothelial cells[36], and vascular accumulation of oxidized low-density lipoprotein (oxLDL)[32]. In addition, adult zebrafish fed on a cholesterol supplemented diet showed higher plasma levels of cholesterol, triglycerides and lipoproteins, and formed vascular lesions[37,38].

Proof-of-principle experiments for atherosclerosis in zebrafish described so far have typically been based on observations in fewer than 25 larvae per condition, at least in part because mounting larvae in low melting agarose for imaging is time-consuming. In addition, analyses of whole-body cholesterol and triglyceride levels are usually performed on samples of 20-100 pooled larvae[38,39]. While suitable and efficient for dietary and drug treatment interventions, pooling larvae for phenotypic characterization is not optimal in CRISPR-based genetic interventions, where sequencing of individual larvae is desirable. Hence, confirmation of initial findings, an improved resolution of quantitative readouts, and a higher throughput are required if zebrafish larvae are to be used as a model system for large-scale characterization of candidate genes for dyslipidemia, atherosclerosis and CAD.

Advances in automated positioning of non-embedded zebrafish larvae[40,41], custom-written image-quantification pipelines in publicly available tools, sensitive enzymatic assays and multiplexed mutagenesis using CRISPR-Cas9 enabled us to develop an experimental pipeline that allows for high-throughput genetic interventions. We here present validation results from a large-scale dietary intervention, a treatment intervention with lipid lowering drugs, and a

multiplexed, CRISPR-Cas9-based genetic intervention for proof-of-concept genes. The results of this three-tiered approach confirm that zebrafish larvae can be used to systematically examine the role of drugs and candidate genes in dyslipidemia, atherosclerosis and CAD. We subsequently characterized three candidate genes in a GWAS-identified pleiotropic locus on chr 19p13.11 that showed evidence of association with LDLc, triglyceride and total cholesterol levels[42] in humans. Our results confirm that our pipeline will increase our understanding of disease etiology at a molecular level, will help prioritize the most promising putative causal genes for further in-depth characterization, and will likely help identify novel targets that can be translated into efficient new medication for prevention and treatment of CAD.

Results

Overfeeding and cholesterol supplementation have independent pro-atherogenic effects

To quantify and distinguish between the atherogenic potential of overfeeding and dietary cholesterol, >2000 larvae from three transgenic backgrounds (**Fig. 1, Supplementary Tables 1 and 2**) were fed on one of six diets starting from the age of 5 days post-fertilization (dpf) until 9 dpf (**Methods**).

Five days of overfeeding on average resulted in longer larvae, with a larger body surface area and volume normalized for length (**Fig. 2a-i, Supplementary Fig. 1, Supplementary Table 3**). Overfeeding induced a triglyceride-driven increase in total cholesterol levels, without materially affecting LDLc, HDLc or glucose levels (**Fig. 2a-iii, Supplementary Fig. 2, Supplementary Table 4**). Overfeeding resulted in more lipid deposition (**Fig. 2a-ii, Supplementary Fig. 3, Supplementary Table 5**). We further ensured that the observed lipid deposition was indeed located inside the vascular endothelium using larvae with fluorescently labelled endothelial cells (*Tg:flk-EGFP*) (**Fig. 1d, Supplementary Table 1**). Of the 361 *Tg:flk-EGFP* positive larvae that showed at least some vascular lipid deposition, 355 (98.3%) had all lipid deposits co-localize with circulating lipids and/or vascular endothelial cells, implying that almost all deposits were at least partly located inside the endothelial cell layer. The remaining deposits appear to be false positives, illustrating the high sensitivity (72%) and specificity (93%) of our image quantification pipeline for detection of vascular lipid deposition. Overfeeding also resulted in more vascular accumulation of oxLDL; more co-localization of oxLDL with macrophages; and more vascular co-localization of lipids with neutrophils. We also observed some evidence for a positive effect of overfeeding on vascular infiltration by neutrophils and on endothelial thickness (**Fig. 2a-ii, Supplementary Fig. 3, Supplementary Table 5**).

Five days of dietary cholesterol supplementation resulted in shorter larvae, without affecting body surface area or volume normalized for length (**Fig. 2b-i, Supplementary Fig. 1, Supplementary Table 3**), and without influencing food intake (**Supplementary Fig. 4**). Cholesterol supplementation induced an LDLc-driven increase in total cholesterol levels, while lowering HDLc (trend) and triglyceride levels (**Fig. 2b-iii, Supplementary Fig. 2, Supplementary Table 4**). Cholesterol supplementation did not influence vascular accumulation of lipids and oxLDL, but tended to result in more co-localization of lipids with neutrophils, and in less co-localization of oxLDL with macrophages (**Fig. 2b-ii, Supplementary Fig. 3, Supplementary Table 5)**.

As described in earlier studies[36,37,39], we supplemented regular dry food with extra cholesterol using diethyl ether, which may itself affect endogenous cholesterol levels[43]. Our results show that diethyl ether per se indeed resulted in: 1) higher triglyceride (trend) and total cholesterol levels (**Supplementary Table 4**); 2) less vascular co-localization of lipids with neutrophils; 3) a lower endothelial thickness (**Supplementary Table 5**); and 5) a lower food intake (**Supplementary Fig. 4**). Hence, absence of a control group fed on diethyl ether-treated food without cholesterol supplementation would have resulted in biased estimates for the effect of cholesterol supplementation.

Neither overfeeding, nor cholesterol supplementation or diethyl ether supplementation was associated with suboptimal image quality or image quantification. Hence, exclusion of larvae based on these criteria likely did not influence the results of the dietary intervention **(Supplementary Table 6)**.

Combined treatment with atorvastatin and ezetimibe has an atheroprotective effect

To examine whether the commonly prescribed LDLc lowering drugs atorvastatin and ezetimibe exert similar effect in zebrafish, we overfed >1,000 larvae on a cholesterol supplemented diet with or without concomitant atorvastatin and ezetimibe treatment, from 5 dpf until 9 dpf. Compared with untreated larvae, five days of combined treatment with atorvastatin and ezetimibe resulted in leaner larvae (**Fig. 2c-i, Supplementary Fig. 1, Supplementary Table 7**), without affecting food intake (**Supplementary Fig. 4**). On average, atorvastatin and ezetimibe treatment also resulted in lower whole-body LDLc, triglyceride and total cholesterol levels, and in higher glucose levels (**Fig. 2c-iii, Supplementary Fig. 2, Supplementary Table 8**). In larvae with data on LDLc (n=564), atorvastatin and ezetimibe's effect on glucose levels was independent of triglyceride (beta: 0.13 SD; 95% CI: 0.04 to 0.22 SD), but not LDLc levels (0.05, -0.05 to 0.15 SD).

Treatment with atorvastatin and ezetimibe resulted in less vascular lipid deposition and less co-localization of lipids with macrophages and with neutrophils. On the other hand, treated larvae on average had more vascular co-localization of oxLDL with macrophages (**Fig. 2c-ii, Supplementary Fig. 3, Supplementary Table 9**).

Larvae treated with atorvastatin and ezetimibe were more likely to move during imaging (due to their leaner bodies) and had lower odds of many false positive oxLDL deposits. Exclusion of larvae with such suboptimal imaging or quantification data is unlikely to have influenced the results (**Supplementary Table 10**).

Mutations in zebrafish orthologues of APOE and APOB exert pro-atherogenic effects

To further validate the zebrafish as a model system, orthologues of genes with an established role in dyslipidemia and atherosclerosis - *APOE*, *APOB* and *LDLR* - were targeted together using a

multiplexed CRISPR-Cas9 approach. These three genes together have seven orthologues in zebrafish (*apoea*, *apoeb*, *apoba*, *apobb.1*, *apobb.2*, *ldlra* and *ldlrb*) (**Supplementary Tables 11 and 12**). Across the seven CRISPR-Cas9-targeted orthologues, we observed a median of 15 unique amplicons per targeted site in the 384 sequenced F_1 larvae (**Supplementary Table 13**). Compared with the reference genome, the 384 sequenced F_1 larvae together contained 55 frameshift variants, nine variants that introduced a premature stop codon, 34 missense variants, 13 in frame deletions, two in frame insertions, four synonymous variants, and 18 upstream variants within ±30 bp of the targeted sites (**Supplementary Table 14**). The mutant allele frequency was typically high across the seven targeted sites (i.e. median 0.883, **Supplementary Table 15**).

Most larvae carried two functionally knocked alleles in *apoba* and *apobb.2* – i.e. frame shift mutations and/or variants introducing a premature stop codon in both alleles – as well as bi-allelic mutations immediately upstream of *ldlrb* that were predicted to modify *ldlrb* gene expression (**Supplementary Tables 14 and 15**). Since there were no wildtype larvae for *apoba*, *apobb.2* and *ldlrb*, we could not examine the role of these three orthologues. For the four remaining orthologues (*apoea*, *apoeb*, *apobb.1* and *ldlra*), a genetic burden score comprising the sum of the number of mutated alleles across the four genes, weighted by their predicted effect on protein function was normally distributed. The score was associated with higher HDLc levels, more vascular lipid deposition, and more vascular co-localization of lipids with neutrophils (**Supplementary Fig. 5, Supplementary Tables 16-18**).

When examining the influence of mutations in each gene separately, we observed that larvae carrying two functionally knocked alleles in *apoea* had higher whole-body LDLc and lower triglyceride (trend) levels, without an effect on body size or early-stage atherosclerosis (**Fig. 2d-ii, Supplementary Tables 20 and 21**). Larvae with two functionally knocked *apoeb* alleles

showed at most a trend for more vascular accumulation of lipids and co-localization of macrophages with neutrophils, without affecting whole-body lipoprotein or glucose levels (**Supplementary Fig. 6b, Supplementary Tables 20 and 21**). On average, larvae with two functionally knocked *apobb.1* alleles were shorter than larvae with two unmodified alleles (**Fig. 2e-i, Supplementary Table 19**), and had higher triglyceride (trend) and lower total cholesterol and glucose levels (**Fig. 2e-iii, Supplementary Table 20**). They were also characterized by more vascular accumulation of lipids, and by more vascular co-localization of lipids with macrophages and with neutrophils, independently of whole-body lipoprotein or glucose levels (**Fig. 2e-ii, Supplementary Table 21**). While less than half of the larvae carrying no mutated *apobb.1* alleles showed any vascular co-localization of lipids with macrophages (44%) and neutrophils (15%), more than two out of three larvae carrying two functionally knocked *apobb.1* alleles showed such vascular co-localization. Finally, larvae with two functionally knocked *ldlra* alleles were similar on all accounts to larvae free from CRISPR-induced mutations in the gene, except for having less vascular co-localization of macrophages with neutrophils (**Supplementary Fig. 6d, Supplementary Tables 19-21)**.

Across the four zebrafish orthologues (*apoea*, *apoeb*, *apobb.1* and *ldlra*), results were similar when data were analyzed using an additive model in which the number of mutated alleles was weighted by their predicted effect on protein function (**Supplementary Tables 22-24**). In the presence of a genetic effect, the effect size of two vs. zero functionally knocked alleles was typically approximately twice the additive per allele effect (**Figs. 2d-e, Supplementary Fig. 6**), consistent with an underlying additive model. Additional analyses showed that suboptimal image quality or image quantification in a small subset of larvae is unlikely to have influenced the results (**Supplementary Table 25**).

Since *APOE*, *APOB* and *LDLR* interact to process triglyceride-rich LDLc in humans, we next examined two-way gene x gene interactions for *apoea*, *apobb.1* and *ldlra*; i.e. the genes that showed the most promising results individually. Focusing on interactions that were observed under an additive model and that were confirmed when comparing larvae with two vs. zero functionally knocked alleles only shows cautious evidence of a positive interaction between mutations in *apoea* and *ldlra* for vascular accumulation of lipids and co-localization of lipids with macrophages (**Supplementary Tables 26-28**).

Vascular atherogenic traits are associated with whole-body triglyceride levels

Data from the dietary, drug treatment and genetic interventions combined showed that LDLc, HDLc and triglyceride levels together explained 47% of the variance in directly assessed total cholesterol levels (n=1,867). Interestingly, the Friedewald equation (i.e. LDLc + HDLc + triglycerides/5)[44] did not perform much worse, explaining 43% of the variance in total cholesterol levels (**Supplementary Fig. 7**). We next explored the mutually adjusted association of vascular atherogenic traits with whole-body LDLc, HDLc, triglyceride and glucose levels in data from the dietary, drug treatment and proof of concept genetic intervention studies combined. Vascular accumulation of lipids, co-localization of lipids with macrophages and neutrophils, and co-localization of oxLDL with macrophages were all positively associated with whole-body triglyceride levels, independently of LDLc, HDLc and glucose levels. Furthermore, vascular accumulation of oxLDL and co-localization of lipids with neutrophils showed some evidence of a positive association with whole-body HDLc levels, in line with the absence of effects on primary clinical endpoint events observed in large clinical trials that therapeutically elevated HDLc levels and reduced triglyceride and/or LDLc levels[45–48]. Interestingly, vascular co-localization of lipids with neutrophils showed independent positive associations with LDLc, HDLc and triglyceride

levels. Finally, we observed negative associations of whole-body glucose levels with vascular accumulation of lipids, co-localization of lipids with macrophages, and co-localization of macrophages with oxLDL, suggesting that hyperglycemia per se is perhaps not responsible for the elevated risk of CAD in diabetes patients, at least not by increasing early stage atherosclerosis (**Supplementary Fig. 8, Supplementary Table 29**).

Identifying putative causal genes for circulating lipids and early-stage atherosclerosis

Based on the positive association of vascular atherogenic traits with triglyceride levels in our combined analysis, in combination with the known causal effect of high triglyceride levels on CAD incidence[49], we used DEPICT[50] to prioritize candidate genes in 23 triglyceride-associated loci[42]. In one of these loci represented by the intronic rs10401969 in *SUGP1* on chr 19p13.11, DEPICT prioritized *LPAR2, GMIP, GATAD2A* and *TM6SF2*. The four prioritized genes together have six orthologues in zebrafish (**Supplementary Table 30**), which we targeted simultaneously (**Supplementary Table 31**).

Across the six CRISPR-Cas9-targeted orthologues (*lpar2a*, *lpar2b*, *gmip*, *gatad2ab*, *tm6sf2* and *zgc:85843*), we observed a median of 2.5 unique amplicons per targeted site (**Supplementary Table 32**). Compared with the reference genome, the 547 sequenced F_1 larvae together contained four frameshift variants, three missense variants, and four in-frame deletions that were located within ±30 bp of the CRISPR targeted sites (**Supplementary Table 33**). In spite of having pre-tested the CRISPR gRNAs for efficiency, all F_1 larvae carried two unmodified alleles for the zebrafish orthologues of *TM6SF2* (*tm6sf2* and *zgc:85843*) and *GMIP* (*gmip*), and mutant allele frequencies were low for *gatad2ab* (0.029), *lpar2a* (0.010), and *lpar2b* (0.005) (**Supplementary Table 34**).

In spite of the low statistical power to find associations, we observed evidence for lower LDLc, triglyceride and total cholesterol levels in the 11 larvae with a mutated *lpar2a* allele when compared with larvae with two unmodified alleles. Counterintuitively, these larvae also showed some evidence for having more vascular co-localization of lipids with macrophages and with neutrophils. (**Fig. 3a**, **Supplementary Tables 35-37**). In addition to the effects observed for *lpar2a*, the six larvae with a mutated *lpar2b* allele were longer and and tended to have lower HDLc levels compared with larvae free from CRISPR-induced *lpar2b* mutations (**Fig. 3b**, **Supplementary Tables 35-37**). Finally, the 32 larvae with a mutated *gatad2ab* allele were larger and tended to have lower HDL levels and higher triglyceride levels when compared with larvae with two unmodified alleles (**Fig. 3c**, **Supplementary Table 36**). Exclusion of larvae with suboptimal image quality or image quantification is unlikely to have influenced the results (**Supplementary Table 38**).

Discussion

We developed and validated a largely image-based experimental pipeline in zebrafish larvae that is suitable to systematically characterize candidate genes and drugs for dyslipidemia and early-stage atherosclerosis and inflammation. Our dietary intervention showed that five days of overfeeding and cholesterol supplementation are sufficient to induce early-stage atherosclerosis and vascular inflammation in zebrafish larvae, without the need to use an *APOE* or *LDLR* and *CETP* knockout background as is customary in mouse models. Our drug treatment intervention showed that the pro-atherogenic effects of overfeeding and cholesterol supplementation can be diminished by concomitant treatment with atorvastatin and ezetimibe. A proof-of-concept genetic screen showed that CRISPR-Cas9-induced mutations in zebrafish orthologues of *APOE* and *APOB* trigger a pro-dyslipidemia, pro-atherogenic and pro-inflammatory phenotype that is in line with the known role of these genes. Finally, we illustrate the merit of our pipeline by attributing a role in cholesterol metabolism and atherosclerosis to *LPAR2* and *GATAD2A*; two genes in a pleiotropic locus on chr 19p13.11.

The evidence for high dietary cholesterol levels being a risk factor for CAD in the general population is conflicting[51–53]. In an adequately powered dietary intervention, we showed that overfeeding and cholesterol supplementation have independent pro-inflammatory and pro-atherogenic effects in zebrafish larvae. Both induced higher whole-body total cholesterol levels, albeit via different mechanisms. While overfeeding resulted in higher triglyceride levels, cholesterol supplementation induced higher LDLc levels. Both overfeeding and cholesterol supplementation resulted in more vascular co-localization of lipids with neutrophils, with a comparable effect size. However, cholesterol supplementation did so without affecting vascular accumulation of lipids per se, suggesting that primary accumulation of lipids in the vessel wall is likely mostly driven by triglyceride levels. In line with this, data from the dietary, drug treatment

and genetic interventions combined showed a positive association for triglyceride levels – but not LDLc – with vascular lipid deposition. Furthermore, mutations in *apobb.1* that resulted in higher whole-body triglyceride levels also induced more vascular accumulation of lipids – albeit independently of triglyceride levels – while mutations in *apoea* that resulted in higher whole-body LDLc levels had no effect on vascular lipid deposition.

Treating larvae with atorvastatin and ezetimibe resulted in lower whole-body LDLc and total cholesterol levels; and in less vascular co-localization of lipids with macrophages; yet – paradoxically – in more vascular co-localization of oxLDL with macrophages. A directionally consistent (i.e. opposite) effect was observed for the effect of dietary cholesterol supplementation on vascular co-localization of oxLDL with macrophages. Moreover, cholesterol supplementation or drug treatment did not affect accumulation of oxLDL or macrophages per se. Taken together, these observations suggest that ezetimibe's exogenous cholesterol lowering effect may be responsible for improved recruitment of macrophages to oxLDL; engulfing of oxLDL by macrophages; survival of macrophages that successfully engulfed oxLDL; and/or clearing of neutral lipid deposits by macrophages. The opposite rationale applies to elevated exogenous cholesterol levels following dietary cholesterol supplementation.

In line with results from clinical trials[54,55] and genetic association studies[56,57] in humans, zebrafish larvae treated with atorvastatin and ezetimibe were characterized by higher glucose levels, on average. Additional analyses indicated that the drugs' effect on glucose levels is likely mediated by LDLc. Hence, main effects and mediation analyses based on whole-body cholesterol and glucose levels in zebrafish larvae are sufficiently sensitive to provide valuable new insights.

The *apobb.1* orthologue accounts for ~95% of zebrafish apob protein. Like human apoB-48, apobb.1 catabolizes triglyceride-rich chylomicrons in the intestine[58], which explains the higher whole-body triglyceride levels with each additional mutated *apobb.1* allele and the more severe

pro-atherogenic and pro-inflammatory profiles in *apobb.1* mutant larvae. These findings together suggest that *apobb.1*$^{-/-}$ zebrafish are likely a promising model to examine candidate genes and drugs for a role in dyslipidemia and atherosclerosis. The observation that *apobb.1* mutant zebrafish larvae have lower glucose levels is directionally consistent with higher plasma Apo B levels being associated with a higher incidence of diabetes in humans[59,60].

Mutations in *ldlra* were not associated with dyslipidemia, early-stage atherosclerosis or vascular inflammation in our study. This contrast with established results in humans and mouse models likely reflects the presence of a second – albeit downregulated - *LDLR* orthologue in zebrafish (*ldlrb*); the possibility of *cetp*-mediated reverse cholesterol transport to remove excess cholesterol from the body in zebrafish; or the early stage of development at which we performed our screen, i.e. at 10 days post-fertilization. Two studies previously did implicate *ldlra* in dyslipidemia and early-stage atherosclerosis in zebrafish larvae[39,61]. While differences in age, food intake, microbial environment, enzymatic assays, normalization for protein content[62], genetic manipulation[63] and adjustment for co-variables across studies may have influenced the results, the difference in sample size between studies is most noteworthy. O'Hare et al. compared combined LDLc and VLDLc levels using repeated measures on samples of 100 pooled morpholino-injected and 100 pooled control-injected larvae[39], while Liu et al. compared triglyceride and total cholesterol levels in four wildtype larvae and four larvae that were homozygous for mutations in *ldlra*[61]. In contrast, we compared cholesterol levels in 181 and 120 individual larvae with two and zero functionally knocked alleles, respectively, and included data from 381 larvae in our additive analyses.

While mutations in *ldlra* and *apoea* alone did not trigger early-stage atherosclerosis , mutations in these genes showed a positive interaction for vascular accumulation of lipids and co-

localization of lipids with macrophages. It appears that absence of both *ldlra* and *apoea* cannot be compensated in zebrafish larvae.

Like humans, zebrafish are genetically heterogeneous, and we observed a normal or negative binomial distribution for the examined outcomes, with substantial variance by transgenic background and batch in the dietary, drug treatment and genetic interventions. These findings stress the importance of including data from a large number of larvae to acquire meaningful results. We show it is now feasible to objectively quantify dyslipidemia, early-stage vascular atherosclerosis and inflammation, and body size using image-based as well as enzymatic approaches in large numbers of individual zebrafish larvae with relative ease, thus enabling adequately powered, systematic characterization of candidate genes and drugs in zebrafish model systems.

Our characterization of zebrafish orthologues of candidate genes in a pleiotropic locus on chr 19p13.11 suggested a role for *LPAR2* in cholesterol metabolism and early-stage atherosclerosis, and for *GATAD2A* in cholesterol metabolism. *LPAR2* belongs to family I of the G-protein receptors and functions to mobilize calcium in response to lysophosphatidic acid (LPA), while *GATAD2A* encodes a transcriptional repressor. Unfortunately, all larvae in our screen were wildtype for the two CRISPR-targeted orthologues of *TM6SF2*. Knockdown and knockout of *Tm6sf2* in mice was previously shown to result in lower circulating triglyceride, LDLc, HDLc and total cholesterol levels; as well as in higher hepatic triglyceride and cholesteryl esters; more and larger neutral lipid droplets in the liver; a higher risk of hepatic steatosis; and less atherosclerosis[64–66]. Like *Tm6sf2* deficient mice, *lpar2a* mutant zebrafish larvae had lower triglyceride, LDLc and total cholesterol levels. However, in contrast with *Tm6sf2* mutant mice, *lpar2a* mutant zebrafish larvae had more early-stage atherosclerosis, possibly driven by higher

lysophosphatidic acid levels. Lysophosphatidic acid has been shown to increase NFκB, IL-8 and MCP-1 secretion from endothelial cells, which attract neutrophils and macrophages[67,68]; and induces barrier dysfunction and elevated monocyte adhesion to the minimally modified LDL within the intima of vasculature[69]. The range of bi-directional effects of genes in this pleiotropic locus on cardiovascular risk factors explains why the C allele of rs10401969 is only associated with a trend towards a lower risk of CAD in humans (OR=0.95, P=2.8E-3, n=268,744)[12].

In conclusion, zebrafish larvae can be used as a time and cost-efficient model system for image- and CRISPR-Cas9-based genetic interventions, as illustrated by the identification of putative causal genes for cholesterol metabolism (*LPAR2* and *GATAD2A*) and for early-stage atherosclerosis and inflammation (*LPAR2*). Our approach represents an opportunity to reduce the hundreds of candidate genes in GWAS-identified loci to a more feasible number for: 1) further in-depth characterization using animal models; 2) more targeted whole-genome or whole-exome sequencing efforts; and 3) characterization using genotype-based recall efforts. In addition, our pipeline can be used to characterize mechanisms of action for existing drugs, and may prove useful for target-specific small molecule screens.

Online Methods

1 Transgenic backgrounds and atherogenic traits

We used three combinations of fluorescent transgenes (backgrounds) with a lipid-staining dye[30] (see below) to visualize and quantify (see '*Image quantification'*) molecular processes that are known to play a role in early-stage atherosclerosis (**Table 1**). Firstly, zebrafish carrying transgenes to fluorescently label macrophages (*Tg:mpeg1-mCherry*[33]) and neutrophils (*Tg:mpo-EGFP*[35]) were crossed to yield a stable line in which we can visualize and quantify vascular accumulation and co-localization of lipids[30], macrophages[33] and neutrophils[35] (**Fig. 1b**). Secondly, we in-crossed zebrafish that express a fluorescently labelled antibody (IK17) against oxLDL (*Tg:hsp70:IK17-EGFP*)[32] to allow visualization and quantification of vascular accumulation of lipids[30] and oxLDL[32], and we crossed *Tg:hsp70:IK17-EGFP*[32] carriers with *Tg:mpeg1-mCherry* carriers to yield a stable line in which we can visualize and quantify vascular accumulation and co-localization of lipids[30], oxLDL[32] and macrophages[33] (**Fig. 1b-c**). Thirdly, carriers of the flk:EGFP transgene (*Tg:flk-EGFP*[34]) allowed us to quantify vascular accumulation of lipids, confirm or refute whether vascular lipid deposits are located inside the endothelial cell layer, and quantify the endothelial thickness (**Fig. 1d**). In all backgrounds, circulating lipids and vascular lipid deposits were visualized using a dye that preferentially partitions in lipid droplets and that has a blue-shifted, highly enhanced emission in lipophilic environments (monodansylpentane cadaverase [MDH], Abgent, Nordic Biosite, Täby, Sweden)[30].

After imaging, we used enzymatic assays to assess whole-body LDLc, HDLc, triglyceride, total cholesterol and glucose levels. DNA was isolated from the remaining tissue for paired-end sequencing of CRISPR-Cas9 targeted sites in the genetic interventions (see '*genetic intervention*').

2 Husbandry

All experiments described below were performed in zebrafish larvae. Adult transgenic fish and CRISPR founders were raised and kept solely for breeding purposes. Adult fish were fed twice daily on rotifers and dry food (Sparos, Olhão, Portugal), and were maintained in circulating and filtered water (Aquaneering Inc., San Diego, CA), in accordance with Swedish regulations. To generate the required offspring, transgenic adult fish were in-crossed, and fertilized eggs were raised in an incubator at 28.5°C until 5 days post-fertilization (dpf). At 3dpf, embryos were optically screened for fluorescence in 96-well plates (EVOS FL Auto, Thermo Fisher Scientific, MA, USA), and embryos carrying the fluorescent transgene(s) were retained and placed back in the incubator. From 5 to 10dpf, zebrafish larvae were kept in 1L tanks filled with 300mL of water at a density of 30 larvae/tank. Larvae were fed twice daily until 9dpf. At 7dpf, waste products and debris were removed from the water, followed by replenishing of the water level to 300ml. *Tg:hsp70:IK17-EGFP* larvae were subject to a 37°C heat shock for 1 hour at 9dpf, to induce expression of the transgene for screening (see 'Experimental procedure, imaging').

3 Dietary intervention

To identify the atherogenic potential of overfeeding and dietary cholesterol supplementation, larvae from all backgrounds were fed on one of six diets from 5 to 9dpf before being screened at 10dpf. Diets consisted of a normal (~5mg/feeding/tank) or larger amount (~15mg/feeding/tank) of: 1) standard dry food (Golden Pearls, 50-100 μm particles, Alcester, UK); 2) standard dry food supplemented with 4% (wt/wt) extra cholesterol (≥99%, Sigma-Aldrich, Stockholm, Sweden) using a 1:1 volume ratio of diethyl ether to food (>99%, Fisher Scientific, Stockholm, Sweden)[36]; or 3) standard dry food treated with the same amount of diethyl ether without extra cholesterol. The latter condition was added to distinguish between effects of dietary cholesterol

supplementation and/or treatment of the food with diethyl ether per se. To ensure the standard and cholesterol-supplemented diets were provided in energy balance, we assessed the energy density of both diets using blinded bomb calorimetry measurements on four samples per diet (C200 calorimeter, IKA-Werke GmbH & Co. Kg., Staufen, Germany). Since the energy density was on average slightly higher for the cholesterol-supplemented diet than for the regular dry food (i.e. 22.40 vs. 21.70 kJ/g), we fed larvae on slightly more regular dry food with and without treatment with diethyl ether (5.2mg and 15.5mg/feeding/tank for normal and overfeeding) than cholesterol-supplemented diet (5mg and 15mg/feeding/tank).

At 10dpf, larvae were subject to optical screening of atherogenic traits (see '*Imaging*'), followed by assessment of whole-body lipid and glucose levels (see '*Lipid, glucose and protein quantification*'). To reach a sample size of ~100 larvae per background per dietary condition, we repeated the experimental procedure 5-9 times per background (total 27 times). To avoid batch effects, all dietary conditions were included on each occasion, and we adjusted for batch in the statistical analysis. To avoid bias by the time of imaging, the six dietary conditions were imaged in a randomized manner across imaging days, and time of imaging was recorded for each larva and adjusted for in the statistical analysis.

4 Treatment with atorvastatin and ezetimibe

Combined treatment with atorvastatin and ezetimibe is a widely-used strategy to lower LDLc – as well as other key atherogenic parameters – in patients with hypercholesterolemia[70–72]. Results from small-scale studies in samples of 20 to 100 pooled larvae suggest that treating larvae fed on a cholesterol-supplemented diet with statins and/or ezetimibe may prevent the elevated whole-body LDLc and/or total cholesterol levels that are otherwise observed[38,39]. In addition, evidence suggests that treatment with atorvastatin and ezetimibe may reduce vascular lipid deposition[39,73].

To examine the anti-atherogenic potential of combined treatment with atorvastatin and ezetimibe, we overfed larvae of three backgrounds on a cholesterol-supplemented diet – as described earlier – in the presence or absence of 6µg atorvastatin and 80µg ezetimibe per 1g of dry food[73] from 5 to 9dpf. At 10dpf, larvae were optically screened for atherogenic traits (see '*Imaging*') and used for enzymatic assessment of whole-body lipid and glucose levels (see '*Lipid, glucose and protein quantification*'). To reach a sample size of 100 to 200 larvae per background per condition (treated vs. untreated), we repeated the experimental procedure 3 to 4 times across the three backgrounds (total 10 times). To avoid batch effects, treated and untreated larvae were included on each occasion. To avoid bias by the time of imaging, both conditions were alternated during imaging and time of imaging was recorded for each larva.

5 Food intake

To examine if supplementation of food with extra cholesterol and/or atorvastatin and ezetimibe affect food intake, we examined food intake in 204 additional larvae that were overfed on: 1) standard dry food; 2) standard dry food supplemented with 4% extra cholesterol using diethyl ether; 3) standard dry food treated with diethyl ether without cholesterol supplementation; or 4) standard dry food supplemented with 4% extra cholesterol using diethyl ether and further enrichment with atorvastatin and ezetimibe. Larvae were overfed on one of the four diets from 5 to 7dpf as described earlier. Before the morning feeding of 8dpf, larvae were transferred to fresh water before feeding them on diet that had (additionally) been supplemented with a fluorescent tracer. The fluorescently labelled diet was prepared as described previously[74]. Briefly, 75µl of yellow-green 2.0 µm polysterene microspheres (FluoSpheres carboxylate-modified microspheres, Invitrogen, Carlsbad, CA, USA), supplied as a 2% solution, were mixed with 50 mg of food and 25µl of deionized water for each of the four diets. The mixture was left to dry overnight in the

dark and crashed into fine powder the next day. We subsequently acquired Z-stacks of the gastrointestinal tract (30 images, 1.5μm apart) between 20 mins and 5 hours after the morning feeding (**Supplementary Fig. 4**). Two rounds of imaging were performed to reach the final sample size. With the exception of atorvastatin and ezetimibe (2nd round only), all conditions were included in both rounds to avoid batch effects. To avoid bias by the time of imaging, conditions were alternated during imaging – consistently imaging two consecutive larvae per condition – and time of imaging was recorded for each larva to allow for statistical adjustment.

6 Genetic interventions

A rich body of literature supports the role of *APOE*, *APOB*, and *LDLR* in familial hypercholesterolemia and CAD[15–17]. To examine if zebrafish can be used for high-throughput screening of candidate genes for dyslipidemia, atherosclerosis and CAD, we performed a multiplexed, CRISPR-Cas9-based genetic intervention for these genes using the protocol described by Varshney et al.[28].

The zebrafish can have multiple orthologues of any human gene, thanks to a duplication of the genome early in the evolution of teleost fish. Hence, we firstly identified two zebrafish orthologues for *APOE*, three for *APOB* and two for *LDLR* using Ensembl, a synteny search in Genomicus[75], and a literature search[58] (**Supplementary Table 10**). We then designed CRISPR guide RNAs (gRNAs) to target these zebrafish orthologues – aiming for an early exon – using chopchop[76] and CRISPRscan[77], and tested their efficiency by micro-injecting gRNAs and Cas9 into the cell at the single-cell stage in multiplex. Eight larvae per multiplex were sacrificed at 3dpf and used for fragment length PCR analysis, to establish the efficiency of the gRNAs. For each orthologue, we selected a gRNA that showed moderate to high mutagenic efficiency, i.e. additional peaks in the fragment length spectrum in at least four of the eight larvae, while also

retaining the wildtype peak (**Supplementary Table 11**). Pilot experiments in our lab indicated this approach can be anticipated to yield an adequate number of homozygous mutants for each orthologue in the F_1 generation.

Identifying a gRNA with moderate to high mutagenic efficiency on average required six attempts for the seven orthologues (range 2 to 10) (**Supplementary Table 11**). The seven selected gRNAs for orthologues of *APOE*, *APOB*, and *LDLR* – one per orthologue – were subsequently co-injected in the cell of fertilized eggs from *Tg*(*mpeg1-mCherry*; *mpo-EGFP*) parents at the single-cell stage. Founder mutants were optically screened for the presence of the *Tg:mpeg1-mCherry* and *Tg:mpo-EGFP* transgenes at 4dpf, and carriers were raised to maturity. Founder mutants were then in-crossed, and offspring (F_1) were overfed on a cholesterol-supplemented diet from 5 to 9dpf, followed by optical screening for atherogenic traits at 10dpf (see '*Imaging*') and enzymatic assessment of whole-body LDLc, HDLc, triglyceride, total cholesterol, and glucose levels (see '*Lipid, glucose and protein quantification*'). DNA was then extracted and larvae were paired-end sequenced for the CRISPR-targeted sites (see '*DNA extraction and paired-end sequencing*'). To reach a sample size of 384 larvae per multiplex and background, we repeated the experimental procedure eight times. This sample size allows automated downstream sample preparation for paired-end sequencing in multiplex (see '*DNA extraction, sample preparation and paired-end sequencing*').

The procedure described for the proof-of-concept genetic intervention was repeated for four DEPICT[50]-identified candidate genes in triglyceride-associated loci[42], i.e. *LPAR2*, *TM6SF2*, *GATAD2A* and *GMIP*. Together, these four genes have six orthologues in zebrafish (**Supplementary Table 29**), and identifying moderate or highly active gRNAs on average required two attempts (range 2 to 4) (**Supplementary Table 30**). Phenotypically characterizing

384 larvae for the multiplexed mutant line with six targeted candidate genes required repeating the experiment four times.

7 Experimental procedure

7.1 Imaging

On the morning of 10dpf – before the usual morning feeding – all tanks were blinded for dietary or drug treatment condition (not applicable to the genetic interventions) to ensure unbiased imaging, annotation, and quality control of images (see '*Image quantification*'). Immediately before imaging each tank, 15 to 20 larvae were simultaneously soaked in 25µM MDH in PBS for 30 mins, to enable visualization of circulating lipids and vascular lipid deposition. After soaking in MDH, the larvae were placed in a petri dish and anesthetized using tricaine (0.04 mg/ml). Larvae were subsequently aspirated one-by-one using a Vertebrate Automated Screening Technology (VAST) BioImager (Union Biometrica Inc, Geel, Belgium)[40,41], which was mounted on the stage of a Leica DM6000B LED automated upright fluorescence microscope (MicroMedic AB, Stockholm, Sweden). The VAST BioImager automatically loads and positions larvae into a borosilicate capillary, where they are detected by the system's camera. Whole-body images (n=12) were acquired during one full rotation, followed by automated rotation to the lateral orientation, as pre-specified using template images. The VAST BioImager subsequently positioned the larva so the caudal vein and dorsal aorta immediately caudal of the rectum were located within the field of view of the microscope (i.e. ~2.9 mm from the tip of the nose), and triggered the microscope to start imaging. The researcher then manually focused on the center of the vasculature in z using the MDH channel, followed by the automated acquisition of 17 optical sections above, and 17 below the focal point – one every 1.5µm – using a Leica dip-in objective with 20X magnification (Leica OBJ HCX APO L 20X/0.50 W). This procedure was

automatically repeated for each of the up-to-three channels per larva – i.e. to visualize the MDH dye as well as the *EGFP*- and *mCherry*-labelled transgenes – using the Leica 405, L5, and TXR filters, respectively. For each channel, the fluorescence signal was recorded using a Leica DFC365 FX CCD camera. Upon completion of optical sectioning in all channels, the larva was dispensed into a 96-well plate for further processing, and the next larva was loaded for imaging. This procedure takes up to 2 mins per larva.

7.2.1 Quantification of morphological features in zebrafish larvae

Whole-body images of larvae acquired by the bright field camera of the VAST BioImager were used to quantify body length, dorsal and lateral body surface area, and body volume. To distinguish the larva from the capillary in which it was positioned, the capillary was assumed to be horizontal and the position of the capillary was obtained by projecting all pixel intensity values to the y-axis. That is, for each y-level, the sum of all pixels on that level in x was computed (**Fig. 1a**). The edges of the capillary appeared as minima of the projection, and the position of the inner walls were defined as the inner slopes of those minima with the steepest angle, i.e. the highest absolute derivative. Once the region inside the capillary was defined, larvae were segmented from the image background using grey-level thresholding based on optimized precision with regards to a given size interval[78]. This method efficiently tries all possible threshold levels and selects the threshold level that maximizes the per-threshold-precision (true positive / (true positive + false positive), where true positive is defined as the number of pixels in objects within the size interval and false positive is defined as the number of pixels in objects outside the size interval. This pre-processing was performed in ImageJ. Holes within the binary mask were filled automatically using CellProfiler[79], and the largest connected component was extracted as the final segmentation. The dorsal and lateral surface area of the larva was computed

as the number of pixels in this final mask, and the body length was estimated as the largest distance between two points on the larva outline touching a bounding box in the dorsal orientation (**Fig. 1a**).

Fluorescence signals from MDH (lipids), *mCherry* (macrophages) and *EGFP* (neutrophils, oxLDL, endothelial cells) were quantified using custom-written scripts in ImageJ, CellProfiler and ilastik[80]. Firstly, the maximal projection of each fluorescent channel was computed across all optical sections in z using ImageJ, to yield a single image containing signal (and noise) from multiple focal depths. Next, CellProfiler was used to quantify the surface area for each fluorescence signal across the z-stack. Images were first cropped in y using the MDH signal to only include the region from the center of the dorsal aorta to immediately caudal of the caudal vein. The fluorescence signal was then separated from background and noise using an ilastik-based, lenient pixel classifier that takes fluorescence intensity into account. Further segmentation was performed using a CellProfilerAnalyst-based object classifier in which criteria based on area, shape, texture and intensity were summarized in ten rules (see '*code availability*'). Subsequent feature extraction in which the surface area and shape of each identified object were quantified provided the total number of objects and the surface area covered by those objects. In addition, we created a mask to quantify two-way co-localization of MDH-stained lipid deposits or oxLDL with macrophages and neutrophils. Similarly, the proportion of lipid deposits that was located inside the vascular endothelium was calculated by creating a mask for the lipid deposits on top of the segmented vascular endothelial cells. Lipid deposits that overlapped with the endothelial cell layer and/or circulating lipids were considered to reside inside the endothelium; a requirement for atherogenic lipid deposits.

Food intake was quantified in the acquired images by first computing maximal projection of the acquired z-stacks using ImageJ[81], to yield a single image containing signal (and noise) from

multiple focal depths. Next, grey-level thresholding was applied in CellProfiler to quantify the total surface area of the fluorescence signal.

All procedures have been incorporated in pipelines that can be run in an automated manner on at least 2000 images simultaneously.

7.2.2 Sensitivity and specificity for vascular lipid deposition

Accurate identification and quantification of vascular lipid deposits in an automated manner is challenging, since the MDH dye stains both vascular lipid deposits and circulating lipids. To ensure adequate detection of vascular lipid deposits, we calculated the sensitivity and specificity of the image quantification pipeline. To this end, researchers MKB and MdH manually annotated vascular lipid deposits in 30 randomly selected images from the *Tg:mpeg1-mCherry*; *mpo-EGFP* background across the six dietary conditions (blinded) in 3D using the acquired z-stacks. These 6x30 images had not been used to train the pixel and object classifiers. MKB and MdH subsequently discussed the results of the manual annotation process, and resolved discrepancies in judgment where needed. The results of the manual annotation process (gold standard) were then compared with the projections generated by the image quantification pipeline, in which the lipid deposits identified by both pixel and object classifier had been highlighted. Doing so allowed us to quantify the number of true positive (TP), false positive (FP) and false negative (FN) lipid deposits. The average sensitivity and specificity of the image quantification pipeline across the six dietary conditions were 72% and 93%, respectively (calculated using Stata's 'diagti').

7.3 Lipid, glucose and protein profiling

After imaging was completed, the anesthetized larvae were euthanized by exposure to tricaine (MS-222, Sigma, Sweden) and ice. All excess liquid was removed from the well, and one 1.4mm

zirconium bead (Diagnostics, NJ, USA) and 75µl ice-cold PBS 1X were added to each well. The tissue was subsequently homogenized for 2 mins at 1000 rpm (1600 MiniG-Automated homogenizer, Gammadata Instruments, Uppsala, Sweden) and centrifuged at 3500 rpm for 5 mins at 4°C (13,000 rpm when using tubes). After centrifugation, 12.5µl of supernatant was removed and added to a new 96-well plate for protein quantification, together with 12.5µl of ice-cold PBS per well. The remaining supernatant (~60µl/well) was transferred to Eppendorf tubes, together with 160µl of ice-cold PBS 1X (to a total volume of 220µl/well), and stored at -80°C for profiling of LDLc, HDLc, triglyceride, total cholesterol and glucose levels. Samples were subsequently stored at -80°C prior to analysis.

Protein content was assessed using the Pierce bicinchoninic acid (BCA) Protein Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA) and a Varioscan LUX Microplate Reader (Thermo Fisher Scientific, Waltham, MA USA). LDLc, HDLc, triglyceride, total cholesterol and glucose levels were quantified using a fully automated Mindray TM BS-380 analyzer (Mindray Medical International, Shenzhen, China) using direct LDLc (1E31), HDLc (3K33), triglyceride (7D74), cholesterol (7D62), and glucose (3L82) reagents from Abott Laboratories (Abott Park, IL, USA). All analyses were blinded to dietary or treatment condition or genotype, respectively.

7.4.1 DNA extraction, sample preparation and paired-end sequencing

For larvae that were part of the genetic intervention, the pellet that remained after lipid, glucose and protein profiling was used to extract DNA. To this end, 50µl of lysis buffer containing proteinase K (diluted 1:100) was added to each well, followed by incubation at 55°C for 2h, and incubation at 95°C for 10 mins to heat-inactivate the proteinase K. Samples were then centrifuged at 3500 rpm for 2 mins and the supernatant was transferred to a new 96-well plate. A two-step PCR reaction subsequently incorporated Illumina Nextera XT v2 indices into the PCR

products (Illumina Inc, San Diego, CA) using a Hamilton Nimbus 96 liquid handling system (Hamilton Robotics AB, Kista, Sweden), followed by paired-end sequencing (2x250 bp) on a MiSeq (Illumina Inc, San Diego, CA) at the National Genomics Infrastructure (NGI) Sweden. This procedure allows us to combine samples from up to eight 384-well plates – i.e. 8x384 larvae with 8x8 different target sites – in a single sequencing lane while retaining >100X coverage, on average. The combination of sequence and indices allows post-sequencing linking of reads to individual larvae (see 'post-sequencing data analysis').

7.4.2 Post-sequencing data analysis

The MiSeq generated two de-multiplexed, paired-end .fastq files per larva (2x250 bp). A custom-written Perl script was used to split the reads into separate .fastq files for each CRISPR-Cas9 targeted site, and remove the insert sequences from the .fastq files. The paired-end sequences were processed at the same time, extracting the sequence in between the two primers if both primers were present in the read, or the sequence downstream of the first primer if only the first primer was observed (to prevent excluding longer reads *a priori*). No mismatches in the primer(s) were allowed to ensure optimal data quality. We subsequently used the fast and accurate Illumina Paired-End read mergeR (PEAR)[82] to merge the trimmed paired-end reads; FastX version 0.0.14[83] to remove reads containing bases with a quality score below 20 (-q 20, -p 100); and Spliced Transcripts Alignment to a Reference (STAR) version 2.4.1c[84] to map the reads to the reference genome (Danio_rerio.GRCz11.dna.toplevel.fa as downloaded from Ensembl). SAMtools version 0.1.19[85] was used to convert files from SAM to BAM format and sort and index BAM files, as well as to generate a summary of the coverage of mapped reads on a reference sequence at a single bp resolution (using the 'mpileup' utility).

A custom-written variant calling algorithm in R (DIVaH - Danio rerio Identification of Variants by Haplotype) was used to identify the two most prominent reads per larva and target site that passed quality control. That is, reads with a length difference compared with the reference sequence of less than 170 bp, and with an alignment report string (Concise Idiosyncratic Gapped Alignment Report [CIGAR]) shorter than 50 characters (**Supplementary Tables 12 and 31**). Variants located within 30 bp of the CRISPR target site were subsequently functionally annotated using Ensembl's variant effect predictor (VEP) (**Supplementary Tables 13 and 32**). At each larva, target site and allele, the variant with the highest predicted likelihood of functionally affecting protein function was retained. Allele-specific scores (no annotation=0; modifier=0.2; low=0.33; moderate=0.66; high=1) were then calculated, and summing across the two alleles yielded an orthologue-specific dosage score for each targeted site (i.e. orthologue) in each larva.

In the proof-of-concept genetic screen, a median of 18 unique CRISPR-Cas9 induced mutations with a predicted detrimental effect on protein function were observed across the seven targeted orthologues in offspring of founder mutants (interquartile range 16 to 24.5 mutations, **Supplementary Table 13**). Of the 138 unique mutations identified across the seven target sites, 54 were frameshift deletions (40.0%), nine introduced a premature stop codon, and 34 were missense variants (24.6%). VEP predicted that of the 138 unique mutations, 18 were modifiers (13.0%), while four, 51 and 65 were assigned a low, moderate or high likelihood of affecting protein function (2.9%, 37.0% and 47.1%, respectively, **Supplementary Table 13**). The mutant allele frequency across the seven targeted zebrafish orthologues was typically high in the F_1 generation (median 0.88, interquartile range 0.52 to 0.98, **Supplementary Table 14**).

In the discovery screen for candidate genes in the triglyceride, LDLc, total cholesterol and type-2 diabetes-associated locus on chr 19p13.11, three, one and seven unique CRISPR-Cas9

induced mutations with a predicted detrimental effect on protein function were observed in *lpar2a*, *lpar2b* and *gatad2ab* in offspring of founder mutants (**Supplementary Table 32**). All larvae were wildtype for the zebrafish orthologues of *TM6SF2* and *GMIP*, in spite of having pre-tested the CRISPR gRNAs for efficiency. Of the 11 unique mutations identified across *lpar2a*, *lpar2b* and *gatad2ab*, four were frameshift deletions (36.4%), four were inframe deletions (36.4%), and three were missense variants (27.3%, **Supplementary Table 32**). In addition to all F_1 larvae being wildtype for three of the six targeted orthologues, the mutant allele frequency was very low across *lpar2a*, *lpar2b* and *gatad2ab*, with only 11, 6 and 18 of the 376 successfully sequenced larvae carrying one mutated allele. None of the larvae carried a mutated allele in more than one gene (**Supplementary Table 33**).

8 Quality control

After image quantification and before the statistical analysis, all quantified images were manually screened to ensure adequate quantification had occurred. Larvae for which the automated quantification pipeline had failed for a trait were annotated and excluded from the analysis for that trait, as well as for any traits that rely on adequate quantification of that trait. Annotations include: weak staining of the circulation by MDH (possibly reflecting low levels of circulating lipids), resulting in incorrect segmentation of the region of interest; inadequate segmentation of the region of interest for other reasons, like movement during imaging; more than 20% of true negative objects being detected as objects (i.e. many false positives); less than 20% of true objects being detected (i.e. many false negatives); and circulating neutrophils being present, resulting in the same neutrophil being quantified multiple times (**Supplementary Table 1**). Annotations that resulted in the exclusion of at least ten larvae were examined in more detail, to examine if the underlying reason for exclusion may have influenced the results (see below).

Based on the large proportion of affected larvae and the absence of influence on the results, larvae with many false positive or many false negative oxLDL deposits were included in the analysis.

In the dietary and drug treatment interventions, all continuous outcomes and exposures outside the mean ± 5×SD (standard deviation) range were set to missing before the association analysis, to prevent outliers – be it biological or methodological – from driving the results. This step was omitted in the genetic interventions because larvae carrying two mutated alleles for causal genes were *a priori* anticipated to show extreme phenotypes. In addition, total cholesterol levels were set to missing if triglyceride levels were missing and vice versa. This resulted in the exclusion of images from a median of 2.5 larvae across all outcomes in the dietary intervention (inter quartile range 2.5 to 7), and one larva in the drug treatment intervention (interquartile range 0 to 2.75). Next, residuals were calculated to normalize: 1) vascular endothelial surface area for the surface area of circulating lipids, yielding a variable that reflects endothelial thickness; 2) LDLc, HDLc, triglyceride, total cholesterol and glucose levels for protein content of the sample; and 3) dorsal and lateral body surface area as well as body volume for body length. All analyses with these variables as outcomes or exposures were performed using normalized values. Finally, all continuous outcomes showing an approximately normal distribution were inverse-normally transformed to a mean of 0 and standard deviation (SD) of 1, to ensure all residuals in the association analyses were normally distributed. This transformation implies that all effect sizes (β), standard errors (SE) and 95% confidence intervals (95% CI) for these outcomes can be interpreted as z-scores, allowing a comparison of effect sizes across outcomes, conditions and experiments. Image-based vascular atherogenic outcomes that showed a negative binomial distribution – with or without inflation of zeros –were not inverse-normally transformed.

9 Statistical analysis

In the main analysis, we examined the effect of: 1) overfeeding and cholesterol supplementation (in the dietary intervention); 2) treatment with atorvastatin and ezetimibe (in the drug treatment intervention); and 3) mutations in proof-of-concept and candidate genes (in the genetic interventions) on body size; early-stage vascular atherogenic traits; and whole-body LDLc, HDLc, triglyceride, total cholesterol and glucose levels. This was accomplished using hierarchical linear models (xtmixed in Stata) or negative binomial regression (nbreg). Hierarchical linear models on inverse-normally transformed outcomes provide effect sizes and standard errors for the fixed factors, while providing the standard deviation of the outcome across random factors, for which the intercept – i.e. the value of non-exposed larvae – is allowed to vary. Body size, whole-body lipid and glucose levels, and some image-based atherogenic traits were analyzed this way, i.e. typically vascular infiltration by macrophages or neutrophils. However, most image-based vascular atherogenic traits showed negative binomial distributions. For such traits, the effects of dietary, drug treatment and genetic factors were examined using negative binomial regression.

All models were adjusted for: a) the use of diethyl ether (in the dietary intervention); and b) time of day at which the image was acquired (in all experiments) as fixed factors (xtmixed) or as regular co-variables (nbreg). Models were additionally adjusted for transgenic background and batch as random factors or as regular co-variables. For image-based vascular atherogenic traits, associations were examined with and without adjusting for body length and dorsal body surface area, by adding them as fixed factors or co-variables to the models. To ensure unbiased estimates, we only included data from larvae with information on body length and dorsal body surface area in the adjusted and unadjusted analyses, to ensure that effect estimates were based on data from the same larvae. This step was omitted in the genetic interventions to maximize the sample size

of the analysis that was not adjusted for body size. For image-based atherogenic traits, we also examined if LDLc, HDLc, triglyceride, and/or glucose levels mediated the main effect of dietary, drug treatment and genetic factors, by adding them as additional fixed factors or co-variables to the size-adjusted model. The sample size was typically somewhat lower for the latter analyses due to missing data. Directed acyclic graphs (DAGs) indicated that based on the anticipated causal paths, this analysis plan should not have resulted in biased effect estimates. For image-based atherogenic traits, results from models that were additionally adjusted for body size were considered the main results, and are referred to throughout the results and figures.

A small subset of larvae with suboptimal image or image quantification quality were excluded from the analyses (**Supplementary Table 2**). To examine if exclusion of these larvae may have influenced the results, we examined if the odds of being affected was associated with the main exposures, i.e. diet, drug treatment or mutations. These analyses were performed using logistic regression models for annotations that affected at least ten larvae.

For all analyses, effect sizes, standard errors (robust standard errors for nbreg) and 95% confidence intervals are reported for the exposed compared with the unexposed group. Odds ratios (OR) and 95% confidence intervals are provided for analyses of image-based exclusions. All data management and statistical analyses were performed using Stata/MP 14.0 for Mac.

10 Ethical approval

All procedures were performed in line with Swedish regulations, and all experiments have been approved by Uppsala Djurförsöksetiska nämnd, Uppsala, Sweden (Permit numbers C142/13 and C14/16).

11 Code availability

All custom-written image analysis scripts; all post-sequencing QC and alignment scripts; the custom-written variant calling algorithm in R (i.e. DIVaH - Danio rerio Identification of Variants by Haplotype); and all Stata scripts used for statistical analysis are available from the corresponding author upon request.

12 Data availability

The data that support the findings of the current study are available from the corresponding author upon reasonable request.

Acknowledgments

We are very grateful to Stephen A Renshaw from the University of Sheffield, Graham Lieschke from Monash University, Yury Miller from UCSD, and Dimitris Beis from the Biomedical Research Foundation Academy of Science for kindly providing us with carriers of the *Tg:mpo-EGFP*, *Tg:mpeg1-mCherry*, *Tg:hsp70:IK17-EGFP* and *Tg:flk-EGFP* transgenes, respectively. Input from Shawn Burgess and Gaurav Varshney on mutagenesis using CRISPR-Cas9 is also much appreciated. João Campos Costa's efforts when setting up the lab are gratefully acknowledged, and we would also like to thank Francis Smet from Union Biometrica Inc and Thommie Karlsson from Leica for their help with installing the imaging set-up. Pilou Janssens' work on bomb calorimetry of diets, and Lingjie Tao and Lisa Conrad's help with sample preparation and pre-screening of larvae are also much appreciated. The computations were performed on resources provided by SNIC through Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX) under Project SNIC b2015283. The authors would like to acknowledge support from Science for Life Laboratory, the National Genomics Infrastructure (NGI) and UPPMAX for aiding in massive parallel sequencing and computational infrastructure. Support from the National Bioinformatics Infrastructure Sweden (NBIS) is also gratefully acknowledged, and constructive discussions with the Genome Engineering Zebrafish (GEZ) facility are appreciated. Data on coronary artery disease / myocardial infarction have been contributed by the CARDIoGRAMplusC4D and UK Biobank CardioMetabolic Consortium CHD working group who used the UK Biobank Resource (application number 9922). Data have been downloaded from www.CARDIOGRAMPLUSC4D.ORG.

MdH is a fellow of the Swedish Heart-Lung Foundation (20170872) and a Kjell and Märta Beijer Foundation researcher. This research was supported by project grants from the Swedish Heart-Lung Foundation (20140543, 20170678, 20180706), the Swedish Research Council (2015-

03657), the Knut och Alice Wallenberg Foundation (2013.0126), the European Research Council (ERC-StG-335395) and NIH (R01DK106236, R01DK107786, U01DK105554).

Author contributions

MKB, EI and MdH conceived the study; EI and MdH ascertained funding and provided material support; MKB, AE, BvdH, EM, MMM, TK and MdH performed the experiments; MKB, PR, CW and MdH generated the image quantification pipelines and performed the image-based analysis; MKB, AE, BvdH, TK and MdH optimized the CRISPR-Cas9 multiplex pipeline; EM, OD and MDH generated the post NGS QC and variant calling pipeline; AL assessed whole-body lipid and glucose levels; HLB and MdH performed the statistical analysis; MKB and MdH wrote the manuscript; all authors provided critical feedback to the manuscript.

Competing Financial Interests statement

None of the authors have a competing financial interest to declare. Funding bodies did not influence the results of the study.

References

1. Lusis, A. J. Atherosclerosis. *Nature* **407,** 233 (2000).
2. Ross, R. Atherosclerosis--an inflammatory disease. *N. Engl. J. Med.* **340,** 115–26 (1999).
3. Ross, R. & Glomset, J. A. Atherosclerosis and the arterial smooth muscle cell: Proliferation of smooth muscle is a key event in the genesis of the lesions of atherosclerosis. *Science* **180,** 1332–9 (1973).
4. Badrnya, S., Butler, L. M., Söderberg-Naucler, C., Volf, I. & Assinger, A. Platelets directly enhance neutrophil transmigration in response to oxidised low-density lipoprotein. *Thromb. Haemost.* **108,** 719–729 (2012).
5. Watson, A. D. *et al.* Structural identification by mass spectrometry of oxidized phospholipids in minimally oxidized low density lipoprotein that induce monocyte/endothelial interactions and evidence for their presence in vivo. *J. Biol. Chem.* **272,** 13597–607 (1997).
6. Adiguzel, E., Ahmad, P. J., Franco, C. & Bendeck, M. P. Collagens in the progression and complications of atherosclerosis. *Vasc. Med.* **14,** 73–89 (2009).
7. Kannel, W. B. Some lessons in cardiovascular epidemiology from Framingham. *Am. J. Cardiol.* **37,** 269–282 (1976).
8. O'Gara, P. T. *et al.* 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. *J. Am. Coll. Cardiol.* **61,** e78–e140 (2013).
9. Jneid, H. *et al.* 2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update). *J. Am. Coll. Cardiol.* **60,** 645–681 (2012).
10. Ibanez, B. *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction

in patients presenting with ST-segment elevation. *Eur. Heart J.* **39,** 119–177 (2018).

11. GBD 2016 Causes of Death Collaborators, M. *et al.* Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)* **390,** 1151–1210 (2017).

12. Nelson, C. P. *et al.* Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat. Genet.* **49,** 1385–1391 (2017).

13. Miller, C. L. *et al.* Integrative functional genomics identifies regulatory mechanisms at coronary artery disease loci. *Nat. Commun.* **7,** (2016).

14. Klarin, D. *et al.* Genetics of blood lipids among ~300,000 multi-ethnic participants of the Million Veteran Program. *Nat. Genet.* **50,** 1514–1523 (2018).

15. Beisiegel, U., Weber, W., Ihrke, G., Herz, J. & Stanley, K. K. The LDL–receptor–related protein, LRP, is an apolipoprotein E-binding protein. *Nature* **341,** 162–164 (1989).

16. Zimmermann, T. S. *et al.* RNAi-mediated gene silencing in non-human primates. *Nature* **441,** 111–114 (2006).

17. Brown, Michael S., Goldstein, J. L. The Nobel Prize in Physiology and Medicine. (1985).

18. Jarcho, J. A. & Keaney, J. F. Proof That Lower Is Better — LDL Cholesterol and IMPROVE-IT. *N. Engl. J. Med.* **372,** 2448–2450 (2015).

19. Garcia-Calvo, M. *et al.* The target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1). *Proc. Natl. Acad. Sci.* **102,** 8132–8137 (2005).

20. Sabatine, M. S. *et al.* Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events. *N. Engl. J. Med.* **372,** 1500–1509 (2015).

21. Fitzgerald, K. *et al.* Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1

trial. *Lancet (London, England)* **383,** 60–68 (2014).

22. Dadu, R. T. & Ballantyne, C. M. Lipid lowering with PCSK9 inhibitors. *Nat. Rev. Cardiol.* **11,** 563–75 (2014).

23. Plump, A. S. *et al.* Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. *Cell* **71,** 343–53 (1992).

24. Powell-Braxton, L. *et al.* A mouse model of human familial hypercholesterolemia: markedly elevated low density lipoprotein cholesterol levels and severe atherosclerosis on a low-fat chow diet. *Nat. Med.* **4,** 934–8 (1998).

25. Hogarth, C. A., Roy, A. & Ebert, D. L. Genomic evidence for the absence of a functional cholesteryl ester transfer protein gene in mice and rats. *Comp. Biochem. Physiol. B. Biochem. Mol. Biol.* **135,** 219–29 (2003).

26. Lieschke, G. J. & Currie, P. D. Animal models of human disease: Zebrafish swim into view. *Nat. Rev. Genet.* **8,** 353–367 (2007).

27. Vilella, A. J. *et al.* EnsemblCompara GeneTrees: Complete, duplication-aware phylogenetic trees in vertebrates. *Genome Res.* **19,** 327–35 (2009).

28. Varshney, G. K. *et al.* A high-throughput functional genomics workflow based on CRISPR/Cas9-mediated targeted mutagenesis in zebrafish. *Nat. Protoc.* **11,** 2357–2375 (2016).

29. Spandl, J., White, D. J., Peychl, J. & Thiele, C. Live cell multicolor imaging of lipid droplets with a new dye, LD540. *Traffic* **10,** 1579–84 (2009).

30. Yang, H.-J., Hsu, C.-L., Yang, J.-Y. & Yang, W. Y. Monodansylpentane as a blue-fluorescent lipid-droplet marker for multi-color live-cell imaging. *PLoS One* **7,** e32693 (2012).

31. Flynn, E. J., Trent, C. M. & Rawls, J. F. Ontogeny and nutritional control of adipogenesis

in zebrafish (Danio rerio). *J. Lipid Res.* **50,** 1641–52 (2009).

32. Fang, L. *et al.* In vivo visualization and attenuation of oxidized lipid accumulation in hypercholesterolemic zebrafish. *J. Clin. Invest.* **121,** 4861–4869 (2011).

33. Ellett, F., Pase, L., Hayman, J. W., Andrianopoulos, A. & Lieschke, G. J. mpeg1 promoter transgenes direct macrophage-lineage expression in zebrafish. *Blood* **117,** e49-56 (2011).

34. Beis, D. *et al.* Genetic and cellular analyses of zebrafish atrioventricular cushion and valve development. *Development* **132,** 4193–204 (2005).

35. Renshaw, S. A. *et al.* A transgenic zebrafish model of neutrophilic inflammation. *Blood* **108,** 3976–3978 (2006).

36. Stoletov, K. *et al.* Vascular Lipid Accumulation, Lipoprotein Oxidation, and Macrophage Lipid Uptake in Hypercholesterolemic Zebrafish. *Circ. Res.* **104,** 952–960 (2009).

37. Fang, L. *et al.* Oxidized cholesteryl esters and phospholipids in zebrafish larvae fed a high cholesterol diet: macrophage binding and activation. *J. Biol. Chem.* **285,** 32343–51 (2010).

38. Baek, J. S., Fang, L., Li, A. C. & Miller, Y. I. Ezetimibe and simvastatin reduce cholesterol levels in zebrafish larvae fed a high-cholesterol diet. *Cholesterol* **2012,** 564705 (2012).

39. O'Hare, E. A. *et al.* Disruption of ldlr causes increased LDL-c and vascular lipid accumulation in a zebrafish model of hypercholesterolemia. *J. Lipid Res.* **55,** 2242–53 (2014).

40. Chang, T.-Y., Pardo-Martin, C., Allalou, A., Wählby, C. & Yanik, M. F. Fully automated cellular-resolution vertebrate screening platform with parallel animal processing. *Lab Chip* **12,** 711–716 (2012).

41. Pardo-Martin, C. *et al.* High-throughput hyperdimensional vertebrate phenotyping. *Nat. Commun.* **4,** (2013).

42. Willer, C. J. *et al.* Discovery and refinement of loci associated with lipid levels. *Nat. Genet.* **45,** 1274–1285 (2013).

43. Mahler, A. Blood cholesterol during ether anesthesia. *J Biol Chem* **69,** 653–659 (1926).

44. Friedewald, W. T., Levy, R. I. & Fredrickson, D. S. Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. *Clin. Chem.* **18,** (1972).

45. Investigators, T. A.-H. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. *N. Engl. J. Med.* **365,** 2255–2267 (2011).

46. Group, T. H.-T. C. Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients. *N. Engl. J. Med.* **371,** 203–212 (2014).

47. Lincoff, A. M. *et al.* Evacetrapib and Cardiovascular Outcomes in High-Risk Vascular Disease. *N. Engl. J. Med.* **376,** 1933–1942 (2017).

48. HPS3/TIMI55–REVEAL Collaborative Group *et al.* Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. *N. Engl. J. Med.* **377,** 1217–1227 (2017).

49. Do, R. *et al.* Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat. Genet.* **45,** 1345–1352 (2013).

50. Pers, T. H. *et al.* Biological interpretation of genome-wide association studies using predicted gene functions. *Nat. Commun.* **6,** 5890 (2015).

51. Rosch, P. J. Genes and stress cause coronary atherosclerosis not saturated fat. *Lancet (London, England)* **375,** 1780–1; author reply 1781 (2010).

52. Rosch, P. J. Stress, cholesterol, and coronary heart disease. *Lancet (London, England)* **2,** 851–2 (1983).

53. Djoussé, L. & Gaziano, J. M. Dietary cholesterol and coronary artery disease: a systematic review. *Curr. Atheroscler. Rep.* **11,** 418–22 (2009).

54. Sattar, N. *et al.* Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet (London, England)* **375,** 735–42 (2010).

55. Swerdlow, D. I. *et al.* HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet (London, England)* **385,** 351–61 (2015).

56. Ference, B. A. *et al.* Variation in *PCSK9* and *HMGCR* and Risk of Cardiovascular Disease and Diabetes. *N. Engl. J. Med.* **375,** 2144–2153 (2016).

57. Lotta, L. A. *et al.* Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis. *JAMA* **316,** 1383–1391 (2016).

58. Otis, J. P. *et al.* Zebrafish as a model for apolipoprotein biology: comprehensive expression analysis and a role for ApoA-IV in regulating food intake. *Dis. Model. Mech.* **8,** 295–309 (2015).

59. Ley, S. H. *et al.* Association of apolipoprotein B with incident type 2 diabetes in an aboriginal Canadian population. *Clin. Chem.* **56,** 666–70 (2010).

60. Lim, H. H. & Kim, O. Y. Association of Serum Apolipoprotein B with the Increased Risk of Diabetes in Korean Men. *Clin. Nutr. Res.* **5,** 204 (2016).

61. Liu, C. *et al.* Modeling hypercholesterolemia and vascular lipid accumulation in LDL receptor mutant zebrafish. *J. Lipid Res.* **59,** 391–399 (2018).

62. Heymsfield, S. B. *et al.* Evolving concepts on adjusting human resting energy expenditure measurements for body size. *Obes. Rev.* **13,** 1001–14 (2012).

63. Rossi, A. *et al.* Genetic compensation induced by deleterious mutations but not gene knockdowns. *Nature* **524,** 230–3 (2015).

64. Holmen, O. L. *et al.* Systematic evaluation of coding variation identifies a candidate causal

variant in TM6SF2 influencing total cholesterol and myocardial infarction risk. *Nat. Genet.* **46,** 345–51 (2014).

65. Kozlitina, J. *et al.* Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. *Nat. Genet.* **46,** 352–6 (2014).

66. Smagris, E., Gilyard, S., BasuRay, S., Cohen, J. C. & Hobbs, H. H. Inactivation of Tm6sf2, a Gene Defective in Fatty Liver Disease, Impairs Lipidation but Not Secretion of Very Low Density Lipoproteins. *J. Biol. Chem.* **291,** 10659–76 (2016).

67. Palmetshofer, A., Robson, S. C. & Nehls, V. Lysophosphatidic acid activates nuclear factor kappa B and induces proinflammatory gene expression in endothelial cells. *Thromb. Haemost.* **82,** 1532–7 (1999).

68. Lin, C. I., Chen, C.-N., Chen, J. H. & Lee, H. Lysophospholipids increase IL-8 and MCP-1 expressions in human umbilical cord vein endothelial cells through an IL-1-dependent mechanism. *J. Cell. Biochem.* **99,** 1216–1232 (2006).

69. Siess, W. Athero- and thrombogenic actions of lysophosphatidic acid and sphingosine-1-phosphate. *Biochim. Biophys. Acta - Mol. Cell Biol. Lipids* **1582,** 204–215 (2002).

70. Stein, E. *et al.* Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. *Am. Heart J.* **148,** 447–55 (2004).

71. Bays, H. E. *et al.* Influence of age, gender, and race on the efficacy of adding ezetimibe to atorvastatin vs. atorvastatin up-titration in patients at moderately high or high risk for coronary heart disease. *Int. J. Cardiol.* **153,** 141–7 (2011).

72. Conard, S. *et al.* Ezetimibe added to atorvastatin compared with doubling the atorvastatin dose in patients at high risk for coronary heart disease with diabetes mellitus, metabolic syndrome or neither. *Diabetes. Obes. Metab.* **12,** 210–8 (2010).

73. Yang, Y.-C., Chang, W.-T., Huang, S.-K. & Liau, I. Characterization of the pharmaceutical effect of drugs on atherosclerotic lesions in vivo using integrated fluorescence imaging and Raman spectral measurements. *Anal. Chem.* **86,** 3863–8 (2014).

74. Field, H. A., Kelley, K. A., Martell, L., Goldstein, A. M. & Serluca, F. C. Analysis of gastrointestinal physiology using a novel intestinal transit assay in zebrafish. *Neurogastroenterol. Motil.* **21,** 304–12 (2009).

75. Louis, A., Nguyen, N. T. T., Muffato, M. & Roest Crollius, H. Genomicus update 2015: KaryoView and MatrixView provide a genome-wide perspective to multispecies comparative genomics. *Nucleic Acids Res.* **43,** D682-9 (2015).

76. Montague, T. G., Cruz, J. M., Gagnon, J. A., Church, G. M. & Valen, E. CHOPCHOP: a CRISPR/Cas9 and TALEN web tool for genome editing. *Nucleic Acids Res.* **42,** W401-7 (2014).

77. Moreno-Mateos, M. A. *et al.* CRISPRscan: designing highly efficient sgRNAs for CRISPR-Cas9 targeting in vivo. *Nat. Methods* **12,** 982–8 (2015).

78. Ranefall, P. & Wählby, C. Global gray-level thresholding based on object size. *Cytometry. A* **89,** 385–90 (2016).

79. Jones, T. R. *et al.* CellProfiler Analyst: data exploration and analysis software for complex image-based screens. *BMC Bioinformatics* **9,** 482 (2008).

80. Sommer C., Strähle C., K. U. Ilastik: Interactive Learning and Segmentation Toolkit. in *Eighth IEE international Symposium on Biomedical Imaging (ISBI). Proceedings* 230–233 (2011).

81. Schneider, C. A., Rasband, W. S. & Eliceiri, K. W. NIH Image to ImageJ: 25 years of image analysis. *Nat. Methods* **9,** 671–5 (2012).

82. Zhang, J., Kobert, K., Flouri, T. & Stamatakis, A. PEAR: a fast and accurate Illumina

Paired-End reAd mergeR. *Bioinformatics* **30,** 614–20 (2014).

83. Pearson, W. R., Wood, T., Zhang, Z. & Miller, W. Comparison of DNA Sequences with Protein Sequences. *Genomics* **46,** 24–36 (1997).

84. Dobin, A. *et al.* STAR: ultrafast universal RNA-seq aligner. *Bioinformatics* **29,** 15–21 (2013).

85. Li, H. *et al.* The Sequence Alignment/Map format and SAMtools. *Bioinformatics* **25,** 2078–2079 (2009).

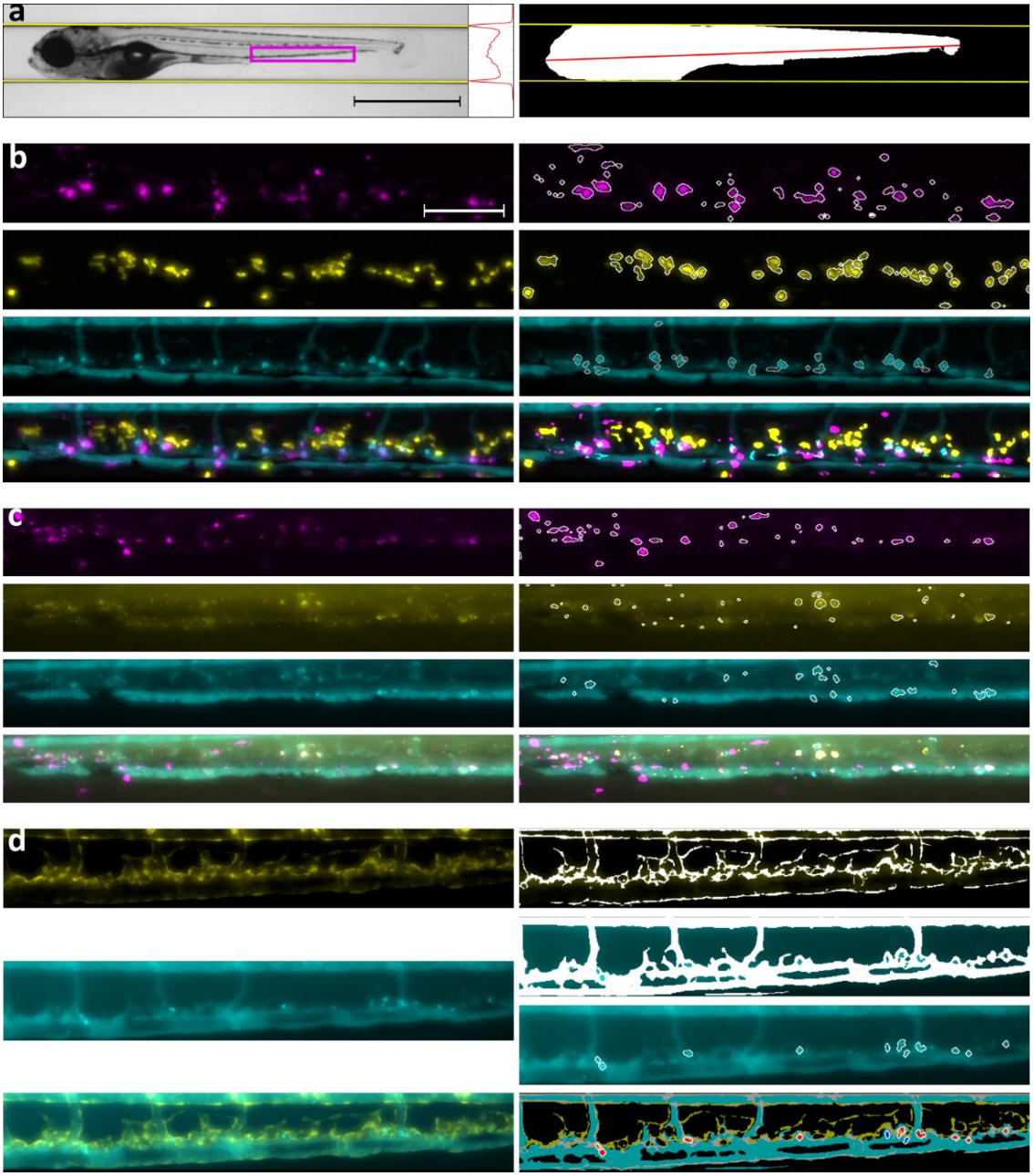


Figure 1. Raw data (left) and objective, semi-automated quantification (right) of body size and early-stage atherosclerosis in 10-day-old zebrafish larvae. a) Left: A bright field image of a zebrafish larva in lateral orientation with projection of all intensity values to the y-axis. The two distinct minima in the projection represent the walls of the capillary, outlined in yellow (scale bar = 1 mm). The region of the tail that was imaged to quantify vascular atherogenic traits is highlighted in magenta. Right: a binary mask of the same larva, with lateral surface area in white, and body length in red. b) A Tg(mpeg1-mCherry; mpo-EGFP) transgenic larva with fluorescently labelled macrophages (top, magenta) and neutrophils (2nd from top, yellow). Circulating lipids and vascular lipid deposits were stained with a dye (3rd from the top, cyan). The overlay (bottom) shows co-localization of all traits (scale bar = 100µm). c) A Tg(mpeg1-mCherry; hsp70:IK17-EGFP) transgenic larva with fluorescently labelled macrophages (top, magenta) and oxidized LDL (2nd from top, yellow) with stained lipids (3rd from top, cyan). The overlay shows co-localization of all traits (bottom). d) A Tg(flk-EGFP) transgenic larva with fluorescently labelled endothelial cells showing endothelial surface area (top, yellow); stained lipids (2nd from top, cyan) from which both circulating lipids (right, 2nd from top) and vascular lipid deposition (right, 3rd from top) were quantified; and an overlay that enabled distinguishing between lipid deposition inside (in red) and outside the endothelium (bottom right, blue).

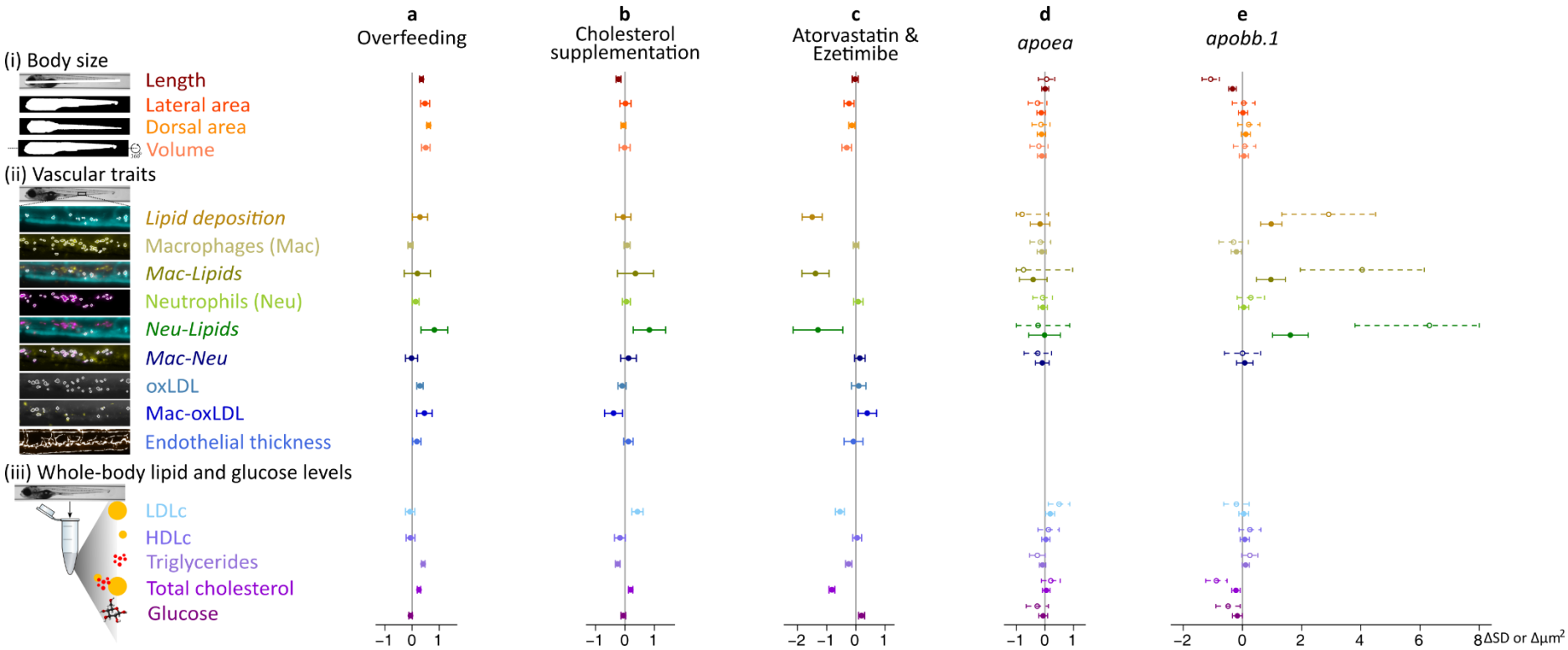


Figure 2. The effect of overfeeding and cholesterol supplementation (n>2000); treatment with atorvastatin and ezetimibe (n>1000); and mutations in apoea and apobb.1 (n=384) on body size (i), vascular atherogenic traits (ii) and whole-body lipid and glucose levels (iii). Across a-e, dorsal and lateral body surface area and body volume were normalized for body length before the analysis; whole-body lipid and glucose levels were normalized for protein levels; and endothelial thickness was normalized for surface area of the circulation. For normally distributed traits, associations were examined using hierarchical linear models on inverse-normally transformed outcomes. For these traits effect sizes and 95% confidence intervals are expressed in standard deviation units (SD). The remaining vascular atherogenic traits (shown in italics) showed a negative binomial distribution and data were analyzed accordingly. For these traits, effect sizes and 95% confidence intervals are expressed in μm^2. In d and e, open circles and the dotted lines represent the effect of two functionally knocked-out alleles vs. two unmodified alleles, and full circles and filled lines represent the additive per mutated allele effect. Associations were adjusted for time of day; use of diethyl ether (for overfeeding and cholesterol supplementation); cholesterol supplementation (for overfeeding); the amount fed (for cholesterol supplementation); body length and dorsal body surface area (for vascular outcomes); batch; and transgenic background.

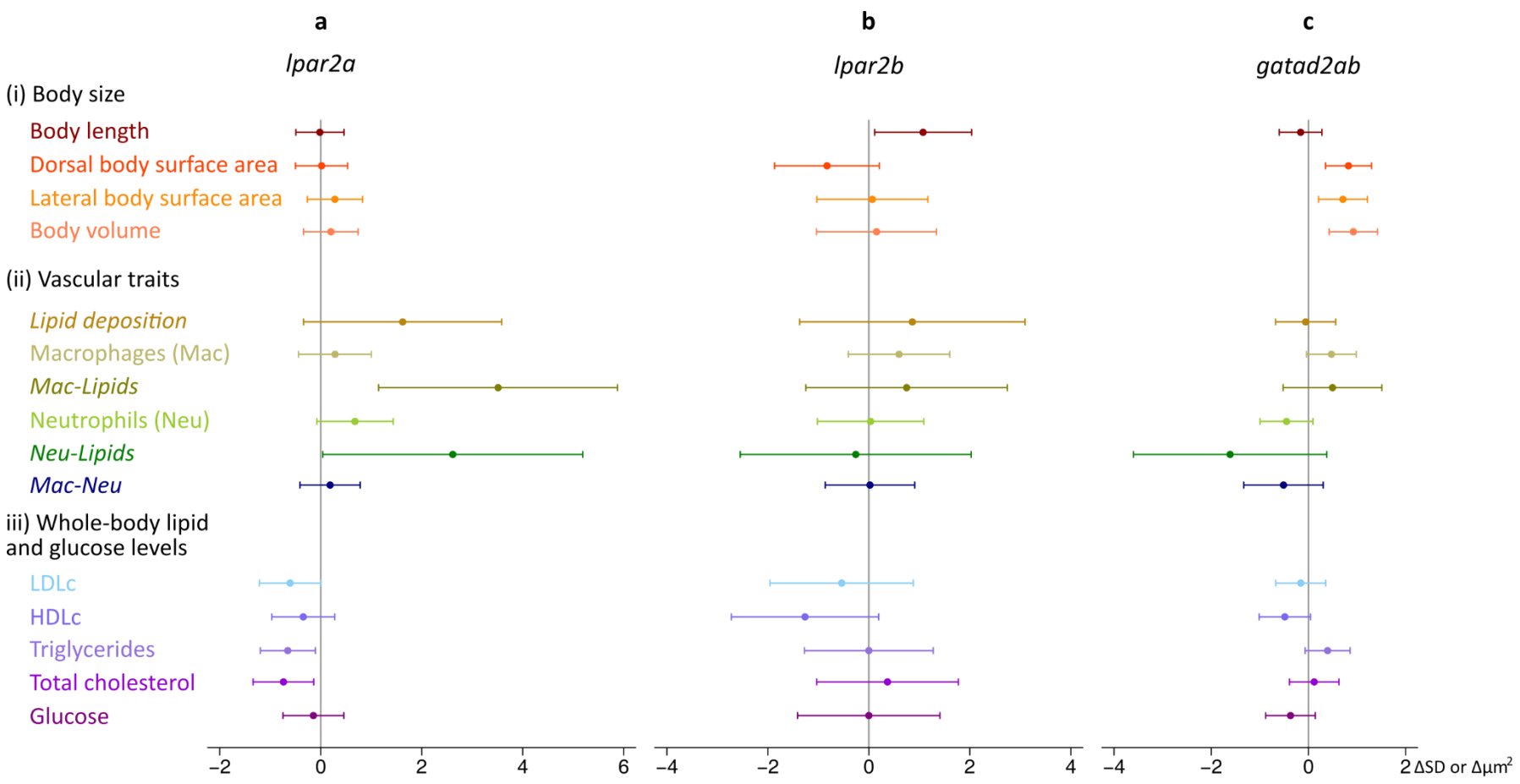


Figure 3. The mutually adjusted effect of mutations in zebrafish orthologues of LPAR2 and GATAD2A (n=547) on body size (i), vascular atherogenic traits (ii) and whole-body lipid and glucose levels (iii) using an additive model. Dorsal and lateral body surface area and body volume were normalized for body length; and whole-body lipid and glucose levels were normalized for protein levels before the analysis. For normally distributed traits, associations were examined using hierarchical linear models on inverse-normally transformed outcomes. For these traits, effect sizes and 95% confidence intervals are expressed in standard deviation units (SD). Some vascular atherogenic traits showed a negative binomial distribution and associations were analyzed accordingly. For these traits (shown in italics), effect sizes and 95% confidence intervals are expressed in μm^2. Associations were adjusted for time of day; body length and dorsal body surface area (for vascular outcomes); and batch.

SUPPLEMENTARY FIGURES

Supplementary Figure 1 - The effect of overfeeding, cholesterol supplementation and treatment with atorvastatin and ezetimibe on body size (p56)

Supplementary Figure 2 - The effect of overfeeding, cholesterol supplementation and treatment with atorvastatin and ezetimibe on whole-body lipid and glucose levels (p57)

Supplementary Figure 3 - The effect of overfeeding, cholesterol supplementation and treatment with atorvastatin and ezetimibe on vascular atherogenic traits (p58-59)

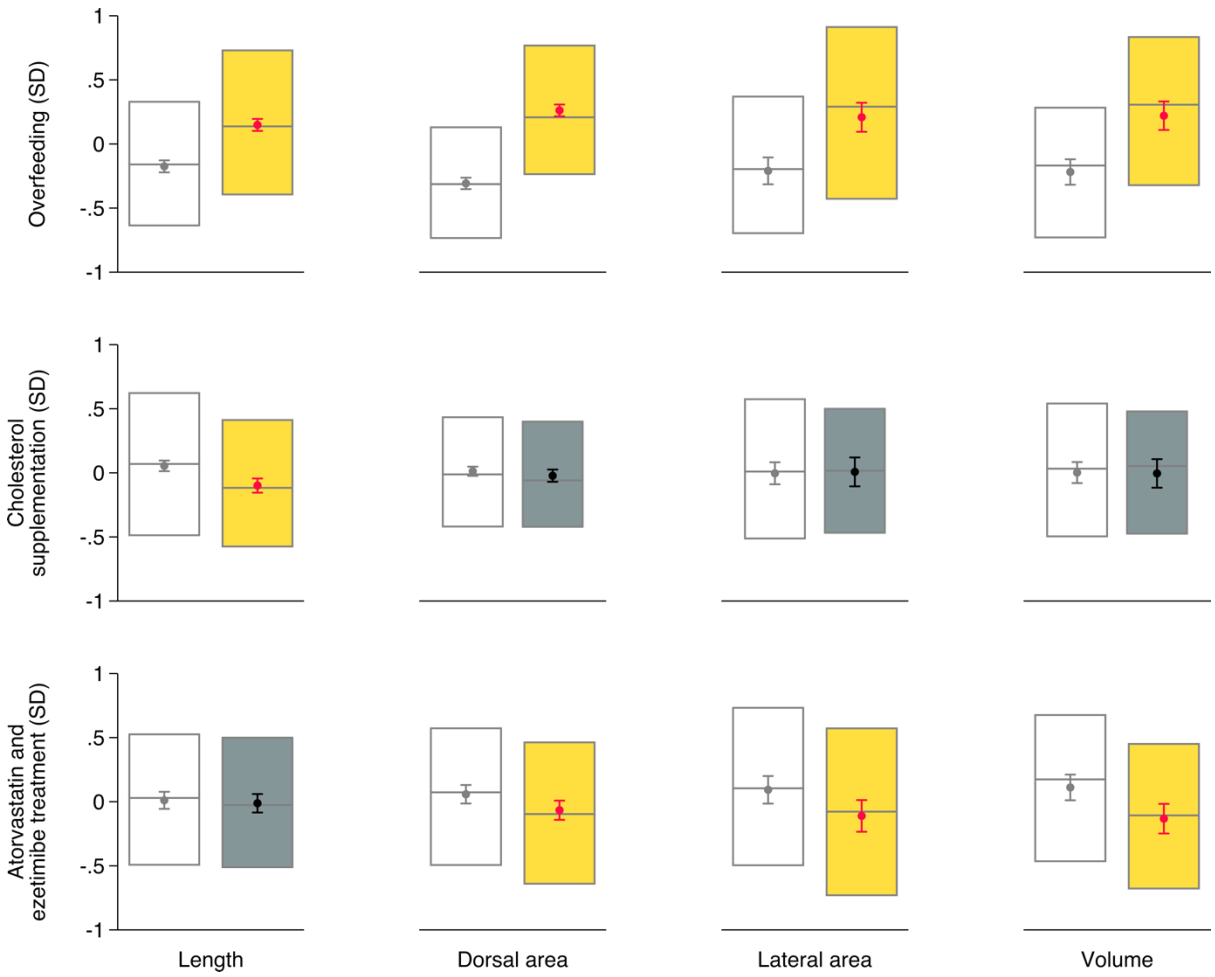
Supplementary Figure 4 - Food intake as a function of dietary or drug treatment intervention (p60)

Supplementary Figure 5 - Histogram of the number of mutated alleles and genetic burden score across apoea, apoeb, apobb.1 and ldlra and association of whole-body LDL cholesterol levels, vascular lipid deposition and vascular co-localization of lipids and neutrophils with the genetic burden score (p61)

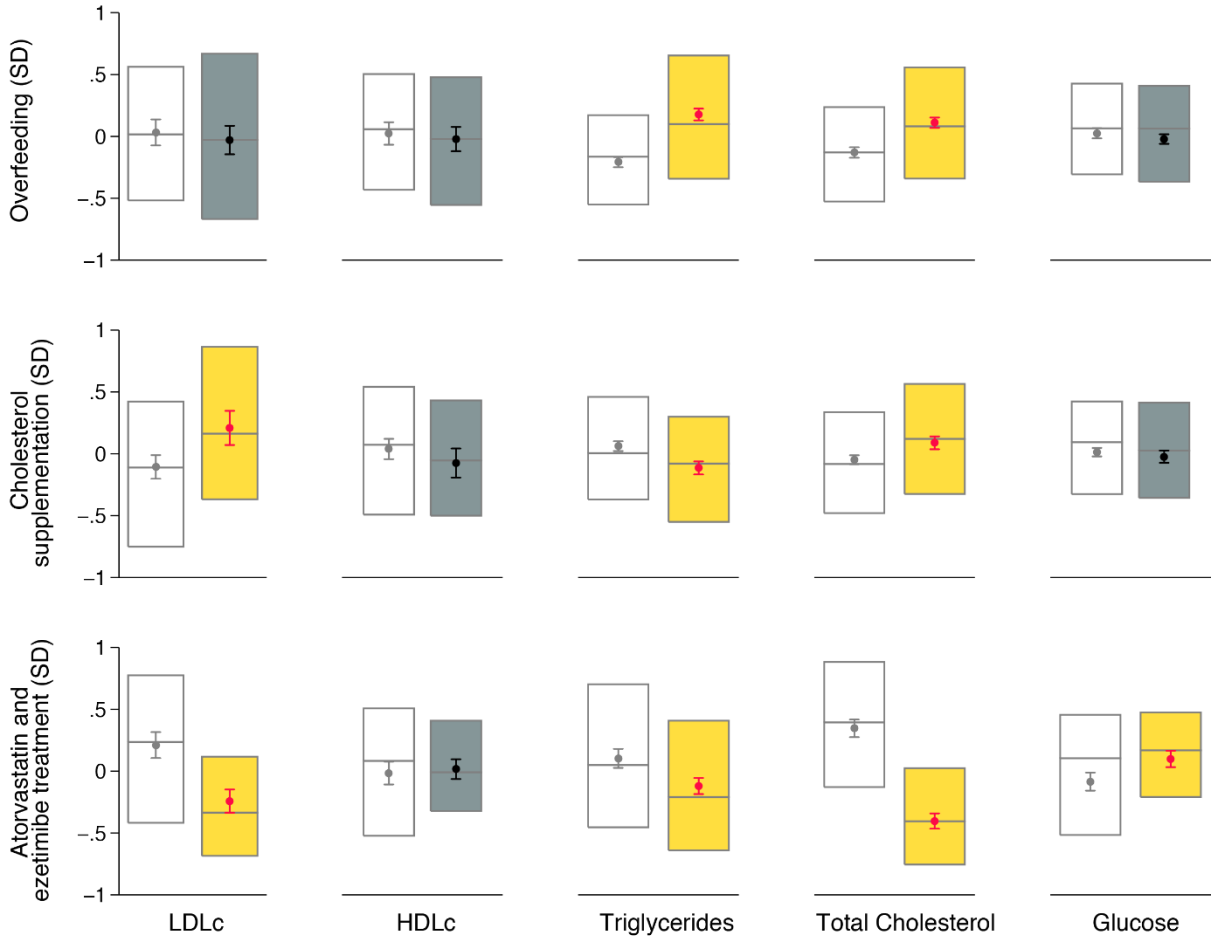
Supplementary Figure 6 - The effect of mutations in apoea, apoeb, apobb.1 and ldlra on body size, vascular atherogenic traits and whole-body lipid and glucose levels (p62-63)

Supplementary Figure 7 - The association of predicted total cholesterol levels using regression of directly assessed LDLc, HDLc and triglyceride levels with directly assessed total cholesterol levels (p64)

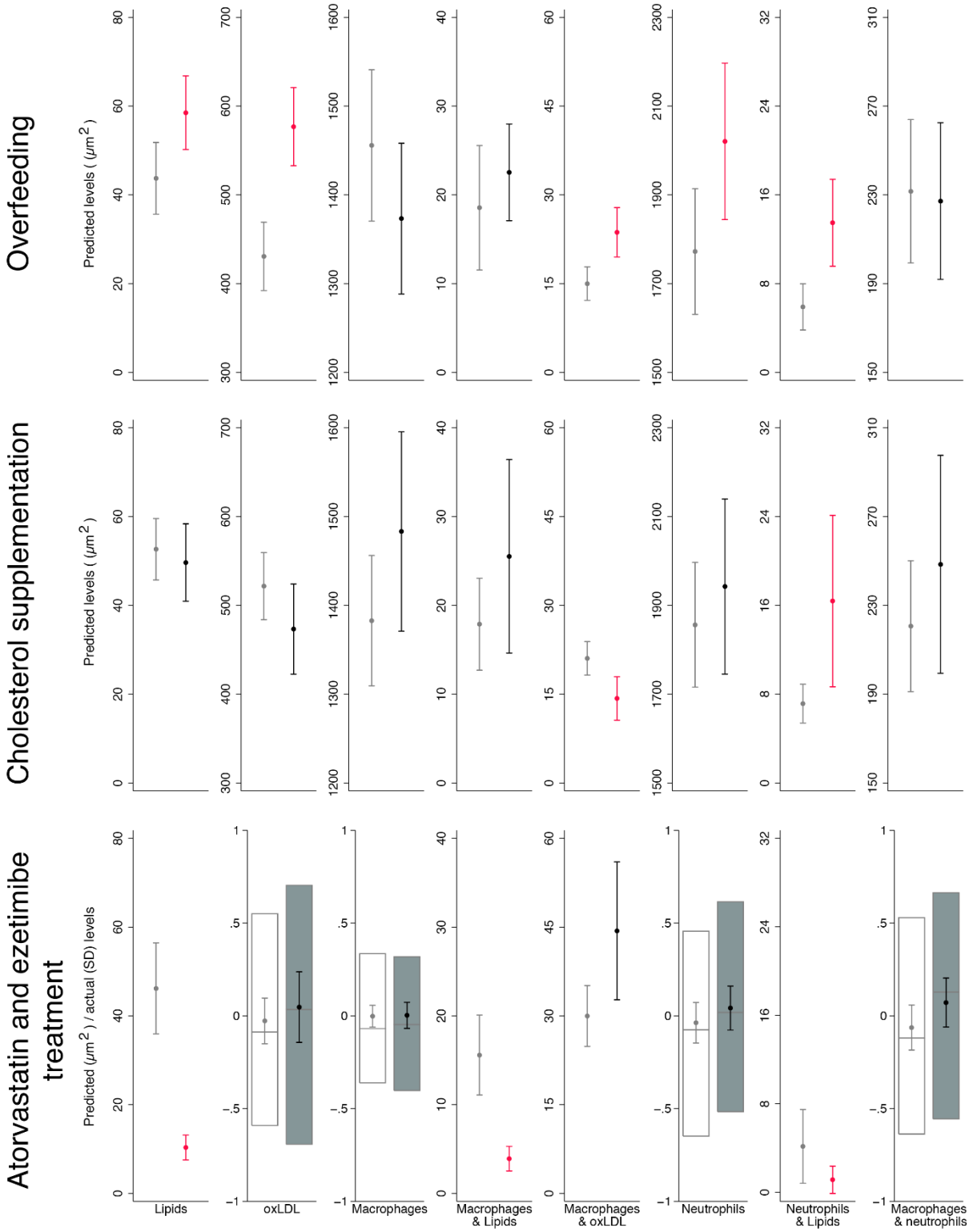
Supplementary Figure 8 - The association of vascular atherogenic traits with whole-body lipid and glucose levels in data from the dietary, drug treatment and genetic intervention for proof-of-concept genes combined (p65-66)



Supplementary Figure 1. The effect of overfeeding (top), cholesterol supplementation (middle) and treatment with atorvastatin and ezetimibe (bottom) on body size. Dots and whiskers show mean and 95% confidence interval (CI); boxes show median and inter quantile range. Analyses were performed using residuals acquired using hierarchical linear models on inverse-normally transformed outcomes, adjusted for the use of diethyl ether (for overfeeding and cholesterol supplementation), cholesterol supplementation (for overfeeding), the amount fed (for cholesterol supplementation), and time of day as fixed factors. Larvae were nested in batches and transgenic backgrounds (random factors). White boxes with grey mean and 95% CI (left) show results for unexposed larvae; grey boxes with black mean and 95% CI (right) show results for exposed larvae that are not different from unexposed ones; yellow boxes with red mean and 95% CI (right) show results for exposed larvae that are different from unexposed ones at $P<0.05$.

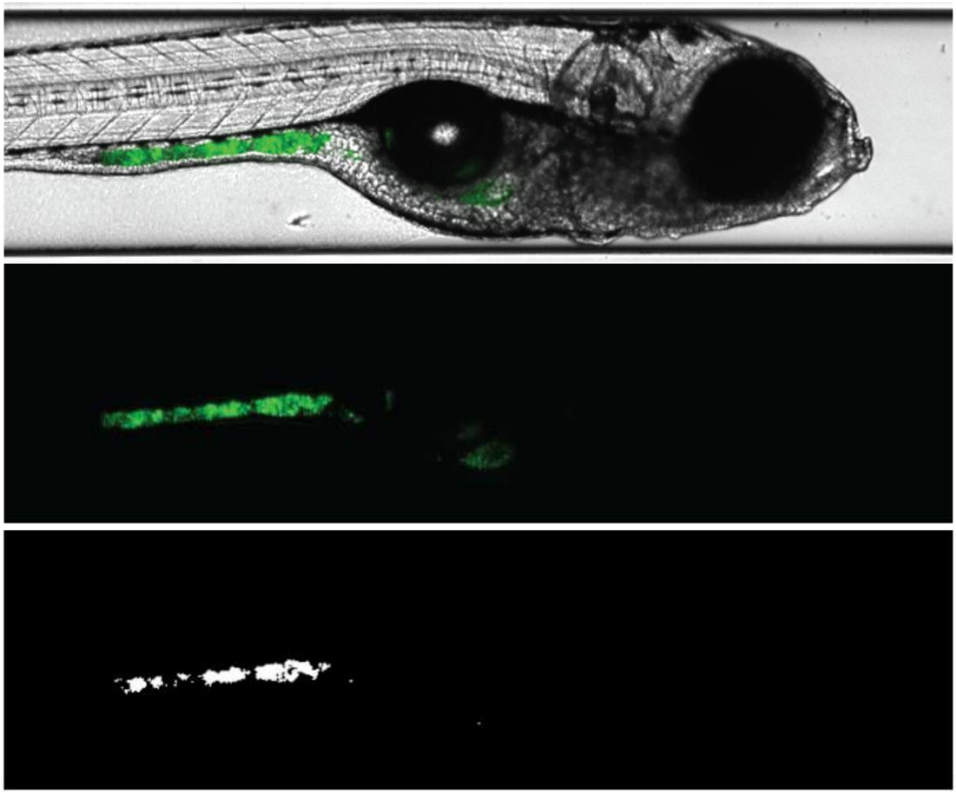


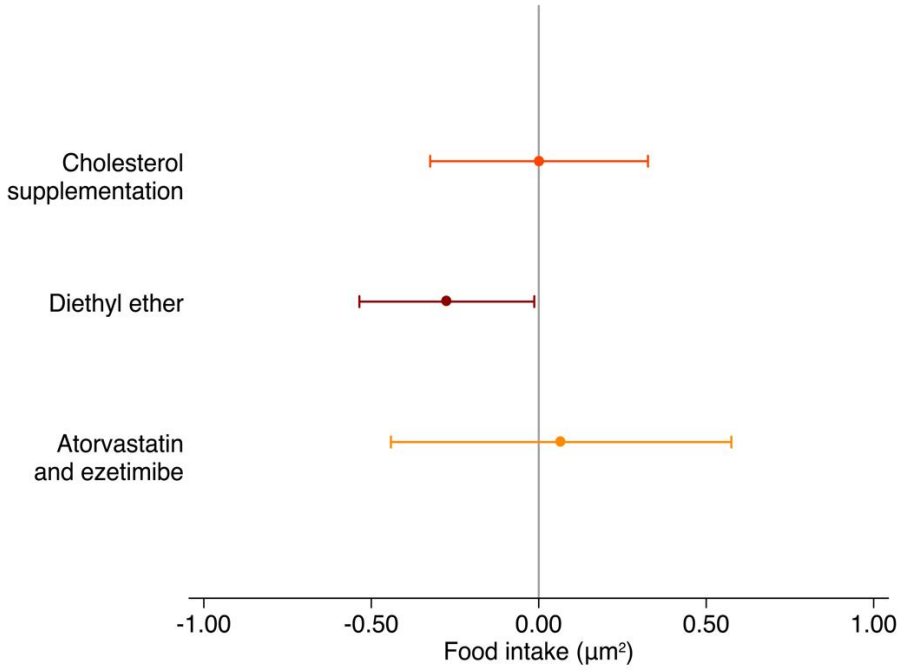
Supplementary Figure 2. The effect of overfeeding (top), cholesterol supplementation (middle) and treatment with atorvastatin and ezetimibe (bottom) on whole-body lipid and glucose levels. Dots and whiskers show mean and 95% confidence interval (CI); boxes show median and inter quantile range. Analyses were performed using residuals acquired using hierarchical linear models on inverse-normally transformed outcomes, adjusting for the use of diethyl ether (for overfeeding and cholesterol supplementation), cholesterol supplementation (for overfeeding), the amount fed (for cholesterol supplementation) and time of day as fixed factors. Larvae were nested in batches and transgenic backgrounds (random factors). White boxes with grey mean and 95% CI (left) show results for unexposed larvae; grey boxes with black mean and 95% CI (right) show results for exposed larvae that are not different from unexposed ones; yellow boxes with red mean and 95% CI (right) show results for exposed larvae that are different from unexposed ones at P<0.05.



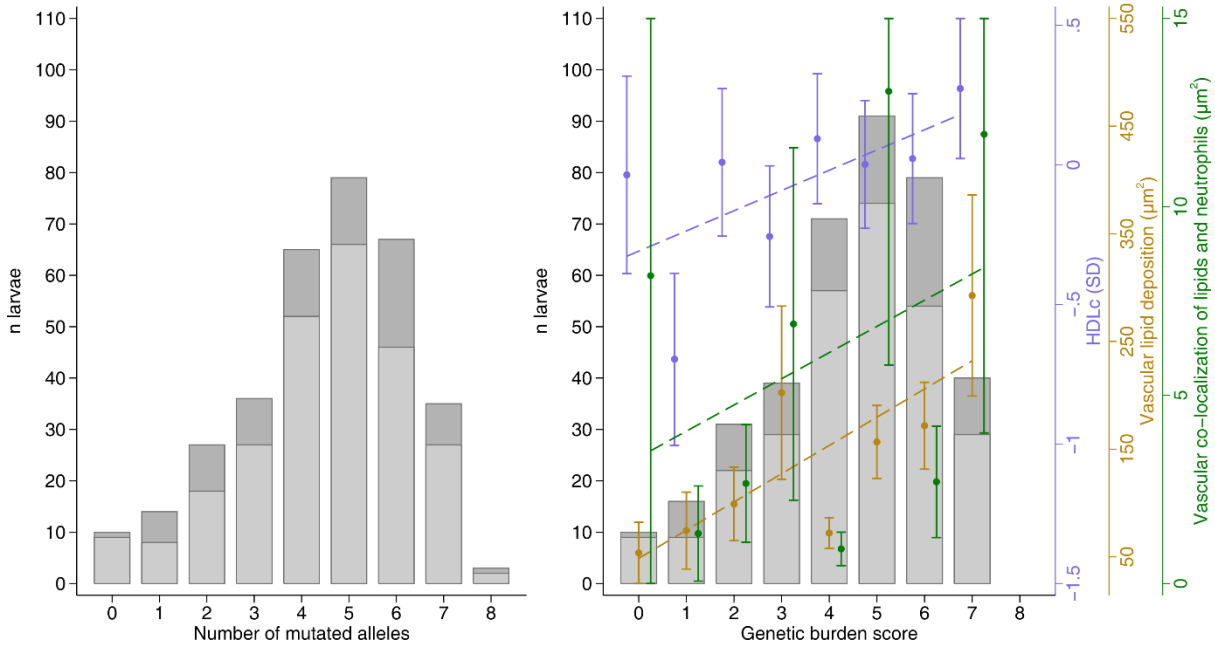
Supplementary Figure 3. The effect of overfeeding (top), cholesterol supplementation (middle) and treatment with atorvastatin and ezetimibe (bottom) on vascular atherogenic traits. Outcomes showing effect estimate and 95% CI for predicted values have been analyzed using negative binomial regression, with adjustment for the same co-variables. Outcomes showing only effect estimate and 95% CI for predicted values have been analyzed using regular negative binomial regression, adjusting for the use of diethyl ether (for overfeeding and cholesterol supplementation), cholesterol supplementation (for overfeeding), the amount fed (for cholesterol supplementation), body length, dorsal body surface area, and time of day. Outcomes showing mean and 95% confidence interval (CI) as well as boxes for median and inter quartile range have been analyzed using hierarchical linear models on residuals after

adjusting inverse-normally transformed outcomes for body length, dorsal body surface area, and time of day as fixed factors. Larvae were nested in batches and transgenic backgrounds (random factors). White boxes and/or light grey mean and 95% CI (left) show results for unexposed larvae; grey boxes and/or black mean and 95% CI (right) show results for exposed larvae that are not different from unexposed ones; red mean and 95% CI (right) show results for exposed larvae that are different from unexposed ones at $P<0.05$.

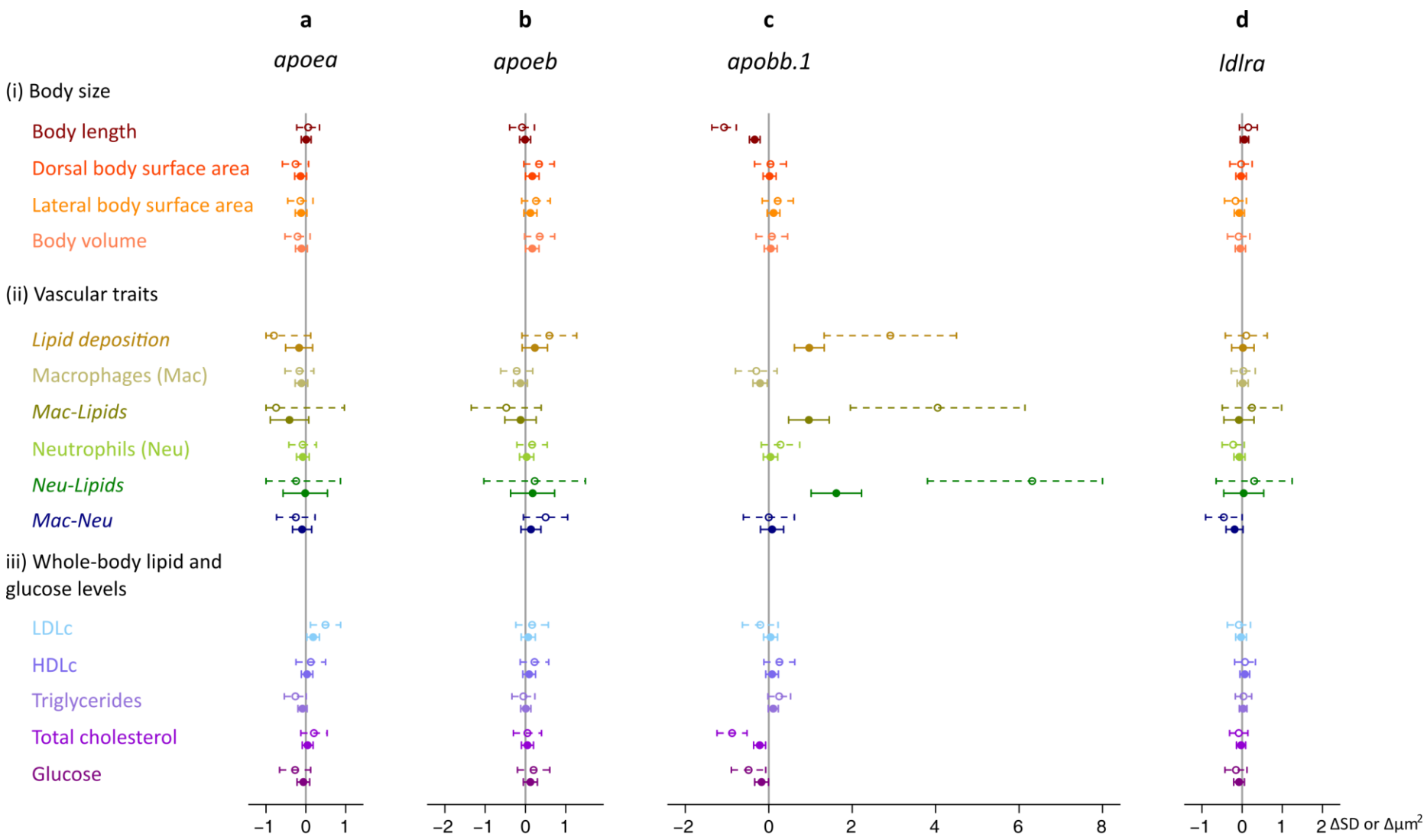




Supplementary Figure 4. Food intake as a function of dietary or drug treatment intervention. Mixing fluorescently labelled tracers in with standard dry food, standard dry food enriched with 4% extra cholesterol using diethyl ether, standard dry food treated with diethyl ether, and standard dry food enriched with 4% extra cholesterol using diethyl ether and further enriched with atorvastatin and ezetimibe allowed image-based quantification of food intake - i.e. surface area of fluorescence in the gastrointestinal tract - in eight-day-old zebrafish larvae (top). Bottom: mutually adjusted effect of cholesterol supplementation, treatment of the diet with diethyl ether, and enrichment with atorvastatin and ezetimibe on food intake, assessed using dummy variables and negative binomial regression, additionally adjusted for time since feeding and batch (n=204). Dots and whiskers show effect size and 95% confidence interval.

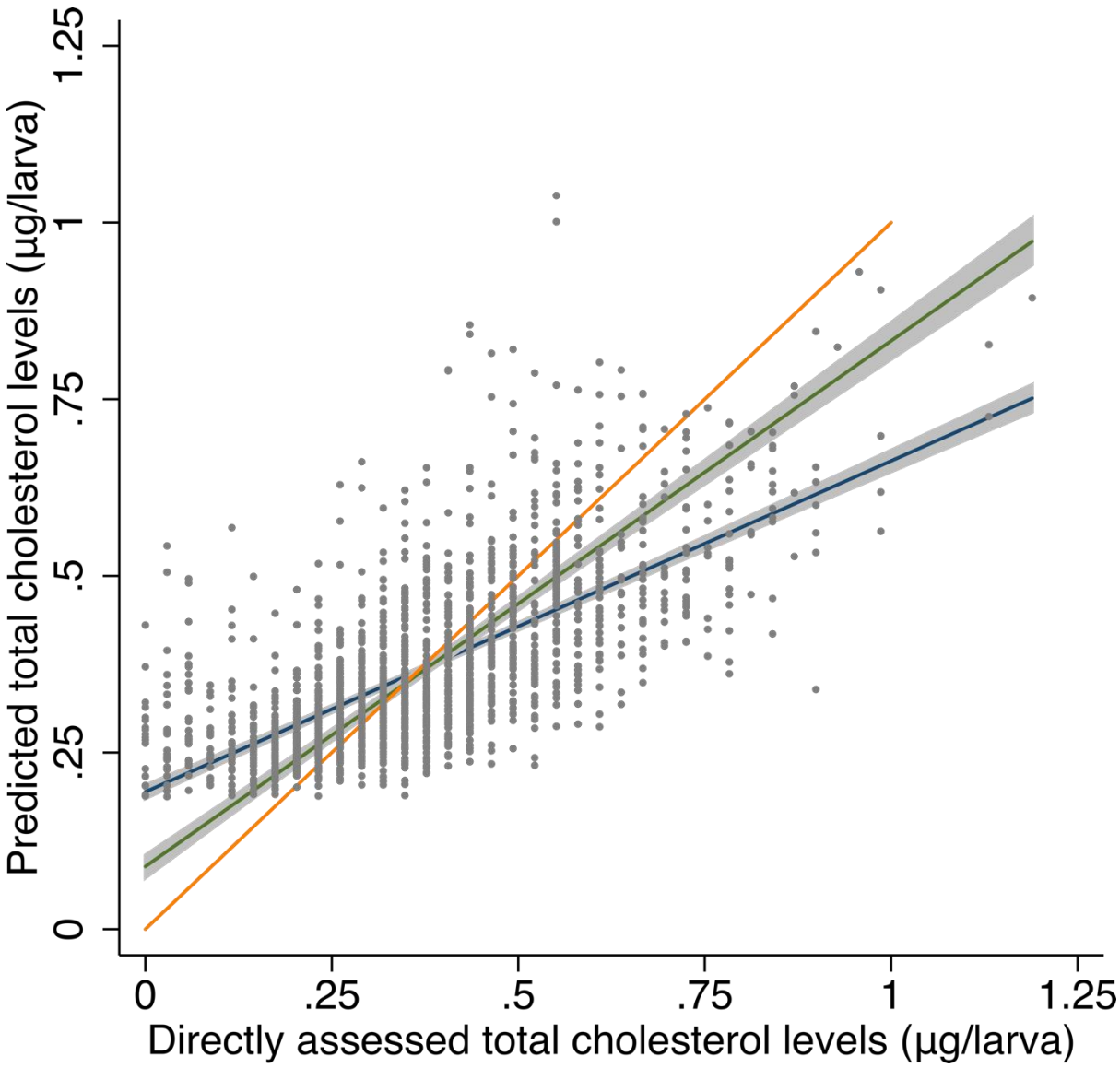


Supplementary Figure 5. Histogram of the number of mutated alleles and genetic burden score across apoea, apoeb, apobb.1 and ldlra and association of whole-body HDL cholesterol levels, vascular lipid deposition and vascular co-localization of lipids and neutrophils with the genetic burden score. Left: histogram of the number of mutated alleles across apoea, apoeb, apobb.1 and ldlra. Larvae with two mutated alleles in apoba, apobb.2 and ldlrb are shown in light grey (bottom); larvae with at least one unaffected allele in these three genes are shown in dark grey (top). Right: as before, but with each affected allele weighed by the probability that it affects protein function, based on annotation using Ensembl's variant effect predictor (VEP) (i.e. a genetic burden score). This figure also shows the association between atherogenic traits and the genetic burden score for significantly associated traits, adjusted for the number of mutated alleles in apoba, apobb.2 and ldlrb, i.e: 1) HDLc (n=381, in purple), assessed using a hierarchical linear model after inverse-normal transformation of LDLc, adjusted for time of day (fixed factors) and with larvae nested in batches; 2) vascular lipid deposition (n=272, in yellow); and 3) vascular co-localization of lipids and neutrophils (n=271, in green), using negative binomial regression, adjusted for body length, dorsal body surface area, time of day and batch. Dots and whiskers show mean and standard error of the mean, acquired using the margins command.

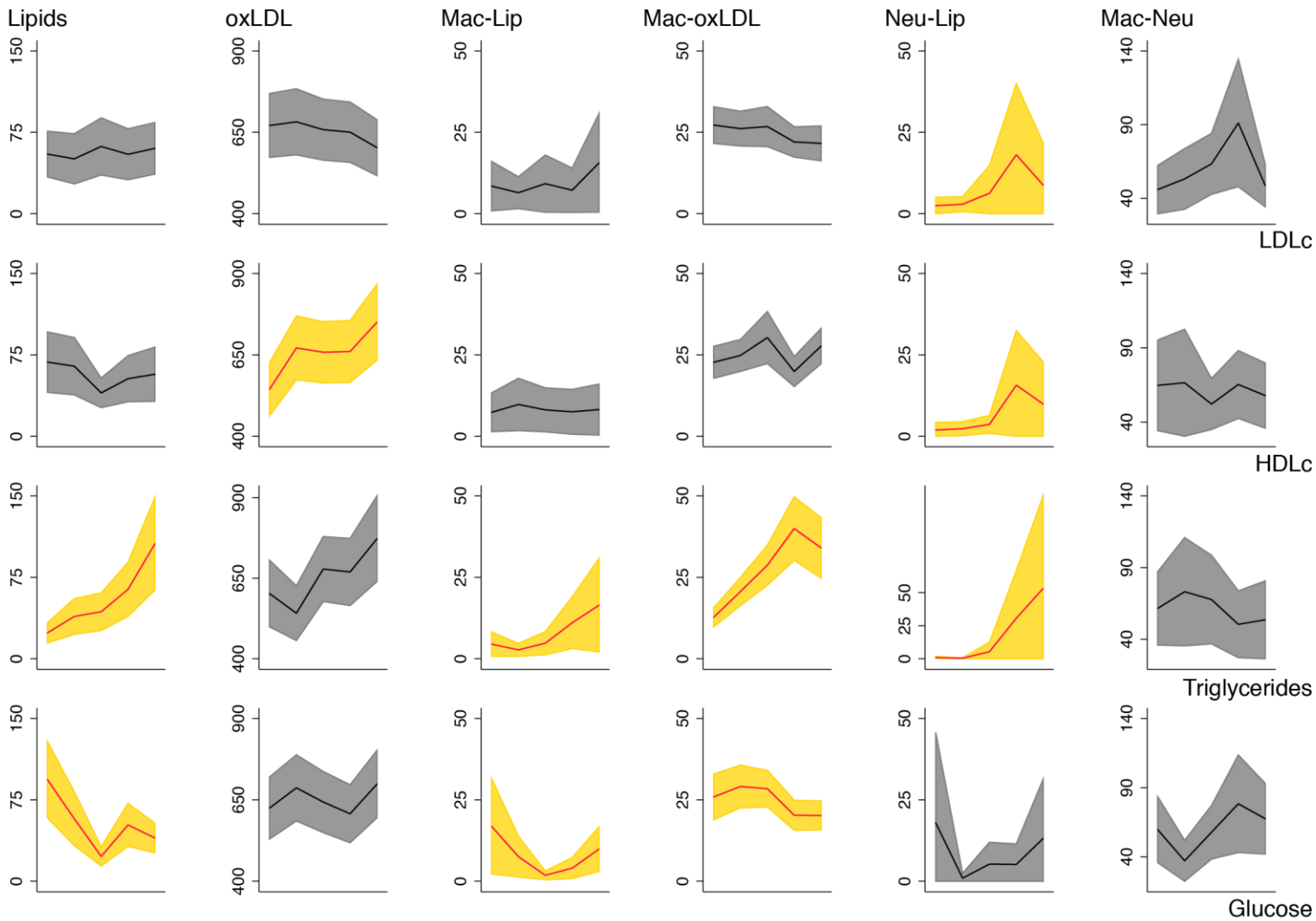


Supplementary Figure 6. The effect of mutations in apoea, apoeb, apobb.1 and ldlra on body size (i), vascular atherogenic traits (ii) and whole-body lipid and glucose levels (iii). Dorsal and lateral body surface area and body volume were normalized for body length before the analysis; and whole-body lipid and

glucose levels were normalized for protein levels. For normally distributed traits (shown in regular font), associations were examined using hierarchical linear models on inverse-normally transformed values. For these traits effect sizes and 95% confidence intervals are expressed in standard deviation units (SD). The remaining vascular atherogenic traits (shown in italic) were analyzed using negative binomial regression analyses. For these traits, effect sizes and 95% confidence intervals are expressed in μm^2. Dotted lines represent the effect of two functionally knocked out alleles compared with zero mutated alleles. Regular lines show the additive per-allele effect. Associations were adjusted for time of day; batch; body length and dorsal body surface area (for vascular outcomes); and the number of mutated alleles in the other genes.



Supplementary Figure 7. The association of predicted total cholesterol levels using regression of directly assessed LDLc, HDLc and triglyceride levels with directly assessed total cholesterol levels. In blue and grey are the regression line and 95% confidence interval (CI) (r^2=0.468). In green and grey are the regression line and 95% CI for the association of total cholesterol levels calculated using the formula that is typically applied in humans (i.e. LDLc + HDLc + triglycerides/5) with directly assessed total cholesterol levels (r^2=0.430). In orange is a line with a slope of 1 (n=1,867 larvae).



Supplementary Figure 8. The association of vascular atherogenic traits with whole-body lipid and glucose levels in data from the dietary, drug treatment and genetic intervention for proof-of-concept genes combined. For each vascular atherogenic outcome (i.e. vascular lipid deposition [Lip] and accumulation of oxidized LDL [oxLDL]; and vascular co-localization of lipids and oxLDL with macrophages [Mac] and neutrophils [Neu]), mutually adjusted associations with

protein-normalized levels of LDL cholesterol (LDLc), HDL cholesterol (HDLc), triglyceride and glucose levels were examined using negative binomial regression. Besides for the other main exposures, associations were adjusted for body length and dorsal body surface area, transgenic background and batch. Graphs show margins plots – highlighting mean and 95% confidence intervals – for the vascular atherogenic outcomes, expressed in μm^2 (y-axes) with exposures grouped by quintile (x-axes). Significant associations are shown in yellow.

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Supplementary Table 1 - Descriptive information for larvae at 10 days post-fertilization in the dietary, drug treatment and genetic interventions

		Dietary intervention			Drug treatment intervention			Genetic intervention					
								Proof of concept			Discovery		
	Transgenic background(s)	n_{total}	Mean / Median	SD / IQR	n_{total}	Mean / Median	SD / IQR	n_{total}	Mean / Median	SD / IQR	n_{total}	Mean / Median	SD / IQR
Body size													
Body length (μm)		2193	4327	260	1004	4343	234	339	4628	266	505	4451	230
Dorsal surface area (μm^2)		2193	1.1×10^6	1.6×10^5	1004	1.2×10^6	1.2×10^5	339	1.2×10^6	1.7×10^5	505	1.1×10^6	1.6×10^5
Lateral surface area (μm^2)		524	1.5×10^6	1.6×10^5	553	1.4×10^6	1.5×10^5	336	1.6×10^6	2.0×10^5	502	1.5×10^6	1.9×10^5
Body volume (μm^3)		514	4.3×10^8	6.1×10^7	512	4.3×10^8	6.0×10^7	328	4.6×10^8	8.4×10^7	495	4.0×10^8	8.1×10^7
Whole-body lipid and glucose levels													
LDL cholesterol (μg)		564	0.04	0.04	567	0.12	0.08	339	0.18	0.12	513	0.49	0.34
HDL cholesterol (μg)		549	0.06	0.02	564	0.06	0.04	339	0.15	0.05	513	0.29	0.16
Triglyceride levels (μg)		2123	0.93	0.80	1005	0.61	0.51	339	1.10	0.82	513	1.27	1.07
Total cholesterol levels (μg)		2123	0.29	0.17	1005	0.36	0.18	339	0.45	0.21	513	0.29	0.14
Glucose (μg)		2128	0.92	0.66	1008	0.38	0.42	339	0.30	0.16	513	0.80	0.53
Vascular atherogenic traits													
Lipid deposition (μm^2)	-	*1954*	*0*	*36*	*837*	*0*	*20*	*272*	*43*	*133*	*280*	*94*	*135*
oxLDL deposition (μm^2)	*Tg:hsp70:IK17-EGFP*	*885*	*338*	*590*	236	852	674	-	-	-	-	-	-
Infiltration by macrophages (μm^2)	*Tg:mpeg1-mCherry*	*994*	*942*	*1607*	633	1881	1057	328	1475	1005	363	1705	729
Infiltration by neutrophils (μm^2)	*Tg:mpo-EGFP*	*494*	*1545*	*2116*	404	2438	873	330	1050	911	363	1806	941
Co-localizing macrophages and lipids (μm^2)	*Tg:mpeg1-mCherry*	*917*	*0*	*10*	*605*	*0*	*0*	*269*	*1*	*13*	*263*	*23*	*48*
Co-localizing macrophages and oxLDL (μm^2)	*Tg:hsp70:IK17-EGFP & Tg:mpeg1-mCherry*	*433*	*10*	*22*	*212*	*20*	*39*	-	-	-	-	-	-
Co-localizing neutrophils and lipids (μm^2)	*Tg:mpo-EGFP*	*440*	*0*	*8*	*393*	*0*	*0*	*271*	*0*	*0*	*260*	*5*	*12*
Co-localizing macrophages and neutrophils (μm^2)	*Tg:mpeg1-mCherry & Tg:mpo-EGFP*	*488*	*140*	*306*	394	139	124	*327*	*25*	*68*	*345*	*84*	*122*
Circulating lipids (μm^2)	*Tg:flk-EGFP*	*467*	2.4×10^4	3.5×10^3	185	17,829	5767	-	-	-	-	-	-
Endothelial surface area (μm^2)	*Tg:flk-EGFP*	*467*	4.8×10^3	2.1×10^3	185	6652	4198	-	-	-	-	-	-

oxLDL: oxidized LDL; co-localization defined by overlap of fluorescence signal. Mean and standard deviation (SD) are shown for normally distributed outcomes; median and interquatrile range (IQR) are shown for outcomes showing a negative binomial distribution (shown in italics).

Supplementary Table 2 - Annotation-based exclusions in the image-based analyses

Rationale for exclusion	Traits for which exclusion is relevant	Dietary Intervention			Drug treatent intervention			Genetic intervention					
								Proof-of-concept			Discovery (19p13.11 locus)		
		Available (n)	Excluded (n)	Excluded (%)	Available (n)	Excluded (n)	Excluded (%)	Available (n)	Excluded (n)	Excluded (%)	Available (n)	Excluded (n)	Excluded (%)
Monodansylpentane cadaverase													
Inadequate detection of vasculature in Y (vessel missing)	Lipids, macrophages, neutrophils and their co-localization	2050	94	4.6	927	92	9.9	231	6	2.6	212	30	14.2
Fish moved during imaging resulting in a bad quality image	Lipids	1959	3	0.2	873	38	4.4	225	0	0.0	183	1	0.5
>20% of true negative objects falsely detected (many false positives)	Lipids	2043	87	4.3	853	18	2.1	278	48	17.3	219	37	16.9
<20% of true positive objects detected (many false negatives)	Lipids	1959	3	0.2	844	9	1.1	225	0	0.0	201	19	9.5
Tg(IK17:EGFP)													
Fish moved during imaging resulting in a bad quality image	oxLDL	893	8	0.9	238	2	0.8		NA			NA	
>20% of true negative objects falsely detected (many false positives)	No exclusion	885	202	22.8	236	100	42.4		NA			NA	
<20% of true positive objects detected (many false negatives)	No exclusion	885	1	0.1	236	0	0.0		NA			NA	
Many false positives outside the area of interest	No exclusion	885	3	0.3	236	4	1.7		NA			NA	
Tg(mpeg1:mCherry)													
Fish moved during imaging resulting in a bad quality image	Macrophages and their co-localization with lipids and oxLDL	996	2	0.2	634	1	0.2	276	0	0.0	299	3	1.0
>20% of true negative objects falsely detected (many false positives)	Macrophages and their co-localization with lipids and oxLDL	997	3	0.3	635	2	0.3	278	2	0.7	307	11	3.6
<20% of true positive objects detected (many false negatives)	Macrophages and their co-localization with lipids and oxLDL	1010	16	1.6	633	0	0.0	276	0	0.0	301	5	1.7
Presence of (a) moving macrophage(s)	Macrophages and their co-localization with lipids and oxLDL	994	0	0.0	634	1	0.2	276	0	0.0	298	2	0.7
Many false positive macrophages outside the area of interest	Macrophages and their co-localization with lipids and oxLDL	996	2	0.2	634	1	0.2	276	0	0.0	311	15	4.8
Many macrophages co-localizing		994	0	0.0	633	0	0.0	276	0	0.0	307	11	3.6
Tg(mpo:EGFP)													
<20% of true positive objects detected (many false negatives)	Neutrophils and their co-localization with lipids	537	43	8.0	404	0	0.0	278	0	0.0	299	1	0.3
Presence of circulating neutrophils	Neutrophils and their co-localization with lipids	504	10	2.0	409	5	1.2	278	0	0.0	301	3	1.0
Many neutrophils co-localizing		494	0	0.0	404	0	0.0	278	0	0.0	332	34	10.2
Bright field													
Debris included in the segmentation	Body size	2194	1	0.0	1004	0	0.0	279	23	8.2	344	0	0.0
Air bubble included in the segmentation	Body size	2197	4	0.2	1004	0	0.0	256	0	0.0	345	1	0.3
Bad segmentation	Body size	2193	0	0.0	1004	0	0.0	257	1	0.4	344	0	0.0
Part of the fish not imaged	Body size	2202	9	0.4	1004	0	0.0	260	4	1.5	344	0	0.0
The fish has a curved body, resulting in a non representative length	Body size	2197	4	0.2	1004	0	0.0	256	0	0.0	345	1	0.3
Larvae optically cut off during preprocessing	Body size	2306	113	4.9	1004	0	0.0	256	0	0.0	344	0	0.0

Available (n): the number of larvae with a value within mean ± 5xSD that are free from the image quality-based annotation of interest plus the number of larvae that were excluded due to the quality-based annotation of interest for vascular infiltration by lipids (monodansylpentane cadaverase), oxidized LDL (Tg([IK17:EGFP]), macrophages (Tg[mpeg1:mCherry]), neutrophils (Tg[mpo:EGFP]), and body size (Bright field). For Tg(IK17:EGFP), larvae with many false positive or negative deposits were not excluded from further analysis. For all other traits, larvae with suboptimal image or quantification quality were excluded from further analyses.

Supplementary Table 3 - The effect of overfeeding and cholesterol supplementation on body size

		Body length (n=2193)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	0.350	0.040	9.15E-23	0.280	0.420
	cholesterol supplementation	-0.220	0.040	2.32E-07	-0.300	-0.140
	diethyl ether treatment	-0.070	0.040	9.57E-02	-0.160	0.010
	time of day (in hours since 9AM)	0.010	0.010	1.28E-01	0.000	0.030
	intercept	-0.150	0.210	4.80E-01	-0.550	0.260
random factors	***variation by transgenic background***	*0.380*	*0.150*	-	*0.170*	*0.830*
	variation by batch	*0.350*	*0.060*	-	*0.250*	*0.480*
	residual	*0.790*	*0.010*	-	*0.770*	*0.820*

		Dorsal body surface area (n=2193)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	0.610	0.030	3.54E-71	0.540	0.680
	cholesterol supplementation	-0.050	0.040	1.82E-01	-0.140	0.030
	diethyl ether treatment	0.040	0.040	3.84E-01	-0.050	0.120
	time of day (in hours since 9AM)	0.040	0.010	6.82E-08	0.020	0.050
	intercept	-0.500	0.210	1.58E-02	-0.910	-0.090
random factors	***variation by transgenic background***	*0.360*	*0.160*	-	*0.150*	*0.870*
	variation by batch	*0.420*	*0.070*	-	*0.310*	*0.580*
	residual	*0.770*	*0.010*	-	*0.750*	*0.790*

		Lateral body surface area (n=524)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	0.480	0.080	1.17E-08	0.320	0.650
	cholesterol supplementation	0.020	0.100	8.69E-01	-0.170	0.210
	diethyl ether treatment	0.010	0.100	9.04E-01	-0.180	0.200
	time of day (in hours since 9AM)	0.020	0.020	3.96E-01	-0.020	0.050
	intercept	-0.310	0.210	1.37E-01	-0.720	0.100
random factors	***variation by transgenic background***	-	-	-	-	-
	variation by batch	*0.390*	*0.120*	-	*0.220*	*0.720*
	residual	*0.900*	*0.030*	-	*0.850*	*0.960*

		Body volume (n=514)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	0.510	0.080	5.39E-10	0.350	0.660
	cholesterol supplementation	-0.010	0.090	9.18E-01	-0.190	0.170
	diethyl ether treatment	-0.010	0.090	9.25E-01	-0.190	0.170
	time of day (in hours since 9AM)	0.020	0.020	2.94E-01	-0.020	0.060
	intercept	-0.300	0.230	1.85E-01	-0.750	0.150
random factors	***variation by transgenic background***	-	-	-	-	-
	variation by batch	*0.460*	*0.140*	-	*0.260*	*0.830*
	residual	*0.860*	*0.030*	-	*0.810*	*0.910*

Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models. Effects shown for overfeeding, cholesterol supplementation and diethyl ether treatment are compared with unexposed controls. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 4 - The effect of overfeeding and cholesterol supplementation on whole-body lipid and glucose levels

		LDL cholesterol levels (n=564)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	-0.072	0.086	4.05E-01	-0.241	0.097
	cholesterol supplementation	0.422	0.098	1.68E-05	0.230	0.615
	diethyl ether treatment	-0.126	0.099	2.00E-01	-0.320	0.067
	time of day (in hours since 9AM)	-0.006	0.019	7.69E-01	-0.043	0.031
	intercept	0.041	0.172	8.10E-01	-0.296	0.379
random factors	***variation by batch***	*0.261*	*0.089*	-	*0.134*	*0.508*
	residual	*0.952*	*0.028*	-	*0.897*	*1.009*

		HDL cholesterol levels (n=594)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	-0.058	0.083	4.83E-01	-0.221	0.105
	cholesterol supplementation	-0.170	0.094	7.01E-02	-0.355	0.014
	diethyl ether treatment	0.012	0.095	8.99E-01	-0.174	0.198
	time of day (in hours since 9AM)	-0.041	0.018	2.18E-02	-0.077	-0.006
	intercept	0.358	0.236	1.29E-01	-0.104	0.820
random factors	***variation by batch***	*0.480*	*0.146*	-	*0.264*	*0.871*
	residual	*0.903*	*0.027*	-	*0.850*	*0.958*

		Triglyceride levels (n=2123)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	0.409	0.034	5.66E-34	0.343	0.475
	cholesterol supplementation	-0.249	0.040	7.98E-10	-0.328	-0.169
	diethyl ether treatment	0.081	0.041	5.07E-02	0.000	0.162
	time of day (in hours since 9AM)	-0.042	0.007	4.88E-10	-0.056	-0.029
	intercept	0.068	0.182	7.07E-01	-0.288	0.425
random factors	***variation by transgenic background***	*0.253*	*0.178*	-	*0.064*	*1.005*
	variation by batch	*0.574*	*0.096*	-	*0.414*	*0.795*
	residual	*0.750*	*0.012*	-	*0.727*	*0.773*

		Total cholesterol levels (n=2123)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	0.256	0.032	5.93E-16	0.194	0.318
	cholesterol supplementation	0.193	0.038	4.13E-07	0.118	0.267
	diethyl ether treatment	0.275	0.039	1.54E-12	0.199	0.351
	time of day (in hours since 9AM)	-0.060	0.006	1.46E-20	-0.072	-0.047
	intercept	-0.119	0.275	6.65E-01	-0.658	0.420
random factors	***variation by transgenic background***	*0.505*	*0.208*	-	*0.226*	*1.133*
	variation by batch	*0.459*	*0.077*	-	*0.331*	*0.637*
	residual	*0.706*	*0.011*	-	*0.685*	*0.727*

		Glucose levels (n=2128)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	-0.056	0.033	9.14E-02	-0.122	0.009
	cholesterol supplementation	-0.057	0.040	1.57E-01	-0.135	0.022
	diethyl ether treatment	0.013	0.041	7.44E-01	-0.067	0.094
	time of day (in hours since 9AM)	0.003	0.007	6.73E-01	-0.010	0.016
	intercept	0.102	0.281	7.16E-01	-0.448	0.652
random factors	***variation by transgenic background***	*0.512*	*0.212*		*0.227*	*1.154*
	variation by batch	*0.487*	*0.082*		*0.351*	*0.677*
	residual	*0.744*	*0.011*		*0.722*	*0.767*

All outcomes were normalized for protein level using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models and were adjusted for diethyl ether (used to prepare the diet), time of day, transgenic background and batch. Effects shown for overfeeding, cholesterol supplementation and diethyl ether treatment are compared with unexposed controls. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 5 - The effect of overfeeding and cholesterol supplementation on image-based vascular atherogenic traits

		Vascular lipid deposition														
		Model 1 (n=1954)					Model 2 (n=1954)					Model 3 (n=1769)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**overfeeding**	0.257	0.126	4.08E-02	0.011	0.504	0.292	0.142	4.08E-02	0.012	0.571	0.174	0.152	2.52E-01	-0.124	0.473
	cholesterol supplementation	-0.029	0.132	8.24E-01	-0.288	0.229	-0.059	0.132	6.57E-01	-0.317	0.200	0.025	0.140	8.58E-01	-0.250	0.300
	diethyl ether treatment	0.194	0.154	2.07E-01	-0.107	0.495	0.190	0.151	2.08E-01	-0.106	0.486	0.094	0.156	5.47E-01	-0.212	0.400
	time of day (in hours since 9AM)	0.054	0.020	7.74E-03	0.014	0.094	0.056	0.021	7.55E-03	0.015	0.098	0.070	0.023	1.97E-03	0.026	0.115
	body length (in SD)	-	-	-	-	-	-0.132	0.062	3.36E-02	-0.254	-0.010	-0.148	0.069	3.25E-02	-0.284	-0.012
	dorsal body surface area (in SD)	-	-	-	-	-	0.021	0.070	7.65E-01	-0.116	0.158	-0.001	0.075	9.84E-01	-0.148	0.145
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.222	0.084	7.96E-03	0.058	0.386
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.047	0.068	4.91E-01	-0.181	0.087
	Tg(hsp70:IK17:EGFP) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-4.041	0.357	1.07E-29	-4.740	-3.341	-4.101	0.363	1.31E-29	-4.813	-3.390	-3.738	0.399	7.06E-21	-4.520	-2.956
	Tg(hsp70:IK17:EGFP; mpeg1:mCherry) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-3.356	0.328	1.43E-24	-3.999	-2.713	-3.330	0.336	4.02E-23	-3.988	-2.671	-3.126	0.403	8.75E-15	-3.916	-2.336
	Tg(flk:EGFP) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-2.969	0.294	5.27E-24	-3.545	-2.393	-3.132	0.308	3.03E-24	-3.736	-2.527	-3.168	0.357	6.45E-19	-3.867	-2.469
	batch 1	-0.531	0.192	5.69E-03	-0.907	-0.154	-0.514	0.201	1.07E-02	-0.909	-0.119	-0.438	0.217	4.40E-02	-0.864	-0.012
	batch 2	0.671	0.174	1.20E-04	0.329	1.013	0.725	0.188	1.20E-04	0.356	1.094	0.828	0.211	8.48E-05	0.415	1.241
	batch 3	-0.835	0.221	1.61E-04	-1.269	-0.402	-0.925	0.237	9.39E-05	-1.389	-0.461					
	batch 6	-0.078	0.246	7.50E-01	-0.559	0.403	-0.110	0.248	6.59E-01	-0.596	0.377	-0.128	0.266	6.31E-01	-0.648	0.393
	batch 7	-2.103	0.447	2.55E-06	-2.979	-1.227	-2.258	0.413	4.68E-08	-3.068	-1.448	-1.854	0.449	3.69E-05	-2.735	-0.973
	batch 9	-2.195	0.717	2.21E-03	-3.602	-0.789	-2.277	0.692	9.96E-04	-3.632	-0.921	-2.426	0.654	2.06E-04	-3.707	-1.145
	batch 10	0.780	0.469	9.65E-02	-0.140	1.699	0.710	0.474	1.34E-01	-0.219	1.639	0.674	0.479	1.59E-01	-0.265	1.613
	batch 11	-1.900	0.924	3.97E-02	-3.710	-0.089	-1.847	0.934	4.80E-02	-3.679	-0.016	-1.935	0.951	4.18E-02	-3.799	-0.072
	batch 12	-0.171	0.580	7.69E-01	-1.307	0.965	-0.154	0.581	7.91E-01	-1.294	0.985	-0.231	0.598	6.99E-01	-1.403	0.941
	batch 14	-0.112	0.600	8.52E-01	-1.289	1.065	0.014	0.614	9.82E-01	-1.189	1.218	0.004	0.618	9.94E-01	-1.208	1.217
	batch 15	1.295	0.368	4.28E-04	0.574	2.015	1.358	0.371	2.52E-04	0.631	2.085	1.224	0.383	1.39E-03	0.474	1.975
	batch 16	0.393	0.393	3.18E-01	-0.378	1.164	0.453	0.404	2.62E-01	-0.338	1.244	0.311	0.407	4.44E-01	-0.486	1.108
	batch 17	1.113	0.386	3.91E-03	0.357	1.868	1.161	0.398	3.57E-03	0.380	1.942	1.009	0.408	1.34E-02	0.209	1.810
	batch 18	0.390	0.399	3.29E-01	-0.393	1.172	0.446	0.417	2.84E-01	-0.371	1.263	0.262	0.432	5.44E-01	-0.585	1.109
	batch 20	2.733	0.269	3.34E-24	2.205	3.261	2.830	0.273	3.04E-25	2.296	3.364	3.018	0.307	8.26E-23	2.417	3.620
	batch 21	-0.078	0.321	8.08E-01	-0.707	0.551	-0.019	0.318	9.53E-01	-0.642	0.605	0.412	0.358	2.50E-01	-0.290	1.114
	batch 22	0.398	0.283	1.59E-01	-0.156	0.952	0.542	0.292	6.39E-02	-0.031	1.115	0.918	0.342	7.17E-03	0.249	1.588
	batch 23	1.155	0.303	1.41E-04	0.560	1.750	1.232	0.301	4.32E-05	0.642	1.823	1.576	0.345	4.78E-06	0.901	2.251
	batch 24	1.343	0.300	7.63E-06	0.755	1.931	1.441	0.303	2.01E-06	0.847	2.035	1.737	0.339	3.05E-07	1.072	2.403
	batch 25	0.211	0.342	5.37E-01	-0.459	0.881	0.220	0.340	5.18E-01	-0.446	0.885	0.521	0.387	1.79E-01	-0.239	1.280
	batch 26	2.023	0.367	3.64E-08	1.303	2.743	1.966	0.376	1.71E-07	1.229	2.704	-	-	-	-	-
	intercept	4.564	0.243	1.84E-78	4.087	5.041	4.574	0.262	4.40E-68	4.060	5.089	4.397	0.320	6.33E-43	3.769	5.024

continued **Supplementary Table 5**

		Vascular accumulation of oxLDL														
		Model 1 (n=885)					Model 2 (n=885)					Model 3 (n=876)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**overfeeding**	0.291	0.058	4.67E-07	0.178	0.405	0.292	0.061	1.68E-06	0.173	0.412	0.278	0.061	5.86E-06	0.158	0.399
	cholesterol supplementation	-0.115	0.069	9.52E-02	-0.249	0.020	-0.097	0.070	1.62E-01	-0.234	0.039	-0.094	0.072	1.92E-01	-0.234	0.047
	diethyl ether treatment	0.016	0.067	8.10E-01	-0.115	0.148	0.008	0.067	9.00E-01	-0.123	0.140	0.000	0.068	9.94E-01	-0.135	0.134
	time of day (in hours since 9AM)	0.020	0.013	1.19E-01	-0.005	0.046	0.021	0.013	1.06E-01	-0.004	0.046	0.022	0.013	9.46E-02	-0.004	0.049
	body length (in SD)	-	-	-	-	-	0.061	0.037	1.01E-01	-0.012	0.134	0.049	0.039	2.10E-01	-0.028	0.126
	dorsal body surface area (in SD)	-	-	-	-	-	-0.021	0.039	5.90E-01	-0.099	0.056	-0.029	0.041	4.78E-01	-0.110	0.052
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.035	0.041	3.86E-01	-0.045	0.115
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.042	0.042	3.21E-01	-0.124	0.040
	Tg(hsp70:IK17:EGFP; mpeg1:mCherry) carriers vs. Tg(hsp70:IK17:EGFP) carriers	1.762	0.113	4.18E-55	1.541	1.982	1.722	0.117	2.85E-49	1.493	1.950	1.693	0.124	2.06E-42	1.450	1.937
	batch 10	1.614	0.097	1.23E-62	1.425	1.804	1.650	0.098	4.11E-63	1.457	1.842	1.688	0.112	6.37E-51	1.467	1.908
	batch 11	1.475	0.130	1.20E-29	1.219	1.731	1.444	0.133	1.60E-27	1.183	1.704	1.490	0.140	1.40E-26	1.216	1.764
	batch 12	1.716	0.112	6.59E-53	1.497	1.936	1.688	0.113	3.62E-50	1.466	1.910	1.686	0.117	8.35E-47	1.456	1.916
	batch 13	0.753	0.127	2.72E-09	0.505	1.002	0.746	0.129	7.24E-09	0.494	0.999	0.753	0.129	4.94E-09	0.501	1.005
	batch 14	-1.255	0.156	7.54E-16	-1.560	-0.950	-1.303	0.159	2.67E-16	-1.614	-0.991	-1.285	0.161	1.21E-15	-1.599	-0.970
	batch 15	0.012	0.139	9.31E-01	-0.260	0.284	-0.020	0.140	8.84E-01	-0.294	0.253	-0.018	0.141	8.99E-01	-0.294	0.259
	batch 16	-0.689	0.135	3.64E-07	-0.955	-0.424	-0.706	0.138	3.17E-07	-0.977	-0.435	-0.729	0.143	3.32E-07	-1.009	-0.449
	batch 17	-0.708	0.116	1.03E-09	-0.935	-0.481	-0.737	0.122	1.51E-09	-0.975	-0.498	-0.761	0.127	2.07E-09	-1.010	-0.512
	batch 18	-0.160	0.124	1.97E-01	-0.403	0.083	-0.167	0.130	2.01E-01	-0.422	0.089	-0.173	0.141	2.20E-01	-0.451	0.104
	intercept	4.656	0.127	7.20E-296	4.408	4.904	4.666	0.127	1.78E-294	4.416	4.915	4.675	0.130	9.42E-285	4.420	4.929

		Vascular infiltration by macrophages														
		Model 1 (n=994)					Model 2 (n=994)					Model 3 (n=880)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**overfeeding**	-0.013	0.043	7.68E-01	-0.096	0.071	-0.058	0.047	2.20E-01	-0.151	0.035	-0.084	0.051	1.01E-01	-0.185	0.016
	cholesterol supplementation	0.066	0.052	2.03E-01	-0.036	0.168	0.070	0.052	1.79E-01	-0.032	0.172	0.067	0.055	2.18E-01	-0.040	0.174
	diethyl ether treatment	-0.001	0.051	9.86E-01	-0.101	0.099	0.025	0.052	6.30E-01	-0.077	0.126	0.012	0.053	8.25E-01	-0.093	0.117
	time of day (in hours since 9AM)	0.008	0.008	3.39E-01	-0.008	0.023	0.002	0.008	7.70E-01	-0.014	0.019	0.015	0.009	1.05E-01	-0.003	0.033
	body length (in SD)	-	-	-	-	-	0.049	0.025	4.91E-02	0.000	0.099	0.030	0.028	2.84E-01	-0.025	0.084
	dorsal body surface area (in SD)	-	-	-	-	-	0.048	0.026	6.45E-02	-0.003	0.098	0.047	0.028	9.53E-02	-0.008	0.102
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.063	0.039	1.07E-01	-0.014	0.141
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.115	0.029	6.12E-05	-0.171	-0.059
	Tg(hsp70:IK17:EGFP; mpeg1:mCherry) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-0.969	0.087	1.09E-28	-1.140	-0.798	-1.016	0.088	7.75E-31	-1.188	-0.844	-1.054	0.116	8.06E-20	-1.281	-0.828
	batch 1	-0.065	0.076	3.91E-01	-0.213	0.083	-0.093	0.076	2.21E-01	-0.241	0.056	-0.036	0.076	6.37E-01	-0.185	0.113
	batch 2	-0.035	0.080	6.61E-01	-0.192	0.122	-0.087	0.081	2.88E-01	-0.246	0.073	0.007	0.086	9.34E-01	-0.162	0.177
	batch 3	-1.359	0.102	7.57E-41	-1.558	-1.160	-1.379	0.107	7.15E-38	-1.589	-1.169					
	batch 6	0.038	0.092	6.83E-01	-0.143	0.218	0.028	0.093	7.65E-01	-0.154	0.210	0.224	0.103	3.01E-02	0.022	0.427
	batch 7	-1.959	0.108	5.69E-74	-2.170	-1.748	-1.949	0.109	3.42E-71	-2.164	-1.735	-1.818	0.139	7.74E-39	-2.091	-1.544
	batch 14	-0.539	0.122	9.91E-06	-0.778	-0.300	-0.488	0.125	9.08E-05	-0.733	-0.244	-0.415	0.127	1.04E-03	-0.663	-0.167
	batch 15	-0.233	0.091	1.03E-02	-0.411	-0.055	-0.240	0.090	7.44E-03	-0.416	-0.064	-0.271	0.090	2.58E-03	-0.448	-0.095
	batch 16	-1.115	0.116	6.04E-22	-1.342	-0.888	-1.059	0.119	7.06E-19	-1.293	-0.825	-1.062	0.123	0.000	-1.302	-0.822

continued **Supplementary Table 5**

		Vascular infiltration by macrophages														
		Model 1 (n=994)					Model 2 (n=994)					Model 3 (n=880)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
	batch 17	-0.973	0.103	4.04E-21	-1.175	-0.771	-0.916	0.107	1.03E-17	-1.125	-0.706	-0.945	0.111	1.35E-17	-1.162	-0.728
	batch 18	-0.221	0.082	6.77E-03	-0.381	-0.061	-0.154	0.087	7.83E-02	-0.325	0.017	-0.119	0.095	2.10E-01	-0.305	0.067
	intercept	7.880	0.095	0.00E+00	7.694	8.066	7.921	0.099	0.00E+00	7.727	8.114	7.836	0.122	0.00E+00	7.597	8.074

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=870)					Model 2 (n=870)					Model 3 (n=763)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**overfeeding**	0.273	0.225	2.26E-01	-0.169	0.714	0.195	0.248	4.31E-01	-0.291	0.680	0.251	0.285	3.78E-01	-0.307	0.810
	cholesterol supplementation	0.383	0.315	2.24E-01	-0.235	1.001	0.356	0.312	2.54E-01	-0.256	0.968	0.554	0.354	1.18E-01	-0.140	1.248
	diethyl ether treatment	0.291	0.291	3.16E-01	-0.279	0.861	0.207	0.283	4.65E-01	-0.348	0.762	0.281	0.297	3.43E-01	-0.301	0.863
	time of day (in hours since 9AM)	0.005	0.045	9.17E-01	-0.084	0.093	-0.002	0.046	9.63E-01	-0.092	0.087	0.040	0.050	4.24E-01	-0.058	0.139
	body length (in SD)	-	-	-	-	-	-0.240	0.131	6.64E-02	-0.496	0.016	-0.185	0.138	1.79E-01	-0.454	0.085
	dorsal body surface area (in SD)	-	-	-	-	-	0.266	0.154	8.42E-02	-0.036	0.567	0.220	0.165	1.82E-01	-0.103	0.543
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.404	0.186	3.04E-02	0.038	0.769
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.112	0.151	4.60E-01	-0.408	0.184
	Tg(hsp70:IK17:EGFP; mpeg1:mCherry) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-3.913	0.563	3.64E-12	-5.017	-2.810	-4.177	0.517	6.76E-16	-5.191	-3.163	-3.914	0.688	1.26E-08	-5.262	-2.566
	batch 1	-0.741	0.313	1.80E-02	-1.355	-0.127	-0.868	0.337	9.93E-03	-1.527	-0.208	-0.767	0.356	3.12E-02	-1.465	-0.069
	batch 2	0.644	0.302	3.30E-02	0.052	1.236	0.543	0.322	9.21E-02	-0.089	1.174	0.783	0.376	3.72E-02	0.046	1.520
	batch 3	-1.767	0.447	7.63E-05	-2.642	-0.891	-2.255	0.461	9.94E-07	-3.158	-1.352	-	-	-	-	-
	batch 6	0.078	0.373	8.35E-01	-0.654	0.809	-0.159	0.373	6.70E-01	-0.889	0.572	-0.109	0.412	7.91E-01	-0.916	0.698
	batch 7	-3.258	0.617	1.28E-07	-4.467	-2.049	-3.685	0.634	6.18E-09	-4.928	-2.442	-2.598	0.836	1.88E-03	-4.237	-0.960
	batch 15	1.239	0.602	3.95E-02	0.060	2.419	1.372	0.557	1.38E-02	0.280	2.464	1.256	0.544	2.10E-02	0.189	2.323
	batch 16	-1.544	1.034	1.35E-01	-3.572	0.483	-1.250	1.019	2.20E-01	-3.247	0.747	-1.460	0.973	1.33E-01	-3.366	0.446
	batch 17	0.324	0.660	6.23E-01	-0.969	1.617	0.760	0.633	2.30E-01	-0.481	2.002	0.474	0.665	4.75E-01	-0.828	1.777
	batch 18	0.546	0.972	5.74E-01	-1.358	2.451	1.085	0.981	2.69E-01	-0.838	3.009	0.882	0.967	3.62E-01	-1.014	2.778
	intercept	3.297	0.490	1.65E-11	2.338	4.257	3.610	0.510	1.45E-12	2.610	4.609	2.839	0.650	1.27E-05	1.565	4.114

		Vascular co-localization of oxLDL with macrophages														
		Model 1 (n=433)					Model 2 (n=433)					Model 3 (n=430)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**overfeeding**	0.447	0.138	1.22E-03	0.176	0.717	0.456	0.145	1.67E-03	0.172	0.741	0.407	0.146	5.33E-03	0.121	0.694
	cholesterol supplementation	-0.372	0.154	1.55E-02	-0.674	-0.071	-0.389	0.156	1.27E-02	-0.695	-0.083	-0.357	0.158	2.39E-02	-0.667	-0.047
	diethyl ether treatment	-0.109	0.146	4.53E-01	-0.394	0.176	-0.113	0.147	4.41E-01	-0.401	0.175	-0.156	0.148	2.91E-01	-0.446	0.134
	time of day (in hours since 9AM)	0.061	0.028	2.73E-02	0.007	0.115	0.064	0.029	2.59E-02	0.008	0.120	0.075	0.030	1.21E-02	0.016	0.133
	body length (in SD)	-	-	-	-	-	-0.064	0.090	4.79E-01	-0.241	0.113	-0.182	0.107	8.77E-02	-0.392	0.027
	dorsal body surface area (in SD)	-	-	-	-	-	-0.027	0.081	7.42E-01	-0.186	0.133	-0.144	0.097	1.37E-01	-0.334	0.046
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.348	0.161	3.06E-02	0.032	0.663
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.288	0.141	4.18E-02	-0.565	-0.011
	batch 15	0.693	0.254	6.40E-03	0.195	1.192	0.727	0.273	7.76E-03	0.192	1.262	0.491	0.302	1.04E-01	-0.101	1.084
	batch 16	0.549	0.290	5.82E-02	-0.019	1.118	0.527	0.288	6.68E-02	-0.036	1.091	0.217	0.326	5.04E-01	-0.421	0.856
	batch 17	-0.225	0.262	3.90E-01	-0.738	0.288	-0.234	0.263	3.73E-01	-0.750	0.281	-0.652	0.310	3.55E-02	-1.260	-0.044
	batch 18	0.715	0.248	3.97E-03	0.228	1.201	0.690	0.251	5.96E-03	0.198	1.181	0.406	0.289	1.60E-01	-0.160	0.972

continued **Supplementary Table 5**

		Vascular co-localization of oxLDL with macrophages														
		Model 1 (n=433)					Model 2 (n=433)					Model 3 (n=430)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
	batch 19	0.869	0.236	2.26E-04	0.407	1.331	0.892	0.259	5.72E-04	0.385	1.400	0.805	0.273	3.16E-03	0.270	1.340
	intercept	2.076	0.278	7.97E-14	1.531	2.620	2.082	0.303	6.85E-12	1.487	2.677	2.052	0.313	5.92E-11	1.438	2.666

		Vascular infiltration by neutrophils														
		Model 1 (n=494)					Model 2 (n=494)					Model 3 (n=395)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**overfeeding**	0.199	0.054	2.59E-04	0.092	0.306	0.131	0.063	3.80E-02	0.007	0.255	0.196	0.069	4.64E-03	0.060	0.332
	cholesterol supplementation	0.046	0.069	5.07E-01	-0.090	0.181	0.045	0.069	5.13E-01	-0.091	0.181	0.183	0.074	1.39E-02	0.037	0.329
	diethyl ether treatment	-0.033	0.066	6.15E-01	-0.164	0.097	0.001	0.066	9.87E-01	-0.128	0.130	0.018	0.070	8.00E-01	-0.120	0.156
	time of day (in hours since 9AM)	0.033	0.011	2.07E-03	0.012	0.053	0.023	0.011	4.32E-02	0.001	0.045	0.026	0.013	4.46E-02	0.001	0.051
	body length (in SD)	-	-	-	-	-	0.054	0.030	7.75E-02	-0.006	0.113	0.059	0.035	9.34E-02	-0.010	0.129
	dorsal body surface area (in SD)	-	-	-	-	-	0.071	0.038	6.56E-02	-0.005	0.146	0.032	0.042	4.49E-01	-0.051	0.115
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.077	0.056	1.70E-01	-0.187	0.033
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.053	0.036	1.41E-01	-0.124	0.018
	batch 1	-0.209	0.086	1.56E-02	-0.378	-0.040	-0.263	0.088	2.74E-03	-0.435	-0.091	-0.260	0.088	3.21E-03	-0.434	-0.087
	batch 2	-0.245	0.086	4.45E-03	-0.414	-0.076	-0.330	0.087	1.46E-04	-0.500	-0.159	-0.343	0.092	1.98E-04	-0.524	-0.163
	batch 3	-1.742	0.109	2.22E-57	-1.956	-1.528	-1.816	0.116	1.85E-55	-2.043	-1.589	-	-	-	-	-
	batch 6	-0.071	0.118	5.47E-01	-0.301	0.160	-0.114	0.116	3.25E-01	-0.342	0.113	-0.072	0.137	5.97E-01	-0.341	0.196
	batch 7	-2.087	0.105	2.93E-88	-2.293	-1.882	-2.121	0.107	5.84E-87	-2.331	-1.910	-2.310	0.167	1.11E-43	-2.636	-1.983
	intercept	7.658	0.105	0.00E+00	7.451	7.864	7.760	0.115	0.00E+00	7.534	7.985	7.776	0.152	0.00E+00	7.479	8.074

		Vascular co-localization of lipids with neutrophils														
		Model 1 (n=380)					Model 2 (n=380)					Model 3 (n=286)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**overfeeding**	0.727	0.246	3.07E-03	0.246	1.209	0.826	0.251	1.02E-03	0.333	1.319	0.901	0.255	4.01E-04	0.402	1.401
	cholesterol supplementation	0.845	0.284	2.89E-03	0.289	1.401	0.830	0.280	2.98E-03	0.282	1.378	0.882	0.306	3.95E-03	0.282	1.482
	diethyl ether treatment	-0.659	0.319	3.91E-02	-1.285	-0.033	-0.744	0.325	2.21E-02	-1.381	-0.107	-0.258	0.286	3.66E-01	-0.819	0.302
	time of day (in hours since 9AM)	0.017	0.050	7.40E-01	-0.082	0.115	0.039	0.054	4.64E-01	-0.066	0.144	0.049	0.053	3.58E-01	-0.055	0.152
	body length (in SD)	-	-	-	-	-	-0.151	0.140	2.82E-01	-0.425	0.124	-0.059	0.129	6.46E-01	-0.312	0.194
	dorsal body surface area (in SD)	-	-	-	-	-	-0.088	0.162	5.88E-01	-0.405	0.230	-0.082	0.175	6.38E-01	-0.426	0.261
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.102	0.208	6.23E-01	-0.305	0.509
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.132	0.127	2.98E-01	-0.117	0.381
	batch 1	-0.804	0.340	1.79E-02	-1.469	-0.138	-0.701	0.378	6.37E-02	-1.441	0.040	-0.804	0.353	2.27E-02	-1.497	-0.112
	batch 2	0.117	0.356	7.41E-01	-0.580	0.815	0.289	0.402	4.73E-01	-0.500	1.077	0.391	0.414	3.45E-01	-0.421	1.203
	batch 3	-2.749	0.523	1.44E-07	-3.774	-1.725	-2.714	0.572	2.05E-06	-3.834	-1.594	-	-	-	-	-
	batch 6	-0.652	0.441	1.40E-01	-1.517	0.213	-0.557	0.462	2.28E-01	-1.462	0.349	-0.510	0.464	2.71E-01	-1.420	0.399
	intercept	2.288	0.576	7.12E-05	1.159	3.416	2.105	0.602	4.69E-04	0.925	3.284	1.409	0.679	3.79E-02	0.079	2.740

continued **Supplementary Table 5**

		Vascular co-localization of macrophages with neutrophils														
		Model 1 (n=488)					Model 2 (n=488)					Model 3 (n=392)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**overfeeding**	0.096	0.104	3.55E-01	-0.107	0.299	-0.019	0.115	8.67E-01	-0.244	0.205	0.060	0.113	5.99E-01	-0.162	0.281
	cholesterol supplementation	0.153	0.133	2.50E-01	-0.108	0.413	0.119	0.136	3.81E-01	-0.147	0.385	0.299	0.127	1.90E-02	0.049	0.549
	diethyl ether treatment	-0.240	0.136	7.75E-02	-0.506	0.026	-0.164	0.136	2.27E-01	-0.430	0.102	-0.164	0.133	2.18E-01	-0.426	0.097
	time of day (in hours since 9AM)	-0.007	0.021	7.39E-01	-0.048	0.034	-0.027	0.023	2.42E-01	-0.072	0.018	-0.009	0.026	7.23E-01	-0.059	0.041
	body length (in SD)	-	-	-	-	-	0.034	0.054	5.27E-01	-0.071	0.139	-0.022	0.054	6.84E-01	-0.127	0.083
	dorsal body surface area (in SD)	-	-	-	-	-	0.170	0.067	1.08E-02	0.039	0.302	0.097	0.068	1.55E-01	-0.037	0.231
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.231	0.089	9.49E-03	0.056	0.405
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.153	0.066	1.96E-02	-0.282	-0.025
	batch 1	0.223	0.131	8.87E-02	-0.034	0.479	0.090	0.146	5.34E-01	-0.195	0.376	0.225	0.145	1.21E-01	-0.059	0.509
	batch 2	-0.355	0.150	1.79E-02	-0.650	-0.061	-0.523	0.166	1.59E-03	-0.848	-0.198	-0.336	0.175	5.57E-02	-0.679	0.008
	batch 3	-2.971	0.240	4.01E-35	-3.441	-2.500	-3.183	0.279	3.32E-30	-3.729	-2.637	-	-	-	-	-
	batch 6	0.175	0.191	3.60E-01	-0.199	0.549	0.059	0.199	7.67E-01	-0.331	0.448	0.426	0.232	6.61E-02	-0.028	0.880
	batch 7	-4.803	0.258	1.43E-77	-5.308	-4.298	-4.918	0.274	3.21E-72	-5.454	-4.382	-4.433	0.338	2.72E-39	-5.096	-3.771
	intercept	5.839	0.218	1.63E-158	5.412	6.266	6.054	0.250	5.85E-130	5.565	6.543	5.617	0.302	2.18E-77	5.026	6.208

		Endothelial thickness														
		Model 1 (n=467)					Model 2 (n=467)					Model 3 (n=411)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**overfeeding**	0.252	0.073	5.34E-04	0.109	0.395	0.176	0.079	2.69E-02	0.020	0.331	0.171	0.089	5.47E-02	-0.003	0.346
	cholesterol supplementation	0.091	0.082	2.65E-01	-0.069	0.252	0.115	0.082	1.60E-01	-0.045	0.276	0.119	0.090	1.89E-01	-0.058	0.296
	diethyl ether treatment	-0.320	0.087	2.40E-04	-0.490	-0.149	-0.330	0.087	1.42E-04	-0.500	-0.160	-0.337	0.096	4.13E-04	-0.525	-0.150
	time of day (in hours since 9AM)	0.065	0.014	1.43E-06	0.039	0.092	0.066	0.013	8.20E-07	0.040	0.093	0.076	0.015	2.11E-07	0.048	0.105
	body length (in SD)	-	-	-	-	-	0.063	0.043	1.39E-01	-0.020	0.147	0.033	0.049	5.06E-01	-0.064	0.129
	dorsal body surface area (in SD)	-	-	-	-	-	0.073	0.040	6.63E-02	-0.005	0.150	0.076	0.043	7.67E-02	-0.008	0.161
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.023	0.041	5.73E-01	-0.057	0.104
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.045	0.043	3.00E-01	-0.040	0.129
	intercept	-0.445	0.259	8.56E-02	-0.953	0.062	-0.378	0.262	1.49E-01	-0.890	0.135	-0.366	0.288	2.04E-01	-0.930	0.198
random factors	***variation by batch***	*0.672*	*0.173*	-	*0.405*	*1.113*	*0.676*	*0.174*	-	*0.408*	*1.120*	*0.693*	*0.192*	-	*0.402*	*1.192*
	residual	*0.703*	*0.023*	-	*0.659*	*0.750*	*0.698*	*0.023*	-	*0.655*	*0.745*	*0.716*	*0.025*	-	*0.669*	*0.767*

Endothelial thickness is defined as surface area of the endothelium normalized for surface area of the circulating lipids. Associations were examined using negative binomial regresion for outcomes that showed a negative binomial distribution; and using hierarchical linear models on inverse normally transformed outcomes for outcomes that were (borderline) normally distributed (i.e. endothelial thickness). Model 1: adjusted for diethyl ether (used to prepare the diet), time of day, transgenic background and batch; Model 2: additionally adjusted for body length and dorsal body surface area; Model 3: additionally adjusted for whole-body triglyceride and glucose levels. Dorsal body surface area was normalized for body length using residuals; whole-body triglyceride and glucose levels were normalized for protein level using residuals. Effects shown for overfeeding, cholesterol supplementation and diethyl ether treatment are compared with unexposed controls. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 6 - The effect of overfeeding and cholesterol supplementation on suboptimal image or quantification quality

	Larva optically cut during pre-processing				
	Model 1 (n=2306)				
	OR	SE	*P*	lci	uci
overfeeding	1.450	0.290	6.52E-02	0.980	2.150
cholesterol supplementation	1.220	0.280	3.97E-01	0.770	1.920
diethyl ether treatment	1.090	0.270	7.23E-01	0.670	1.790
time of day (in hours since 9AM)	0.950	0.040	1.96E-01	0.890	1.030
intercept	0.050	0.010	6.21E-26	0.030	0.080

	Vasculature not properly detected														
	Model 1 (n=2050)					Model 2 (n=2050)					Model 3 (n=1859)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
overfeeding	0.650	0.140	4.16E-02	0.420	0.980	0.860	0.190	4.89E-01	0.550	1.330	0.790	0.190	3.25E-01	0.500	1.260
cholesterol supplementation	0.920	0.250	7.52E-01	0.540	1.560	0.840	0.230	5.13E-01	0.490	1.430	0.670	0.190	1.62E-01	0.380	1.170
diethyl ether treatment	0.810	0.210	4.13E-01	0.490	1.340	0.820	0.210	4.36E-01	0.490	1.360	0.910	0.240	7.29E-01	0.540	1.540
time of day (in hours since 9AM)	0.910	0.040	2.15E-02	0.840	0.990	0.920	0.040	6.32E-02	0.850	1.000	0.900	0.040	1.87E-02	0.820	0.980
body length (in SD)	-	-	-	-	-	0.770	0.090	2.26E-02	0.610	0.960	0.760	0.100	3.75E-02	0.580	0.980
dorsal body surface area (in SD)	-	-	-	-	-	0.650	0.080	2.45E-04	0.520	0.820	0.710	0.090	5.48E-03	0.560	0.900
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.730	0.090	1.59E-02	0.570	0.940
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.730	0.090	1.15E-02	0.570	0.930
intercept	0.120	0.030	4.79E-14	0.070	0.200	0.080	0.030	5.61E-16	0.050	0.150	0.090	0.030	4.75E-13	0.050	0.170

	Many false positive vascular lipid deposits														
	Model 1 (n=2043)					Model 2 (n=2043)					Model 3 (n=1848)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
overfeeding	0.540	0.120	6.81E-03	0.350	0.840	0.620	0.150	5.05E-02	0.390	1.000	0.450	0.120	3.65E-03	0.270	0.770
cholesterol supplementation	0.940	0.270	8.35E-01	0.530	1.660	0.920	0.270	7.89E-01	0.520	1.640	0.960	0.300	8.92E-01	0.520	1.770
diethyl ether treatment	0.650	0.170	1.06E-01	0.380	1.100	0.650	0.180	1.11E-01	0.380	1.100	0.670	0.190	1.66E-01	0.380	1.180
time of day (in hours since 9AM)	1.040	0.040	3.49E-01	0.960	1.130	1.050	0.040	2.60E-01	0.970	1.140	1.060	0.050	1.98E-01	0.970	1.160
body length (in SD)	-	-	-	-	-	0.930	0.110	5.57E-01	0.740	1.180	0.710	0.090	1.02E-02	0.550	0.920
dorsal body surface area (in SD)	-	-	-	-	-	0.820	0.100	9.58E-02	0.650	1.040	0.730	0.100	1.95E-02	0.550	0.950
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	2.610	0.360	4.40E-12	1.990	3.430
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.020	0.130	8.65E-01	0.790	1.320
intercept	0.060	0.020	5.45E-19	0.030	0.120	0.060	0.020	4.50E-19	0.030	0.110	0.040	0.010	4.59E-19	0.020	0.080

continued **Supplementary Table 6**

	Many false positive oxLDL deposits														
	Model 1 (n=885)					Model 2 (n=885)					Model 3 (n=876)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
overfeeding	1.050	0.180	7.51E-01	0.760	1.460	1.250	0.220	2.00E-01	0.890	1.770	1.020	0.200	9.32E-01	0.700	1.480
cholesterol supplementation	0.840	0.170	3.89E-01	0.560	1.260	0.900	0.190	6.26E-01	0.590	1.370	0.910	0.210	6.77E-01	0.580	1.420
diethyl ether treatment	0.680	0.130	4.50E-02	0.460	0.990	0.670	0.130	4.07E-02	0.450	0.980	0.560	0.120	6.40E-03	0.370	0.850
time of day (in hours since 9AM)	0.870	0.030	1.05E-04	0.810	0.930	0.900	0.030	3.55E-03	0.840	0.970	0.930	0.040	6.35E-02	0.860	1.000
body length (in SD)	-	-	-	-	-	1.260	0.130	2.47E-02	1.030	1.540	0.920	0.110	4.58E-01	0.730	1.150
dorsal body surface area (in SD)	-	-	-	-	-	0.700	0.060	2.61E-05	0.590	0.830	0.720	0.070	4.19E-04	0.600	0.860
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.950	0.260	3.96E-07	1.500	2.520
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.400	0.050	1.59E-14	0.320	0.500
intercept	0.790	0.200	3.46E-01	0.480	1.290	0.530	0.140	1.93E-02	0.310	0.900	0.400	0.110	1.32E-03	0.220	0.700

	Many false negative macrophages														
	Model 1 (n=1010)					Model 2 (n=1010)					Model 2 (n=589)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
overfeeding	0.380	0.210	8.27E-02	0.130	1.130	0.470	0.280	2.04E-01	0.140	1.510	1.520	1.770	7.22E-01	0.150	14.920
cholesterol supplementation	0.390	0.330	2.68E-01	0.080	2.050	0.310	0.270	1.76E-01	0.060	1.680	0.480	0.590	5.53E-01	0.040	5.440
diethyl ether treatment	0.630	0.360	4.13E-01	0.200	1.920	0.550	0.330	3.15E-01	0.170	1.760	-	-	-	-	-
time of day (in hours since 9AM)	0.830	0.090	7.57E-02	0.680	1.020	0.870	0.090	1.84E-01	0.710	1.070	0.650	0.190	1.45E-01	0.360	1.160
body length (in SD)	-	-	-	-	-	0.510	0.150	2.19E-02	0.280	0.910	1.450	0.890	5.41E-01	0.440	4.800
dorsal body surface area (in SD)	-	-	-	-	-	1.580	0.480	1.35E-01	0.870	2.860	1.150	0.700	8.22E-01	0.350	3.790
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.260	0.180	4.62E-02	0.070	0.980
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	2.080	1.360	2.63E-01	0.580	7.500
intercept	0.090	0.050	1.76E-05	0.030	0.270	0.070	0.040	3.40E-06	0.020	0.220	0.060	0.090	8.53E-02	0.000	1.490

	Many false negative neutrophils														
	Model 1 (n=537)					Model 2 (n=537)					Model 3 (n=416)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
overfeeding	1.110	0.360	7.38E-01	0.590	2.110	1.380	0.500	3.69E-01	0.680	2.810	4.270	2.750	2.41E-02	1.210	15.110
cholesterol supplementation	0.730	0.310	4.66E-01	0.320	1.680	0.650	0.280	3.12E-01	0.280	1.510	0.880	0.600	8.53E-01	0.230	3.350
diethyl ether treatment	0.950	0.370	8.89E-01	0.440	2.060	0.830	0.340	6.46E-01	0.370	1.850	6.440	7.440	1.07E-01	0.670	62.010
time of day (in hours since 9AM)	0.790	0.050	4.24E-04	0.690	0.900	0.810	0.060	1.76E-03	0.700	0.920	0.710	0.130	5.77E-02	0.500	1.010
body length (in SD)	-	-	-	-	-	0.630	0.120	1.11E-02	0.440	0.900	0.820	0.260	5.40E-01	0.440	1.540
dorsal body surface area (in SD)	-	-	-	-	-	1.190	0.260	4.16E-01	0.780	1.820	0.570	0.220	1.41E-01	0.270	1.200
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.270	0.090	6.30E-05	0.140	0.510
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.140	0.450	7.44E-01	0.520	2.470
intercept	0.300	0.110	9.49E-04	0.150	0.610	0.240	0.090	2.03E-04	0.110	0.510	0.030	0.020	1.08E-04	0.000	0.160

continued **Supplementary Table 6**

	Circulating neutrophils present in the z-stack														
	Model 1 (n=504)					Model 2 (n=504)					Model 3 (n=404)				
	OR	**SE**	***P***	**lci**	**uci**	**OR**	**SE**	***P***	**lci**	**uci**	**OR**	**SE**	***P***	**lci**	**uci**
overfeeding	1.740	1.140	3.99E-01	0.480	6.290	1.660	1.260	5.04E-01	0.380	7.340	2.630	2.150	2.35E-01	0.530	13.010
cholesterol supplementation	0.980	0.980	9.80E-01	0.140	7.020	1.180	1.210	8.69E-01	0.160	8.740	1.580	1.700	6.70E-01	0.190	12.940
diethyl ether treatment	0.300	0.250	1.46E-01	0.060	1.520	0.330	0.280	1.97E-01	0.060	1.790	0.380	0.350	2.90E-01	0.060	2.270
time of day (in hours since 9AM)	0.970	0.110	7.58E-01	0.780	1.200	0.960	0.110	7.48E-01	0.770	1.210	0.990	0.130	9.26E-01	0.760	1.280
body length (in SD)	-	-	-	-	-	1.580	0.600	2.25E-01	0.750	3.320	1.410	0.610	4.26E-01	0.610	3.270
dorsal body surface area (in SD)	-	-	-	-	-	0.650	0.290	3.37E-01	0.260	1.580	0.570	0.280	2.60E-01	0.220	1.510
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.530	0.750	3.85E-01	0.590	4.010
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.180	0.550	7.21E-01	0.470	2.960
intercept	0.040	0.030	2.24E-05	0.010	0.170	0.030	0.030	3.19E-05	0.010	0.160	0.010	0.010	7.23E-05	0.000	0.110

Associations are shown for criteria that resulted in the exclusion of at least 10 larvae. Vasculature not properly detected typically results from weak staining, possibly due to low levels of circulating lipids; Many false positives: >20% of true negative objects were falsely detected by the qualtification pipeline; Many false negatives: <20% of true positive objects were detected by the qualtification pipeline. Associations were examined using logistic regression models. Model 1: adjusted for use of diethyl ether (to prepare the diet) and time of day; Model 2: additionally adjusted for body length and dorsal body surface area; Model 3: additionally adjusted for whole-body triglyceride and glucose levels. Dorsal body surface area was normalized for body length; whole-body triglyceride and glucose levels were normalized for protein level. Adjusting for transgenic background and batch would have excluded approximately half the larvae. Effects shown for overfeeding, cholesterol supplementation and diethyl ether treatment are compared with unexposed controls. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 7 - The effect of treatment with atorvastatin and ezetimibe on body size

		Body length (n=1004)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**atorvastatin and ezetimibe**	-0.025	0.053	6.29E-01	-0.128	0.078
	time of day (in hours since 9AM)	0.000	0.012	9.78E-01	-0.023	0.024
	intercept	0.012	0.162	9.41E-01	-0.305	0.330
random factors	***variation by transgenic background***	*0.000*	-	-	-	-
	variation by batch	*0.495*	*0.147*	-	*0.276*	*0.886*
	residual	*0.794*	*0.025*	-	*0.747*	*0.845*

		Dorsal body surface area (n=1004)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**atorvastatin and ezetimibe**	-0.135	0.055	1.48E-02	-0.244	-0.026
	time of day (in hours since 9AM)	0.046	0.013	2.72E-04	0.021	0.071
	intercept	-0.185	0.335	5.81E-01	-0.842	0.472
random factors	***variation by transgenic background***	*0.561*	*0.239*	-	*0.244*	*1.291*
	variation by batch	*0.176*	*0.057*	-	*0.093*	*0.330*
	residual	*0.842*	*0.019*	-	*0.806*	*0.880*

		Lateral body surface area (n=553)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**atorvastatin and ezetimibe**	-0.233	0.088	8.05E-03	-0.406	-0.061
	time of day (in hours since 9AM)	0.022	0.019	2.61E-01	-0.016	0.059
	intercept	-0.011	0.187	9.54E-01	-0.376	0.355
random factors	***variation by transgenic background***	*0.221*	*0.122*	-	*0.075*	*0.654*
	variation by batch	*0.066*	*0.079*	-	*0.006*	*0.678*
	residual	*0.972*	*0.029*	-	*0.916*	*1.031*

		Body volume (n=512)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**atorvastatin and ezetimibe**	-0.314	0.087	2.95E-04	-0.484	-0.144
	time of day (in hours since 9AM)	0.024	0.019	2.19E-01	-0.014	0.061
	intercept	-0.026	0.350	9.40E-01	-0.712	0.660
random factors	***variation by transgenic background***	*0.458*	*0.249*	-	*0.158*	*1.332*
	variation by batch	*0.209*	*0.101*	-	*0.082*	*0.538*
	residual	*0.922*	*0.029*	-	*0.867*	*0.981*

Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models. Effects shown for atorvastatin and ezetimibe treatment are compared with unexposed controls. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 8 - The effect of treatment with atorvastatin and ezetimibe on whole-body lipid and glucose levels

		LDL cholesterol levels (n=567)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**atorvastatin and ezetimibe**	-0.544	0.079	5.22E-12	-0.699	-0.390
	time of day (in hours since 9AM)	0.017	0.017	3.28E-01	-0.017	0.050
	intercept	0.173	0.343	6.13E-01	-0.499	0.846
random factors	***variation by transgenic background***	*0.461*	*0.242*	-	*0.165*	*1.288*
	variation by batch	*0.147*	*0.071*	-	*0.057*	*0.378*
	residual	*0.861*	*0.026*	-	*0.812*	*0.913*

		HDL cholesterol levels (n=564)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**atorvastatin and ezetimibe**	0.043	0.078	5.78E-01	-0.109	0.195
	time of day (in hours since 9AM)	0.018	0.017	2.91E-01	-0.015	0.050
	intercept	-0.064	0.387	8.68E-01	-0.822	0.694
random factors	***variation by transgenic background***	*0.516*	*0.278*	-	*0.180*	*1.483*
	variation by batch	*0.228*	*0.094*	-	*0.101*	*0.512*
	residual	*0.837*	*0.025*	-	*0.789*	*0.888*

		Triglyceride levels (n=1005)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**atorvastatin and ezetimibe**	-0.245	0.055	8.68E-06	-0.353	-0.137
	time of day (in hours since 9AM)	0.046	0.013	2.29E-04	0.022	0.071
	intercept	-0.133	0.198	5.04E-01	-0.522	0.256
random factors	***variation by transgenic background***	*0.174*	*0.351*	-	*0.003*	*9.122*
	variation by batch	*0.521*	*0.145*	-	*0.302*	*0.899*
	residual	*0.832*	*0.019*	-	*0.796*	*0.869*

		Total cholesterol levels (n=1005)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**atorvastatin and ezetimibe**	-0.821	0.051	1.23E-58	-0.920	-0.721
	time of day (in hours since 9AM)	0.060	0.012	2.39E-07	0.037	0.083
	intercept	0.089	0.283	7.54E-01	-0.467	0.644
random factors	***variation by transgenic background***	*0.443*	*0.221*	-	*0.166*	*1.178*
	variation by batch	*0.344*	*0.092*	-	*0.203*	*0.581*
	residual	*0.768*	*0.017*	-	*0.735*	*0.803*

		Glucose levels (n=1008)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**atorvastatin and ezetimibe**	0.199	0.053	1.92E-04	0.094	0.303
	time of day (in hours since 9AM)	-0.018	0.012	1.34E-01	-0.042	0.006
	intercept	-0.088	0.313	7.78E-01	-0.702	0.525
random factors	***variation by transgenic background***	*0.520*	*0.223*	-	*0.224*	*1.206*
	variation by batch	*0.204*	*0.059*	-	*0.115*	*0.360*
	residual	*0.810*	*0.018*	-	*0.775*	*0.847*

All outcomes were normalized for protein level using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models and were adjusted for time of day, transgenic background and batch. Effects shown for treatment with atorvastatin and ezetimibe are compared with untreated controls. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 9 - The effect of atorvastatin and ezetimibe on image-based vascular atherogenic traits

		Vascular lipid deposition																			
		Model 1 (n=776)					Model 2 (n=776)					Model 3 (n=728)					Model 4 (n=344)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**atorvastatin and ezetimibe**	-1.523	0.176	4.75E-18	-1.868	-1.178	-1.496	0.177	2.32E-17	-1.842	-1.150	-1.423	0.180	3.04E-15	-1.776	-1.069	-2.001	0.299	2.18E-11	-2.587	-1.415
	time of day (in hours since 9AM)	0.155	0.038	4.83E-05	0.080	0.229	0.145	0.037	1.07E-04	0.072	0.219	0.151	0.040	1.53E-04	0.073	0.229	0.327	0.054	1.88E-09	0.221	0.434
	body length (in SD)	-	-	-	-	-	-0.222	0.119	6.27E-02	-0.456	0.012	-0.221	0.120	6.43E-02	-0.455	0.013	0.352	0.243	1.48E-01	-0.125	0.829
	dorsal body surface area (in SD)	-	-	-	-	-	0.183	0.102	7.15E-02	-0.016	0.383	0.118	0.120	3.28E-01	-0.118	0.354	0.179	0.193	3.51E-01	-0.198	0.557
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.231	0.149	1.21E-01	-0.524	0.061
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.216	0.133	1.06E-01	-0.477	0.046
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.178	0.119	1.36E-01	-0.056	0.412	0.426	0.216	4.87E-02	0.002	0.849
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.125	0.103	2.27E-01	-0.327	0.078	-0.159	0.231	4.91E-01	-0.611	0.293
	Tg(flk:EGFP) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-0.915	0.335	6.37E-03	-1.572	-0.257	-0.823	0.360	2.22E-02	-1.527	-0.118	-0.808	0.383	3.50E-02	-1.560	-0.057	-	-	-	-	-
	Tg(hsp70:IK17:EGFP; mpeg1:mCherry) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-0.477	0.245	5.17E-02	-0.958	0.003	0.103	0.353	7.72E-01	-0.590	0.795	-0.020	0.403	9.60E-01	-0.810	0.770	0.562	0.606	3.54E-01	-0.626	1.751
	batch 1	-0.727	0.456	1.11E-01	-1.621	0.167	-0.600	0.453	1.85E-01	-1.488	0.288	-0.263	0.497	5.97E-01	-1.237	0.711	-	-	-	-	-
	batch 2	-0.480	0.330	1.47E-01	-1.127	0.168	-0.240	0.349	4.92E-01	-0.924	0.444	0.182	0.376	6.28E-01	-0.555	0.920	-	-	-	-	-
	batch 3	-1.264	0.319	7.40E-05	-1.889	-0.639	-1.204	0.311	1.08E-04	-1.814	-0.595	-0.895	0.361	1.32E-02	-1.603	-0.187	-	-	-	-	-
	batch 4	-0.678	0.325	3.70E-02	-1.316	-0.041	-0.611	0.331	6.52E-02	-1.260	0.039	-0.322	0.381	3.97E-01	-1.069	0.424	-	-	-	-	-
	batch 5	-0.385	0.377	3.07E-01	-1.125	0.355	-0.504	0.388	1.94E-01	-1.265	0.257	-0.427	0.384	2.66E-01	-1.179	0.325	-	-	-	-	-
	batch 6	-0.252	0.384	5.11E-01	-1.005	0.500	-0.509	0.392	1.93E-01	-1.277	0.258	-0.492	0.397	2.16E-01	-1.271	0.287	0.269	0.458	5.57E-01	-0.629	1.167
	batch 7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.124	0.454	7.85E-01	-0.766	1.014
	batch 8	-2.432	0.386	3.12E-10	-3.189	-1.674	-2.576	0.374	5.73E-12	-3.309	-1.843	-2.513	0.374	1.85E-11	-3.246	-1.780	-2.101	0.479	1.14E-05	-3.040	-1.163
	intercept	3.849	0.268	1.31E-46	3.322	4.375	3.740	0.274	2.47E-42	3.202	4.277	3.570	0.298	4.95E-33	2.986	4.155	1.707	0.455	1.75E-04	0.815	2.598

		Vascular accumulation of oxLDL																			
		Model 1 (n=236)					Model 2 (n=236)					Model 3 (n=233)					Model 4 (n=229)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	**atorvastatin and ezetimibe**	0.019	0.126	8.78E-01	-0.228	0.267	0.100	0.126	4.29E-01	-0.147	0.347	0.099	0.127	4.35E-01	-0.150	0.349	0.130	0.130	3.19E-01	-0.126	0.385
	time of day (in hours since 9AM)	-0.017	0.024	4.94E-01	-0.064	0.031	-0.018	0.024	4.45E-01	-0.064	0.028	-0.028	0.024	2.44E-01	-0.075	0.019	-0.031	0.024	1.96E-01	-0.079	0.016
	body length (in SD)	-	-	-	-	-	0.111	0.085	1.90E-01	-0.055	0.278	0.143	0.094	1.30E-01	-0.042	0.328	0.157	0.096	1.01E-01	-0.031	0.344
	dorsal body surface area (in SD)	-	-	-	-	-	0.189	0.063	2.46E-03	0.067	0.312	0.206	0.081	1.14E-02	0.046	0.365	0.220	0.081	6.84E-03	0.060	0.379
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.007	0.066	9.16E-01	-0.122	0.135
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.127	0.067	5.80E-02	-0.004	0.258
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.010	0.087	9.06E-01	-0.181	0.160	0.014	0.092	8.76E-01	-0.166	0.195
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.152	0.096	1.13E-01	-0.036	0.341	0.096	0.108	3.76E-01	-0.116	0.308
	intercept	0.169	0.256	5.09E-01	-0.333	0.672	0.261	0.256	3.10E-01	-0.242	0.763	0.433	0.280	1.22E-01	-0.116	0.981	0.323	0.299	2.81E-01	-0.264	0.909
random factors	***variation by batch***	*0.378*	*0.169*	-	*0.157*	*0.907*	*0.373*	*0.173*	-	*0.151*	*0.924*	*0.382*	*0.177*	-	*0.154*	*0.948*	*0.400*	*0.185*	-	*0.162*	*0.988*
	residual	*0.839*	*0.039*	-	*0.767*	*0.919*	*0.820*	*0.038*	-	*0.749*	*0.898*	*0.818*	*0.038*	-	*0.746*	*0.896*	*0.811*	*0.038*	-	*0.739*	*0.889*

		Vascular infiltration by macrophages																			
		Model 1 (n=633)					Model 2 (n=633)					Model 3 (n=585)					Model 4 (n=224)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	**atorvastatin and ezetimibe**	-0.001	0.049	9.80E-01	-0.097	0.094	0.005	0.049	9.17E-01	-0.090	0.101	0.010	0.051	8.50E-01	-0.090	0.109	-0.003	0.072	9.64E-01	-0.144	0.138
	time of day (in hours since 9AM)	0.036	0.011	9.87E-04	0.015	0.058	0.033	0.011	3.11E-03	0.011	0.054	0.029	0.011	1.00E-02	0.007	0.052	0.009	0.013	4.96E-01	-0.017	0.035
	body length (in SD)	-	-	-	-	-	0.001	0.031	9.81E-01	-0.060	0.061	0.011	0.032	7.36E-01	-0.051	0.073	0.065	0.053	2.20E-01	-0.039	0.169
	dorsal body surface area (in SD)	-	-	-	-	-	0.059	0.029	4.03E-02	0.003	0.116	0.043	0.032	1.82E-01	-0.020	0.105	0.022	0.044	6.14E-01	-0.065	0.109
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.040	0.036	2.71E-01	-0.110	0.031
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.031	0.037	4.08E-01	-0.042	0.104
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.027	0.030	3.68E-01	-0.032	0.087	0.091	0.051	7.67E-02	-0.010	0.191
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.011	0.025	6.76E-01	-0.039	0.060	-0.007	0.059	9.10E-01	-0.122	0.109
	intercept	-0.285	0.505	5.73E-01	-1.275	0.706	-0.252	0.486	6.04E-01	-1.204	0.701	-0.238	0.483	6.22E-01	-1.186	0.709	-0.877	0.196	7.53E-06	-1.261	-0.493
random factors	***variation by transgenic background***	*0.699*	*0.361*	-	*0.253*	*1.925*	*0.670*	*0.348*	-	*0.242*	*1.857*	*0.666*	*0.347*	-	*0.240*	*1.849*	*0.000*	*0.000*	-	*0.000*	-
	variation by batch	*0.241*	*0.075*	-	*0.131*	*0.442*	*0.247*	*0.077*	-	*0.134*	*0.457*	*0.246*	*0.077*	-	*0.133*	*0.456*	*0.289*	*0.126*	-	*0.123*	*0.680*
	residuals	*0.583*	*0.017*	-	*0.552*	*0.617*	*0.581*	*0.016*	-	*0.550*	*0.614*	*0.567*	*0.017*	-	*0.536*	*0.601*	*0.438*	*0.021*	-	*0.399*	*0.481*

continued **Supplementary Table 9**

		Vascular co-localization of lipids with macrophages																			
		Model 1 (n=549)					Model 2 (n=549)					Model 3 (n=502)					Model 4 (n=157)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**atorvastatin and ezetimibe**	-1.341	0.241	2.46E-08	-1.813	-0.870	-1.383	0.237	5.74E-09	-1.848	-0.917	-1.226	0.252	1.14E-06	-1.720	-0.732	-2.992	0.730	4.10E-05	-4.422	-1.562
	time of day (in hours since 9AM)	0.122	0.052	1.85E-02	0.021	0.224	0.116	0.054	3.25E-02	0.010	0.222	0.120	0.059	4.30E-02	0.004	0.237	0.388	0.125	1.98E-03	0.142	0.633
	body length (in SD)	-	-	-	-	-	-0.471	0.161	3.50E-03	-0.787	-0.155	-0.477	0.170	4.99E-03	-0.810	-0.144	1.020	0.539	5.83E-02	-0.036	2.076
	dorsal body surface area (in SD)	-	-	-	-	-	0.262	0.156	9.32E-02	-0.044	0.569	0.152	0.187	4.16E-01	-0.215	0.519	1.194	0.494	1.58E-02	0.225	2.163
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.696	0.339	4.02E-02	-1.361	-0.031
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.279	0.243	2.51E-01	-0.755	0.197
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.223	0.181	2.19E-01	-0.133	0.578	0.252	0.501	6.14E-01	-0.729	1.234
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.129	0.116	2.65E-01	-0.356	0.098	1.106	0.562	4.92E-02	0.004	2.209
	Tg(hsp70:IK17:EGFP; mpeg1:mCherry) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-1.007	0.316	1.44E-03	-1.626	-0.387	0.019	0.477	9.69E-01	-0.917	0.954	-0.099	0.488	8.40E-01	-1.055	0.858	-	-	-	-	-
	batch 1	-1.223	0.459	7.65E-03	-2.122	-0.324	-1.133	0.448	1.15E-02	-2.011	-0.254	-0.670	0.516	1.94E-01	-1.681	0.340	-	-	-	-	-
	batch 2	-0.512	0.334	1.26E-01	-1.167	0.143	-0.113	0.374	7.63E-01	-0.847	0.621	0.365	0.409	3.72E-01	-0.437	1.166	-	-	-	-	-
	batch 3	-0.964	0.393	1.41E-02	-1.735	-0.194	-0.938	0.383	1.43E-02	-1.688	-0.187	-0.615	0.454	1.75E-01	-1.504	0.274	-	-	-	-	-
	batch 4	-0.717	0.316	2.32E-02	-1.337	-0.098	-0.553	0.346	1.09E-01	-1.231	0.124	-0.117	0.427	7.85E-01	-0.955	0.721	-	-	-	-	-
	batch 8	-5.338	0.946	1.67E-08	-7.192	-3.484	-5.784	0.956	1.45E-09	-7.658	-3.911	-5.495	0.952	7.76E-09	-7.361	-3.630	-	-	-	-	-
	batch 10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4.420	0.874	4.25E-07	2.707	6.133
	intercept	2.892	0.339	1.61E-17	2.226	3.557	2.734	0.353	1.02E-14	2.041	3.426	2.467	0.358	5.73E-12	1.765	3.169	-2.943	0.840	4.56E-04	-4.589	-1.298

		Vascular co-localization of oxLDL with macrophages																			
		Model 1 (n=212)					Model 2 (n=212)					Model 3 (n=209)					Model 4 (n=205)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**atorvastatin and ezetimibe**	0.332	0.166	4.48E-02	0.008	0.656	0.392	0.163	1.61E-02	0.073	0.711	0.388	0.163	1.72E-02	0.069	0.707	0.285	0.166	8.57E-02	-0.040	0.610
	time of day (in hours since 9AM)	-0.019	0.027	4.88E-01	-0.071	0.034	-0.027	0.027	3.25E-01	-0.080	0.027	-0.036	0.028	1.91E-01	-0.091	0.018	-0.035	0.028	2.10E-01	-0.091	0.020
	body length (in SD)	-	-	-	-	-	0.154	0.094	1.03E-01	-0.031	0.339	0.042	0.119	7.25E-01	-0.192	0.276	0.048	0.120	6.88E-01	-0.187	0.284
	dorsal body surface area (in SD)	-	-	-	-	-	0.200	0.074	6.56E-03	0.056	0.345	0.075	0.096	4.36E-01	-0.114	0.264	0.061	0.096	5.28E-01	-0.128	0.250
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.122	0.069	7.59E-02	-0.257	0.013
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.021	0.078	7.86E-01	-0.132	0.174
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.237	0.125	5.72E-02	-0.007	0.481	0.303	0.132	2.16E-02	0.044	0.561
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.102	0.107	3.39E-01	-0.311	0.107	-0.177	0.120	1.41E-01	-0.412	0.058
	batch 9	-0.359	0.211	8.86E-02	-0.771	0.054	-0.342	0.225	1.29E-01	-0.783	0.099	-0.213	0.228	3.52E-01	-0.660	0.235	-0.137	0.237	5.63E-01	-0.602	0.328
	batch 10	0.868	0.169	2.57E-07	0.538	1.198	0.682	0.191	3.66E-04	0.307	1.057	0.745	0.191	9.31E-05	0.371	1.119	0.712	0.198	3.15E-04	0.325	1.100
	intercept	3.020	0.173	2.44E-68	2.682	3.359	3.190	0.187	5.89E-65	2.822	3.557	3.106	0.215	1.75E-47	2.686	3.527	3.026	0.236	1.32E-37	2.564	3.489

		Vascular infiltration by neutrophils															
		Model 1 (n=404)					Model 2 (n=404)					Model 3 (n=359)					
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	
fixed factors	**atorvastatin and ezetimibe**	0.088	0.083	2.87E-01	-0.074	0.251	0.080	0.083	3.36E-01	-0.083	0.242	0.052	0.089	5.60E-01	-0.123	0.227	*no observations*
	time of day (in hours since 9AM)	0.023	0.021	2.76E-01	-0.018	0.063	0.020	0.021	3.49E-01	-0.022	0.062	0.003	0.023	8.83E-01	-0.041	0.048	
	body length (in SD)	-	-	-	-	-	0.100	0.055	6.61E-02	-0.007	0.207	0.111	0.057	5.06E-02	0.000	0.223	
	dorsal body surface area (in SD)	-	-	-	-	-	-0.005	0.057	9.28E-01	-0.117	0.106	-0.015	0.062	8.13E-01	-0.137	0.107	
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.020	0.051	7.02E-01	-0.081	0.120	
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.034	0.040	3.92E-01	-0.044	0.112	
	intercept	-0.012	0.151	9.34E-01	-0.308	0.283	-0.006	0.144	9.68E-01	-0.288	0.276	0.048	0.148	7.45E-01	-0.242	0.338	
random factors	***variation by batch***	*0.234*	*0.086*	-	*0.114*	*0.479*	*0.208*	*0.080*	-	*0.098*	*0.441*	*0.205*	*0.083*	-	*0.093*	*0.452*	
	residual	*0.831*	*0.029*	-	*0.775*	*0.891*	*0.827*	*0.029*	-	*0.772*	*0.887*	*0.812*	*0.031*	-	*0.754*	*0.874*	

continued **Supplementary Table 9**

		Vascular co-localization of lipids with neutrophils															
		Model 1 (n=393)					Model 2 (n=393)					Model 3 (n=348)					
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	
negative binomial terms	**atorvastatin and ezetimibe**	-1.113	0.395	4.87E-03	-1.888	-0.338	-1.297	0.433	2.76E-03	-2.146	-0.448	-1.518	0.578	8.67E-03	-2.652	-0.385	*no observations*
	time of day (in hours since 9AM)	-0.094	0.095	3.25E-01	-0.281	0.093	-0.168	0.106	1.15E-01	-0.376	0.041	-0.120	0.120	3.18E-01	-0.355	0.115	
	body length (in SD)	-	-	-	-	-	-1.512	0.322	2.64E-06	-2.143	-0.881	-1.501	0.328	4.61E-06	-2.143	-0.859	
	dorsal body surface area (in SD)	-	-	-	-	-	0.317	0.314	3.13E-01	-0.299	0.934	0.207	0.366	5.72E-01	-0.511	0.925	
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.043	0.232	8.52E-01	-0.499	0.412	
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.193	0.241	4.23E-01	-0.280	0.667	
	batch 1	-1.376	1.000	1.69E-01	-3.335	0.584	-1.183	0.820	1.49E-01	-2.790	0.424	-0.936	0.866	2.80E-01	-2.632	0.761	
	batch 2	-2.393	0.517	3.60E-06	-3.406	-1.381	-0.732	0.654	2.63E-01	-2.015	0.551	-0.237	0.674	7.25E-01	-1.558	1.084	
	batch 3	-1.164	0.563	3.87E-02	-2.267	-0.061	-0.051	0.588	9.32E-01	-1.204	1.103	0.349	0.796	6.61E-01	-1.211	1.909	
	batch 4	-0.811	0.479	9.01E-02	-1.750	0.127	0.545	0.732	4.56E-01	-0.889	1.979	0.841	0.767	2.73E-01	-0.662	2.344	
	intercept	1.997	0.526	1.45E-04	0.967	3.027	1.290	0.612	3.52E-02	0.090	2.491	0.737	0.676	2.76E-01	-0.588	2.062	

		Vascular co-localization of macrophages with neutrophils															
		Model 1 (n=394)					Model 2 (n=394)					Model 3 (n=349)					
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	
fixed factors	**atorvastatin and ezetimibe**	0.139	0.092	1.29E-01	-0.041	0.319	0.136	0.092	1.39E-01	-0.044	0.316	0.159	0.100	1.10E-01	-0.036	0.355	*no observations*
	time of day (in hours since 9AM)	0.033	0.023	1.45E-01	-0.011	0.078	0.034	0.024	1.49E-01	-0.012	0.080	0.026	0.025	2.97E-01	-0.023	0.076	
	body length (in SD)	-	-	-	-	-	0.036	0.060	5.48E-01	-0.082	0.154	0.062	0.063	3.28E-01	-0.062	0.186	
	dorsal body surface area (in SD)	-	-	-	-	-	-0.016	0.063	8.04E-01	-0.140	0.109	-0.092	0.070	1.89E-01	-0.230	0.045	
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.077	0.057	1.80E-01	-0.035	0.188	
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.085	0.044	5.55E-02	-0.002	0.172	
	intercept	-0.178	0.149	2.32E-01	-0.471	0.114	-0.182	0.149	2.23E-01	-0.474	0.111	-0.190	0.166	2.51E-01	-0.515	0.135	
random factors	***variation by batch***	*0.200*	*0.080*	*-*	*0.092*	*0.438*	*0.194*	*0.079*	*-*	*0.087*	*0.432*	*0.234*	*0.094*	*-*	*0.107*	*0.512*	
	residual	*0.906*	*0.032*	*-*	*0.845*	*0.972*	*0.906*	*0.032*	*-*	*0.844*	*0.972*	*0.894*	*0.034*	*-*	*0.830*	*0.964*	

		Endothelial thickness																			
		Model 1 (n=185)					Model 2 (n=185)					Model 3 (n=184)					Model 4 (n=162)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	**atorvastatin and ezetimibe**	-0.085	0.163	6.00E-01	-0.404	0.234	-0.083	0.164	6.14E-01	-0.405	0.239	-0.036	0.160	8.22E-01	-0.350	0.277	-0.036	0.174	8.36E-01	-0.377	0.305
	time of day (in hours since 9AM)	0.031	0.037	4.05E-01	-0.042	0.103	0.030	0.037	4.15E-01	-0.042	0.102	0.014	0.036	6.87E-01	-0.056	0.085	-0.002	0.035	9.48E-01	-0.071	0.066
	body length (in SD)	-	-	-	-	-	-0.029	0.094	7.59E-01	-0.214	0.156	-0.113	0.094	2.30E-01	-0.297	0.071	-0.113	0.094	2.32E-01	-0.297	0.072
	dorsal body surface area (in SD)	-	-	-	-	-	0.075	0.093	4.19E-01	-0.107	0.257	0.020	0.092	8.31E-01	-0.161	0.200	0.007	0.098	9.39E-01	-0.185	0.200
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.001	0.092	9.92E-01	-0.180	0.182
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.057	0.105	5.84E-01	-0.263	0.148
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.390	0.107	2.71E-04	0.180	0.600	0.428	0.113	1.47E-04	0.207	0.648
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.341	0.180	5.76E-02	-0.693	0.011	-0.241	0.179	1.79E-01	-0.593	0.111
	intercept	0.073	0.190	7.03E-01	-0.301	0.446	0.015	0.197	9.39E-01	-0.371	0.401	-0.122	0.190	5.20E-01	-0.495	0.250	-0.127	0.190	5.04E-01	-0.499	0.245
random factors	***variation by batch***	*0.181*	*0.106*	*-*	*0.058*	*0.572*	*0.167*	*0.105*	*-*	*0.048*	*0.576*	*0.114*	*0.105*	*-*	*0.019*	*0.692*	*0.000*	*0.000*	*-*	*0.000*	*1650*
	residual	*0.976*	*0.051*	*-*	*0.881*	*1.081*	*0.974*	*0.051*	*-*	*0.879*	*1.080*	*0.938*	*0.049*	*-*	*0.846*	*1.040*	*0.890*	*0.049*	*-*	*0.798*	*0.992*

Endothelial thickness is defined as surface area of the endothelium normalized for surface area of the circulating lipids. Associations were examined using negative binomial regresion for outcomes that showed a negative binomial distribution; and using hierarchical linear models on inverse normally transformed outcomes for outcomes that were (borderline) normally distributed (i.e. vascular accumulation of oxLDL; vascular infiltration by macrophages and neutrophils; endothelial thickness). Model 1: adjusted for time of day, transgenic background and batch; Model 2: additionally adjusted for body length and dorsal body surface area; Model 3: additionally adjusted for whole-body LDL cholesterol, HDL cholesterol, triglyceride and glucose levels. Dorsal body surface area was normalized for body length using residuals; whole-body LDL cholesterol, HDL cholesterol, triglyceride and glucose levels were normalized for protein level using residuals. Effects shown for atorvastatin and ezetimibe treatment are compared with untreated controls. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 10 - The effect of treatment with atorvastatin and ezetimibe on suboptimal image or image quantification quality

	Vasculature not properly detected																			
	Model 1 (n=927)					Model 2 (n=927)					Model 3 (n=876)					Model 4 (n=454)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
atorvastatin and ezetimibe	0.910	0.200	6.85E-01	0.590	1.410	0.890	0.200	6.04E-01	0.580	1.380	0.910	0.210	6.95E-01	0.580	1.440	0.390	0.140	6.59E-03	0.200	0.770
time of day (in hours since 9AM)	1.040	0.050	4.72E-01	0.940	1.150	1.030	0.050	5.35E-01	0.930	1.140	1.050	0.050	3.38E-01	0.950	1.160	1.100	0.080	1.69E-01	0.960	1.270
body length (in SD)	-	-	-	-	-	0.880	0.100	2.85E-01	0.700	1.110	0.870	0.110	2.43E-01	0.680	1.100	0.840	0.170	3.89E-01	0.570	1.250
dorsal body surface area (in SD)	-	-	-	-	-	1.180	0.130	1.48E-01	0.940	1.460	1.420	0.180	4.62E-03	1.110	1.820	1.570	0.310	2.20E-02	1.070	2.320
LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.880	0.150	4.53E-01	0.630	1.230
HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.780	0.140	1.54E-01	0.550	1.100
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.670	0.080	1.26E-03	0.520	0.850	0.600	0.150	3.77E-02	0.380	0.970
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.850	0.100	1.70E-01	0.680	1.070	0.930	0.240	7.86E-01	0.560	1.550
intercept	0.100	0.030	8.39E-18	0.060	0.170	0.100	0.030	3.43E-17	0.060	0.170	0.090	0.030	9.41E-18	0.050	0.160	0.110	0.040	4.05E-08	0.050	0.250

	Many false positive lipid deposits																			
	Model 1 (n=853)					Model 2 (n=853)					Model 3 (n=804)					Model 4 (n=421)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
atorvastatin and ezetimibe	0.440	0.230	1.23E-01	0.150	1.250	0.460	0.250	1.48E-01	0.160	1.320	0.780	0.440	6.62E-01	0.260	2.370	0.520	0.320	2.87E-01	0.150	1.740
time of day (in hours since 9AM)	1.010	0.110	9.45E-01	0.820	1.250	1.010	0.110	9.39E-01	0.820	1.250	0.960	0.100	7.20E-01	0.780	1.190	1.030	0.120	7.80E-01	0.830	1.280
body length (in SD)	-	-	-	-	-	1.430	0.380	1.69E-01	0.860	2.400	1.010	0.280	9.58E-01	0.590	1.750	1.000	0.310	9.93E-01	0.540	1.840
dorsal body surface area (in SD)	-	-	-	-	-	1.170	0.280	5.23E-01	0.730	1.870	0.950	0.270	8.44E-01	0.550	1.640	1.350	0.470	3.91E-01	0.680	2.680
LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.650	0.180	1.09E-01	0.380	1.100
HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.950	0.250	8.48E-01	0.570	1.590
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	2.500	0.820	5.08E-03	1.320	4.750	2.640	1.050	1.49E-02	1.210	5.770
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.370	0.110	8.64E-04	0.210	0.670	0.400	0.150	1.70E-02	0.190	0.850
intercept	0.030	0.020	3.80E-11	0.010	0.080	0.030	0.010	2.63E-11	0.010	0.070	0.010	0.010	2.61E-12	0.000	0.050	0.020	0.010	4.01E-09	0.010	0.080

	Larva moved during imaging																			
	Model 1 (n=873)					Model 2 (n=873)					Model 3 (n=824)					Model 4 (n=440)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
atorvastatin and ezetimibe	3.510	1.370	1.23E-03	1.640	7.530	3.410	1.370	2.17E-03	1.560	7.480	3.380	1.360	2.43E-03	1.540	7.430	2.060	0.950	1.19E-01	0.830	5.080
time of day (in hours since 9AM)	1.200	0.100	3.36E-02	1.010	1.410	1.210	0.110	4.02E-02	1.010	1.450	1.220	0.110	3.11E-02	1.020	1.470	1.250	0.130	3.24E-02	1.020	1.540
body length (in SD)	-	-	-	-	-	0.390	0.070	5.54E-07	0.270	0.560	0.410	0.080	3.24E-06	0.280	0.590	0.700	0.200	2.04E-01	0.400	1.220
dorsal body surface area (in SD)	-	-	-	-	-	1.430	0.240	3.66E-02	1.020	2.000	1.460	0.270	4.07E-02	1.020	2.100	1.580	0.390	6.33E-02	0.970	2.560
LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.820	0.200	4.10E-01	0.500	1.320
HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.600	0.160	5.92E-02	0.350	1.020
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.920	0.200	7.07E-01	0.610	1.400	0.340	0.130	3.91E-03	0.160	0.700
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.030	0.230	8.80E-01	0.670	1.590	8.660	4.850	1.16E-04	2.890	25.960
intercept	0.010	0.000	5.15E-18	0.000	0.030	0.010	0.000	2.00E-17	0.000	0.020	0.010	0.000	6.94E-17	0.000	0.020	0.010	0.010	1.60E-09	0.000	0.060

	Many false positive oxLDL deposits																			
	Model 1 (n=236)					Model 2 (n=236)					Model 3 (n=233)					Model 4 (n=229)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
atorvastatin and ezetimibe	0.480	0.130	7.66E-03	0.280	0.820	0.520	0.150	1.96E-02	0.300	0.900	0.510	0.150	2.09E-02	0.290	0.900	0.520	0.160	3.14E-02	0.290	0.940
time of day (in hours since 9AM)	0.970	0.060	5.51E-01	0.860	1.080	0.960	0.060	5.12E-01	0.850	1.080	0.960	0.060	5.09E-01	0.850	1.080	0.960	0.060	5.32E-01	0.850	1.090
body length (in SD)	-	-	-	-	-	1.570	0.250	4.91E-03	1.150	2.150	1.730	0.360	7.91E-03	1.160	2.600	1.820	0.390	4.50E-03	1.200	2.760
dorsal body surface area (in SD)	-	-	-	-	-	1.370	0.230	5.87E-02	0.990	1.890	1.540	0.330	4.19E-02	1.020	2.340	1.640	0.350	2.27E-02	1.070	2.500
LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.070	0.170	6.76E-01	0.780	1.470
HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.440	0.260	3.96E-02	1.020	2.040
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.770	0.170	2.31E-01	0.490	1.190	0.810	0.190	3.67E-01	0.500	1.290
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.050	0.270	8.43E-01	0.640	1.730	0.890	0.260	6.92E-01	0.510	1.570
intercept	2.130	0.680	1.88E-02	1.130	4.000	2.250	0.830	2.74E-02	1.090	4.620	2.320	1.070	6.90E-02	0.940	5.730	1.750	0.880	2.60E-01	0.660	4.670

Associations are shown for criteria that resulted in the exclusion of at least 10 larvae. Vasculature not properly detected typically resulted from weak staining, possibly due to low levels of circulating lipids; Many false positives: >20% of true negative objects were falsely detected by the qualtification pipeline; Many false negatives: <20% of true positive objects were detected by the qualtification pipeline. Associations were examined using logistic regression models. Model 1: adjusted for time of day; Model 2: additionally adjusted for body length and dorsal body surface area; Model 3: additionally adjusted for whole-body triglyceride and glucose levels; Model 4: additionally adjusted for whole-body LDL and HDL cholesterol levels. Dorsal body surface area was normalized for body length; whole-body LDL cholesterol, HDL cholesterol, triglyceride and glucose levels were normalized for protein level. Adjusting for transgenic background and batch would have excluded approximately half the larvae. Effects shown for atorvastatin and ezetimibe treatment are compared with untreated controls. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 11 - Orthologues of proof-of-concept genes for dyslipidemia, atherosclerosis and coronary artery disease

Human gene	ENSG	Zebrafish orthologue	ENSDARG	Target %identity	Query %identity	Main human protein	Top hit BLAST	%identity (protein)	Conserved genes in locus
APOE	ENSG00000130203	*apoea*	ENSDARG00000102004	25.65	21.77	ENSP00000252486	ENSDARP00000137865	27.78	*TOMM40*
		apoeb	ENSDARG00000040295	28.11	24.92		ENSDARP00000119141	32.04	*BCAM, NECTIN2*
APOB	ENSG00000084674	*apoba*	ENSDARG00000042780	33.70	32.63	ENSP00000233242	ENSDARP00000062792	34.51	*C2orf43, GDF7, ITSN2, PFN4*
		apobb.1	ENSDARG00000022767	29.68	24.26		ENSDARP00000119179	30.33	NA
		apobb.2	ENSDARG00000075016	29.64	16.46		ENSDARP00000144532	37.37	NA
LDLR	ENSG00000130164	*ldlra*	ENSDARG00000029476	52.80	55.93	ENSP00000252444	ENSDARP00000115492	58.69	*SMARCA4, KRI1, SPC24*
		ldlrb	ENSDARG00000026759	54.06	49.53		ENSDARP00000141207	58.57	*SMARCA4, AP1M2, CDKN2D*

Target %identity: percentage of the orthologous sequence matching the human sequence; Query %identity: percentage of the human sequence matching the sequence of the orthologue; Main human protein: Ensembl protein ID for the main transcript; %identity protein: percentage of the aligned query (input sequence, i.e. main human protein) which is identical to the subject (hit) sequence; conserved genes in locus: neighbouring genes conserved across danio rerio and homo sapiens locus according to Genomicus.

Supplementary Table 12 - Identification of moderate-to-highly active CRISPR-Cas9 guide RNAs for proof-of-concept genes

Human gene	Zebrafish orthologue	CRISPR gRNA target sequence	Genomic location (danRer11/GRCz11) Chr	Pos	Exon	Strand	GC (%)	Self-complementarity	Off-targets 0	1	2	3	Predicted efficiency	CRISPRscan score	Canonical (yes/no)	Target activity (NA[a], no[b], low[c], moderate[d], high[e] or very high[f])	Forward primer	Reverse primer	Product size
		GGCTCTCTCCTGCGCGTAAG	**19**	**10,856,063**	**3 of 4**	**-**	**65**	**0**	**0**	**0**	**0**	**0**	**0.42**	**54**	**yes**	**high**	**AGCACACTGATCTCTGACAGC**	**GATCCTTCGCCTCCTCCATG**	**160**
	apoea	GGATGAGCCAAGAAGCCGCT	19	10,855,768	2 of 4	+	60	2	0	0	0	0	0.52	37	yes	moderate	TCCGTTTTGACTTTGCAGGC	GAGCTGAGTGGCCTTGATGT	155
		GgGGGGCATCAGCCTGGAAC	16	23,961,545	2 of 4	-	65	1	0	0	0	1	0.61	59	no	very high	TGCCTGACTTGCTAATTGTGAT	CCGTCAGTTTGTGTGTTGAGTT	178
		GgTGACGTGAAGAACCGTGT	16	23,962,014	3 of 4	+	50	0	0	0	0	2	0.62	68	no	very high	AGTGAAAATCTCCAAACCCAGA	TGAAGGAGCATCCCAACTTACT	269
APOE		**GAGGGGCATCAGCCTGGAAC**	**16**	**23,961,545**	**2 of 4**	**-**	**65**	**1**	**0**	**0**	**0**	**1**	**0.61**	**59**	**no**	**high**	**CTGTAAATTGCCTGACTTGCTAA**	**GCCCTTGATGTTTTGCACCA**	**208**
	apoeb	GgTGACGTGAAGAACCGTGT	16	23,962,014	3 of 4	+	50	0	0	0	0	2	0.62	68	no	high	CTGCTGGTCAGCTCAGTAAAGA	TGAAGGAGCATCCCAACTTACT	226
		GgGGATCTTCTGGGAGTAGG	16	23,962,897	4 of 4	-	60	0	0	0	0	0	0.59	85	no	moderate	AGGAGAAGCTGGAGGAGACAG	CTCTTAAGCCTGAGTGGGAAGA	170
		GgCATACATGAGCCAGGCCC	16	23,962,700	4 of 4	+	65	1	0	0	0	0	0.58	59	no	moderate	GCAACCTACATGAGTGAGATGC	GTAGGTTCTCGGCTGTCTCCT	220
		GAACTCAACACACAAACTGA	16	23,961,615	2 of 4	+	40	0	0	0	0	8	0.70	25	no	no	CTCCAAACCCAGATGACCCC	CAGTTTGCGTGTGTAGGTGC	201
		gGGGAGGGCTCTATCTTAGG	**17**	**30,717,989**	**24 of 29**	**+**	**55**	**0**	**0**	**0**	**0**	**0**	**0.69**	**100**	**no**	**high**	**CGCACTTTGGAATTCTCCTTAC**	**TCAATTTTGTATGACAGGGGTG**	**185**
		gGATGAGGCAGACAGAGAGG	17	30,708,635	9 of 29	+	60	0	0	0	0	12	0.74	61	no	high	CTCACATGGCAGACACTCTTTC	GGGCCATACTCAGCATATCTCT	172
	apoba	GGACACATTCTGTGGTGCGG	17	30,705,707	4 of 29	-	60	1	0	0	0	5	0.64	48	yes	no	ATGTCACAACCTCTGCAGCTAA	ACTTCTCCATAGCTGCCTGAAA	944
		GGAAGCACTGAGGTTGCTG	17	30,704,770	2 of 29	+	55	1	0	0	0	7	0.60	35	no	no	AGGCCGCCTATTAATTCAGTTT	ATGTCACAACCTCTGCAGCTAA	173
		GgAGTATGGTATCTCCTCAG	17	30,708,080	8 of 29	+	50	0	0	0	0	0	0.59	74	no	no	ATTTTTGTAAAGGGTGGGAACA	AAAAAGCAACAACCCATTTCAT	224
		GgTGCTTTTTGCACAGGCAG	17	30,709,180	11 of 29	-	57	1	0	0	0	0	0.71	44	no	no	TCATTGGTGTCATGGGAAAATA	CACTAGAATGCAGAAAATCCCC	260
		GgAGCTGACAAAGTACCAAG	**20**	**31,273,917**	**13 of 27**	**+**	**50**	**0**	**0**	**0**	**0**	**1**	**0.75**	**54**	**no**	**high**	**CCCTGATTGGTATTGATGGATT**	**GGCCTAGAGTGAGAGGAGAACA**	**228**
		gGGAGTTGAGTTTGTGACGG	20	31,274,651	16 of 27	+	50	0	0	0	0	0	0.61	81	no	moderate	AACTTGCTCGTGACATGGTATG	TTGAGACCACTCTCGTGGTAGA	227
APOB	***apobb.1***	GAGCCAGTTCAGTGGGCTG	20	31,273,334	11 of 27	-	60	2	0	0	0	22	0.47	38	no	moderate	GCAGAGAGGTGCTAATGAAGGT	TGTATACTCACTCCCCGGTCTC	222
		GgGTTCATCCAGATTTGCAG	20	31,277,737	24 of 27	-	45	0	0	0	0	8	0.73	47	no	moderate	TTGACACTTTGTTTGGAAATCG	CCATTGAATTTGTTCTGCAGTG	217
		GAAATCAAGCAGCAAGATGG	20	31,277,192	24 of 27	+	45	0	0	0	1	5	0.70	-	no	moderate	TGTTTAGGATCAACCTTCCTGG	ATTCAAAGGACCAGCCTTGATA	279
		GGCTCTATTTTCTCCATTTG	20	31,272,363	8 of 27	-	40	0	0	0	0	8	0.32	21	yes	no	CAGTCCATCCAATTCAAGACAA	TACAGAGGAACGGTCAAAGGTT	275
		gGATTAGCTGAGCAAGAGGA	**20**	**53,444,329**	**5 of 22**	**-**	**45**	**1**	**0**	**0**	**0**	**7**	**0.61**	**49**	**no**	**moderate**	**GTGGACCCAGCATAAGACATTT**	**AACAAAATAGCAGGGATGCACT**	**226**
		gGGCAGCCTGTTGGACTGCA	20	53,445,660	9 of 22	-	60	5	0	0	0	0	0.40	80	no	moderate	AACATGGTGGCTGCACTAGG	AGCACTTCTCTTCCCTGTAGG	227
	apobb.2	gGGAGTCACAAGTGAGATCC	20	53,445,352	8 of 22	+	55	1	0	0	0	1	0.50	66	no	low	TGCCAAGGTATTGGGTTAGATT	AAAAACATGTTCCTGGTCACCT	216
		gGACAAGTTCAGACCCATCG	20	53,443,193	4 of 22	+	50	1	0	0	0	2	0.59	38	no	no	CCCAGCATCTATGGTCTGTGTA	TTTAATGGAATTGCACCAGTTG	234
		GATCCCCCTCTTAATGTTG	20	53,442,015	3 of 22	-	45	0	0	0	0	2	0.53	34	no	no	AAATCCTCTGAAATTCACCGT	TGGTTTGAAGTGAAAGGACAAA	238
		gGTGAAGGAAATGTTGGCGA	20	53,445,098	7 of 22	+	45	0	0	0	0	4	0.77	62	no	NA	GAGGTGGATGCTGCTGTATATG	AATCTAACCCAATACCTTGGCA	201
	ldlra	**GATTCACGGCAGTATCAGTG**	**3**	**19,304,761**	**2 of 18**	**+**	**50**	**1**	**0**	**0**	**0**	**25**	**0.50**	**50**	**no**	**high**	**TAGCGCATATATCACAACGGAC**	**CCATCACCACAGTCATCAGTTT**	**228**
		GGAAGTGGGGAATGCATACA	3	19,308,392	4 of 18	+	50	0	0	0	0	3	0.46	75	yes	moderate	GACAATTCAGATGAGTTGCCTG	ATACCATCCAGTGATAATCGGC	274
		GGAGCGGATTCTGCGAGCGG	**6**	**102,541**	**1 of 5**	**-**	**70**	**0**	**0**	**0**	**0**	**0**	**0.79**	**66**	**yes**	**high**	**CCCTGGCCTCAACACTACAG**	**ACCCAGAAGAGCAGCAGAAC**	**215**
		gGCGCTGAGGAGTTCCGCTG	6	103,574	3 of 5	+	65	1	0	0	0	1	0.67	80	no	high	CGAGCAGAACTGCGGTAAAT	TGCACTGGAATGCTGTGG	249
		gGGGCACACACTCTCCGCTG	6	103,852	3 of 5	-	70	2	0	0	0	2	0.68	78	no	no	GTGTCCCACACACACACACAC	gtACTCACTGCAGTTGTCCTCG	271
LDLR		GgGTCACGTTAGAGCTCTGA	6	102,589	1 of 5	-	55	0	0	0	0	0	0.52	61	no	no	TTCTGCTCAGAGAGGGAGAATC	GATCAGTGAAACTCACCGGTTC	182
	ldlrb	GgGGATTCTGCGAGCGGTGG	6	102,538	1 of 5	-	70	0	0	0	1	0	0.56	94	no	no	TAACATCACACCACTGCTGGAG	GATCAGTGAAACTCACCGGTTC	270
		GGGAAGTCTGACTGTGAGAA	6	103,441	2 of 5	+	50	2	0	0	0	5	0.51	63	yes	no	TGCTAATGACTCCTCTGCGT	CACACACACAGCAGAGTCAC	216
		GgGTCGGGTCAGTTCAGCTG	6	103,375	2 of 5	+	60	0	0	0	0	2	0.66	70	no	NA	AGACAGGGTGAAacacacacac	agcagagtcacacacCTGAGAG	249
		GgGGAACTCATCCGGCCGGC	6	104,079	4 of 5	-	70	1	0	0	0	0	0.49	-	no	NA	AGTGAGCAAGCGGACACTAAAt	TGAGTGGGCTTGTGTGTTTAAG	258
		GGCACTGCATCTGCTGCTCC	6	103,831	3 of 5	-	65	1	0	0	0	8	0.47	47	yes	NA	GGGTCAGACGAGTGGCTG	GTACTCACTGCAGTTGTCCTCG	162
		GgGTTCCTCTGTGCAGACGG	6	104,093	4 of 5	+	60	1	0	0	1	6	0.75	-	no	NA	AGTGAGCAAGCGGACACTAAAt	TGAGTGGGCTTGTGTGTTTAAG	258

CRISPR gRNA target sequences were preferably selected based on location (i.e. in an early exon that affects all transcripts), complementarity (i.e. no complementarity), and free from predicted off targets. Target activity was examined by micro-injections in eight fertilized eggs in multiplex, followed by fragment length PCR analysis at 3 days post-fertilization. Results from target efficiency testing are shown, where NA: Not available due to failed capilary electrophoresis while estimating the length of the targeted region of an exon; No: 8 of 8 larvae test-injected with the gRNA only showed wildtype sequences; Low: 8 of 8 larvae showed wildtype sequence and fewer than 4 of 8 also contained indel sequence; Moderate: 8 of 8 larvae showed wildtype sequence and >4 of 8 also contained indel sequence; High: 8 of 8 larvae showed wildtype as well as indel sequence; Very high: Fewer than 4 of 8 larvae showed wildtype sequence and all larvae showed indel sequence. Target sequences highlighted in bold were selected and used to generate multiplexed mutant zebrafish. Of note: after completion of the study a new version of the zebrafish genome was released. Data shown for gRNA target sequences are from the new version of the genome (built GRCz11).

Supplementary Table 13 - Unique CRISPR-Cas9-induced mutations for orthologues of proof-of-concept genes

Zebrafish orthologue	Sequence	Annotation	Number of alleles	mean ± SD number of reads
apoea	**ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCTTACGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA**	**119M**	**430**	**1079 ± 766**
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	41M11D67M	91	861 ± 515
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCTGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M8D60M	67	873 ± 498
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	48M5D66M	50	726 ± 397
	ATGATGGACAGCATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	2M4S47M11D67M	30	735 ± 344
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCTCCAAACGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M1S3I67M	29	698 ± 293
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCCCGAGGAGGAGGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	50M2S1M1S1M1S1I63M	15	782 ± 366
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCCCCTCTCTCGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	49M4I2M2S66M	14	636 ± 204
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	48M9D62M	12	577 ± 355
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCTGGCCCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M2S1M1S64M	7	824 ± 601
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	45M11D63M	7	695 ± 234
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCTTGGAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	52M4D1M1S61M	5	862 ± 430
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	35M22D62M	2	828 ± 729
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCTTGATACGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M3I68M	2	664 ± 109
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	47M6D66M	1	2374
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCACGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	50M2D67M	1	552
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	45M9D65M	1	21
apoeb	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTTGCCCCTCGTATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S44M1I2M3S1M2S81M	157	664 ± 416
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTCAAGTGACAGGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S43M1S5I1S88M	116	683 ± 500
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCTGATGGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S39M3S1M4D86M	100	708 ± 413
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTTCCAGGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S133M	91	677 ± 465
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S39M10D84M	75	619 ± 399
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCAGGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S38M6D89M	46	455 ± 273
	TTGTGATTAACTTAGTTTGGTATAAAGTTCAGAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTTATATATATAACAGGCTGATGCCCCTCAGCCGAGATGGGAGGAGATGGTGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGATGGCA	76M9I1S20M1S9M8I53M1S4M	31	47 ± 26
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTTATATATATAACAGGCTGATGCCCCTCAGCCGAGATGGGAGGAGATGGTGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S44M9I1S20M1S9M8I58M	29	32 ± 19
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTTGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S43M10D80M	22	475 ± 380
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTAGGCTAATGCCCCTCAGCCAAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S41M5D5M1S13M1S67M	16	357 ± 294
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGCCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S40M13D80M	11	596 ± 279
	TTGTGATTAACTTAGTTTGGTATAAAGTTCAGAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTTGATAGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	75M7D4M1I79M	9	409 ± 291
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCAGGCTCGTAGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S38M6D7M2S1M1I79M	8	660 ± 346
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S26M18D89M	8	658 ± 158
	TTGTGATTAACTTAGTTTGGTATAAAGTTCAGAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	69M17D79M	7	576 ± 469
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCATCTGGGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S40M2D1S2M2S86M	6	676 ± 235
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTTCCAGGCTGATGCCCCTCAGCCGAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGATGGCA	31M1S65M1S62M1S4M	3	213 ± 81
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGATGGCA	31M1S26M40D62M1S4M	3	205 ± 157
	TTGTGATTAACTTAGTTTGGTATAAAGTTCAGAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTTATATATATAACAGGCTGATGCCCCTCAGCCGAGATGGGAGGAGATGGTGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	76M9I1S20M1S9M8I58M	2	27 ± 10
	TTGTGATTAACTTAGTTTGGTATAAAGTTCAGAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCAGGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	71M5D89M	1	2044
	TTGTGATTAACTTAGTTTGGTATAAAGTTCAGAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	69M11D85M	1	1032
apoba	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTATCTATGAATGGGAGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M11I3S43M1S25M	122	666 ± 434
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	58M15D42M1S25M	119	782 ± 674
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTAGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	64M5D46M1S25M	91	742 ± 433
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	58M14D69M	90	655 ± 474
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTGTGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M4D1M1S40M1S25M	86	752 ± 426
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTAGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	68M1D46M1S25M	76	758 ± 458
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTAGGGGGCAACATCAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	64M5D10M3I36M1S25M	56	795 ± 540
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	58M14D43M1S25M	29	588 ± 284
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTCCCATTCATAACTGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTATAAAATAATGGCCAGCTGCCCCTTAA	69M8I2M1S2I69M	18	627 ± 372
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M11D35M1S25M	16	805 ± 385
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTCTATCTGGAAGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M1S8I45M1S25M	12	612 ± 275
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTATAGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M1I46M1S25M	8	641 ± 302
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTATAAAATAATGGCCAGCTGCCCCTTAA	58M15D68M	7	380 ± 249
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTGTTGATGTTCCCAATTACATTGCTAAGTATAAAATAATGGCCAGCTGCCCCTTAA	67M17D57M	6	698 ± 295
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCAGCAACTTTTATGAATGGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTATAAAATAATGGCCAGCTGCCCCTTAA	68M14I1S1M1S70M	5	497 ± 382
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTTCACAGCTAGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M7I46M1S25M	4	666 ± 97
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTGGGGGGCAATGGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M9I1M1S44M1S25M	3	590 ± 32
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M9D37M1S25M	3	517 ± 460
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	57M13D45M1S25M	2	816 ± 240
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTACACTGTTGATGTTCCCAATTACATTGCTAAGTATAAAATAATGGCCAGCTGCCCCTTAA	65M16D60M	2	681 ± 57
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTATCTTTTATGAATGGGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTATAAAATAATGGCCAGCTGCCCCTTAA	68M13I1M2S70M	1	1120

continued **Supplementary Table 13**

apobb.1	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTACCAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	160M1I24M	252	772 ± 562
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTACCAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	**184M**	**213**	**750 ± 617**
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTACAATGACATTATGCAGAGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	50M1S1M1S1M10I1M1S104M1I24M	101	639 ± 427
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	44M7D109M1I24M	73	651 ± 346
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTAAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	49M2D109M1I24M	24	444 ± 206
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	44M7D133M	14	887 ± 372
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTACCTAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	51M1I109M1I24M	11	678 ± 327
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTAATGTTAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	49M3I2S109M1I24M	6	907 ± 409
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTACAATGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	50M1S1M1S107M1I24M	2	616 ± 257
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	40M14D106M1I24M	2	577 ± 34
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTACAATGACAAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	48M6I2M1S109M1I24M	1	627
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	39M21D124M	1	444
apobb.2	GTCTTTATTATTTCCAGAGCCATCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	22M3D157M	519	912 ± 862
	GTCTTTATTATTTCCAGAGCCATCCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	24M2D156M	62	665 ± 475
	GTCTTTATTATTTCCAGAGCCATCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	22M9D151M	43	426 ± 240
	GTCTTTATTATTTCCAGAGCCATCCTCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	**182M**	**21**	**437 ± 240**
	GTCTTTATTATTTCCAGAGCCAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	21M16D145M	18	704 ± 578
	GTCTTTATTATTTCCAGAGCCATCCTTGCTTAGCTTGCTCAGCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGC	26M16I156M	13	508 ± 367
	GTCTTTATTATTTCCAGAGCCATCCAGACAACCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	25M7S3M2S2M1S142M	9	467 ± 183
	GTCTTTATTATTTCCAGAGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	18M11D153M	6	751 ± 461
	GTCTTTATTATTTCCAGAGCCATCTTTCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	24M1I1S157M	5	22 ± 35
	GTCTTTATTATTTCCAGAGCCATCCTGGAAATAAGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	26M5I3S153M	4	170 ± 141
	GTCTTTATTATTTCCAGAGCCATCAGAGCATCCAGAGCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	24M11I2S156M	3	730 ± 640
	GTCTTTATTATTTCCAGAGCCATCTTTCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTAGTTTAGAGATCTGCCT	24M1I1S140M1S16M	3	5 ± 3
	GTCTTTATTATGCAGATATTATGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	11M7D2M5S1M2S154M	2	109 ± 13
	GTCTTTATTATTTCCAGAGCCATCAGCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	24M2S156M	1	1439
	GTCTTTATTATTTCCAGAGCCATCCTCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTAGTTTAGAGATCTGCCT	165M1S16M	1	7
ldlra	**GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG**	**184M**	**241**	**1176 ± 838**
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCACTACAGTAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	134M1S2M1S2I1S45M	159	982 ± 595
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCATGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	140M1D43M	119	1179 ± 722
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTATGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S128M	64	888 ± 609
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	139M1I45M	53	937 ± 655
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTATGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S78M8D42M	47	891 ± 617
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	134M8D42M	42	832 ± 397
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	132M6D46M	21	741 ± 441
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTATGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTGATTCACGGCAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S80M7I2S46M	7	528 ± 324
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTATGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S83M1I45M	4	395 ± 245
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAATGGAAAGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	140M1S1M5I42M	2	1236 ± 827
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTATGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S76M6D46M	2	655 ± 65
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTATGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S81M6D9M1I32M	1	1152
ldlrb	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	70M4D101M	208	484 ± 494
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACATTCTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	70M1I2S103M	178	276 ± 256
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	69M3D103M	113	212 ± 180
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACCGCCATCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	73M2I102M	56	238 ± 156
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	69M7D99M	22	164 ± 239
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACCGAAGAATCGCAGAATCCGAGAATCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	72M20I1S102M	16	297 ± 208
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACCGCAGGGAGAATCTCTCTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCACTAACGTGACGCTGATGGAGCCCCGGGTCGGCGCTCGGCTCGTCTGCTCG	72M14I52M1S33M1S16M	15	303 ± 287
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCTCTCTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	68M1D1S1M1S103M	12	143 ± 116
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACCGCTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCACTAACGTGACGCTGATGGAGCCCCGGGTCGGCGCTCGGCTCGTCTGCTCG	63M9D52M1S33M1S16M	11	583 ± 305
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	69M13D93M	11	547 ± 354
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACCGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	71M67D37M	8	822 ± 500
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACCTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	70M2D103M	4	584 ± 872
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCTCCGCATTCTGTTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	68M1S4M7I102M	2	1064
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACCGCTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	**175M**	**2**	**7**

Annotation shows the sequential number of base pairs that - when compared with the reference genome from Ensembl - represent a match (M), deletion (D), insertion (I), or substitution (S). For each unique sequence, the number of alleles in which it was observed is shown, as well as the mean and standard deviation for the number of reads that were observed for the sequence.

Supplementary Table 14 - Unique CRISPR-Cas9-induced variants in the most prominently observed sequence(s) and their predicted functional consequences

Zebrafish orthologue	Chr	Start	End	Mutation	Nett base pair change	Annotation VEP	VEP impact	$n_{affected\ alleles}$
		10,856,052	10,856,073	CTCCAAACTGGCCCCTTACGCG/-	-22	frameshift variant	high	2
		10,856,058	10,856,068	ACTGGCCCCTT/-	-11	frameshift variant	high	116
		10,856,062	10,856,070	GCCCCTTAC/-	-9	inframe deletion	moderate	1
		10,856,062	10,856,072	GCCCCTTACGC/-	-11	frameshift variant	high	7
		10,856,064	10,856,069	CCCTTA/-	-6	inframe deletion	moderate	1
		10,856,065	10,856,069	CCTTA/-	-5	frameshift variant	high	49
		10,856,065	10,856,073	CCTTACGCG/-	-9	inframe deletion	moderate	12
		10,856,066	10,856,065	-/CCCT	4	frameshift variant	high	14
		10,856,067	10,856,068	TT/AG	0	missense variant	moderate	15
		10,856,067	10,856,068	TT/-	-2	frameshift variant	high	1
apoea	19	10,856,068	10,856,067	-/TGA	3	stop gained,inframe insertion	high	2
		10,856,068	10,856,068	T/C	0	missense variant	moderate	29
		10,856,068	10,856,069	TA/GG	0	missense variant	moderate	7
		10,856,068	10,856,069	TA/CT	0	missense variant	moderate	14
		10,856,068	10,856,075	TACGCGCA/-	-8	frameshift variant	high	65
		10,856,069	10,856,068	-/CAA	3	protein altering variant	moderate	29
		10,856,069	10,856,072	ACGC/-	-4	frameshift variant	high	5
		10,856,070	10,856,070	C/G	0	stop gained	high	15
		10,856,071	10,856,071	G/C	0	missense variant	moderate	7
		10,856,072	10,856,072	C/A	0	missense variant	moderate	15
		10,856,073	10,856,072	-/G	1	frameshift variant	high	15
		10,856,074	10,856,074	C/G	0	missense variant	moderate	5
		23,961,533	23,961,550	CCAGGCTCGTAGCCTGTT/-	-18	inframe deletion	moderate	7
		23,961,533	23,961,572	CCAGGCTCGTAGCCTGTTCCAGG CTGATGCCCCTCAGCCC/-	-40	frameshift variant	high	3
		23,961,544	23,961,554	GCCTGTTCCAG/-	-11	frameshift variant	high	1
		23,961,544	23,961,560	GCCTGTTCCAGGCTGAT/-	-17	frameshift variant	high	4
		23,961,545	23,961,550	CCTGTT/-	-6	inframe deletion	moderate	47
		23,961,546	23,961,548	CTG/TGA	0	stop gained	high	58
		23,961,546	23,961,550	CTGTT/-	-5	frameshift variant	high	1
		23,961,546	23,961,555	CTGTTCCAGG/-	-10	frameshift variant	high	45
		23,961,547	23,961,548	TG/-	-2	frameshift variant	high	5
		23,961,547	23,961,559	TGTTCCAGGCTGA/-	-13	frameshift variant	high	8
		23,961,548	23,961,552	GTTCC/-	-5	frameshift variant	high	11
		23,961,549	23,961,549	T/A	0	missense variant	moderate	5
apoeb	16	23,961,550	23,961,550	T/C	0	missense variant	moderate	68
		23,961,550	23,961,553	TCCA/-	-4	frameshift variant	high	58
		23,961,550	23,961,556	TCCAGGC/-	-7	frameshift variant	high	8
		23,961,550	23,961,559	TCCAGGCTGA/-	-10	frameshift variant	high	17
		23,961,551	23,961,550	-/AAGTG	5	frameshift variant	high	68
		23,961,551	23,961,550	-/ATATATATA	9	protein altering variant	moderate	62
		23,961,551	23,961,550	-/G	1	frameshift variant	high	97
		23,961,551	23,961,551	C/A	0	missense variant	moderate	130
		23,961,552	23,961,553	CA/TG	0	missense variant	moderate	5
		23,961,553	23,961,555	AGG/CCT	0	missense variant	moderate	97
		23,961,557	23,961,558	TG/GT	0	missense variant	moderate	97
		23,961,558	23,961,558	G/A	0	missense variant	moderate	11
		23,961,558	23,961,559	GA/CG	0	missense variant	moderate	7
		23,961,561	23,961,560	-/A	1	frameshift variant	high	15
		23,961,572	23,961,572	C/A	0	synonymous variant	low	11
		30,717,993	30,718,005	AGGGCTCTATCTT/-	-13	frameshift variant	high	2
		30,717,994	30,718,007	GGGCTCTATCTTAG/-	-14	frameshift variant	high	119
		30,717,994	30,718,008	GGGCTCTATCTTAGG/-	-15	inframe deletion	moderate	103
		30,718,000	30,718,004	TATCT/-	-5	frameshift variant	high	139
		30,718,001	30,718,016	ATCTTAGGGGGCAACA/-	-16	frameshift variant	high	2
		30,718,003	30,718,019	CTTAGGGGGCAACAACA/-	-17	frameshift variant	high	6
		30,718,004	30,718,003	-/AGCAACTTTTATGA	14	frameshift variant	high	5
		30,718,004	30,718,003	-/TATCTTTTATGAA	13	stop gained,frameshift variant	high	1
		30,718,004	30,718,004	T/-	-1	frameshift variant	high	68
		30,718,004	30,718,004	T/A	0	missense variant	moderate	5
		30,718,005	30,718,004	-/ATCTATGAATG	11	stop gained,frameshift variant	high	103
		30,718,005	30,718,004	-/TCACAGC	7	frameshift variant	high	4
		30,718,005	30,718,004	-/GGGGGGCAA	9	protein altering variant	moderate	3
apoba	17	30,718,005	30,718,004	-/CCCATTCA	8	frameshift variant	high	18
		30,718,005	30,718,004	-/A	1	frameshift variant	high	8
		30,718,005	30,718,005	T/C	0	missense variant	moderate	12
		30,718,005	30,718,006	TA/GG	0	missense variant	moderate	1
		30,718,005	30,718,007	TAG/GGA	0	missense variant	moderate	103
		30,718,005	30,718,008	TAGG/-	-4	frameshift variant	high	70
		30,718,005	30,718,013	TAGGGGGCA/-	-9	inframe deletion	moderate	3
		30,718,005	30,718,015	TAGGGGGCAAC/-	-11	frameshift variant	high	16
		30,718,006	30,718,005	-/TATCTGGA	8	frameshift variant	high	12
		30,718,006	30,718,006	A/G	0	synonymous variant	low	8
		30,718,007	30,718,007	G/A	0	missense variant	moderate	18
		30,718,008	30,718,007	-/CT	2	frameshift variant	high	18
		30,718,010	30,718,010	G/T	0	missense variant	moderate	70
		30,718,015	30,718,014	-/CAT	3	inframe insertion	moderate	48
		31,273,922	31,273,942	TGACAAAGTACCAAGGGGCAA/-	-21	inframe deletion	moderate	1
		31,273,923	31,273,936	GACAAAGTACCAAG/-	-14	frameshift variant	high	2
apobb.1	20	31,273,927	31,273,933	AAGTACC/-	-7	frameshift variant	high	82
		31,273,931	31,273,930	-/ACAATG	6	stop gained,inframe insertion	high	1
		31,273,932	31,273,931	-/ATG	3	inframe insertion	moderate	6
		31,273,932	31,273,933	CC/TT	0	missense variant	moderate	6

continued **Supplementary Table 14**

Zebrafish orthologue	Chr	Start	End	Mutation	Nett base pair change	Annotation VEP	VEP impact	$n_{affected\ alleles}$
		31,273,932	31,273,933	CC/-	-2	frameshift variant	high	24
		31,273,933	31,273,933	C/A	0	missense variant	moderate	94
apobb.1	20	31,273,934	31,273,933	-/T	1	frameshift variant	high	11
		31,273,935	31,273,935	A/T	0	missense variant	moderate	93
		31,273,937	31,273,936	-/ACATTATGCA	10	frameshift variant	high	91
		31,273,938	31,273,938	G/A	0	missense variant	moderate	91
		53,444,321	53,444,327	TTCCAGA/-	-7	splice acceptor variant,coding sequence variant,intron variant	high	2
		53,444,328	53,444,338	GCCATCCTCTT/-	-11	frameshift variant,splice region variant	high	3
		53,444,330	53,444,334	CATCC/AGATA	0	missense variant	moderate	2
		53,444,331	53,444,346	ATCCTCTTGCTCAGCT/-	-16	frameshift variant	high	12
		53,444,332	53,444,334	TCC/-	-3	inframe deletion	moderate	307
		53,444,332	53,444,340	TCCTCTTGC/-	-9	inframe deletion	moderate	33
		53,444,334	53,444,333	-/AGAGCATCCAG	11	frameshift variant	high	3
		53,444,334	53,444,333	-/T	1	frameshift variant	high	8
apobb.2	20	53,444,334	53,444,334	C/T	0	missense variant	moderate	8
		53,444,334	53,444,335	CT/AG	0	missense variant	moderate	4
		53,444,334	53,444,335	CT/-	-2	frameshift variant	high	51
		53,444,335	53,444,341	TCTTGCT/AGACAAC	0	missense variant	moderate	9
		53,444,336	53,444,335	-/GGAAA	5	frameshift variant	high	4
		53,444,336	53,444,335	-/TGCTTAGCTTGCTCAG	16	frameshift variant	high	13
		53,444,336	53,444,337	CT/TA	0	missense variant	moderate	2
		53,444,336	53,444,338	CTT/TAA	0	stop gained	high	4
		53,444,345	53,444,346	CT/AC	0	missense variant	moderate	9
		53,444,349	53,444,349	T/C	0	missense variant	moderate	9
		19,304,770	19,304,775	CAGTAT/-	-6	inframe deletion	moderate	22
		19,304,772	19,304,772	G/C	0	missense variant	moderate	97
		19,304,772	19,304,779	GTATCAGT/-	-8	frameshift variant	high	63
		19,304,774	19,304,773	-/GATTCAC	7	stop gained,frameshift variant	high	7
		19,304,774	19,304,775	AT/GG	0	missense variant	moderate	7
		19,304,775	19,304,775	T/C	0	synonymous variant	low	97
ldlra	3	19,304,775	19,304,780	TCAGTG/-	-6	inframe deletion	moderate	1
		19,304,776	19,304,775	-/AG	2	frameshift variant	high	97
		19,304,776	19,304,776	C/T	0	stop gained	high	97
		19,304,777	19,304,776	-/A	1	frameshift variant	high	39
		19,304,778	19,304,778	G/-	-1	frameshift variant	high	73
		19,304,778	19,304,778	G/A	0	synonymous variant	low	2
		19,304,780	19,304,779	-/GGAAA	5	frameshift variant	high	2
		19,304,790	19,304,789	-/A	1	frameshift variant	high	1
		102,538	102,546	CCGCCACCG/-	-9	upstream gene variant	modifier	7
		102,543	102,543	A/T	0	upstream gene variant	modifier	1
		102,543	102,543	A/-	-1	upstream gene variant	modifier	7
		102,544	102,544	C/T	0	upstream gene variant	modifier	7
		102,544	102,546	CCG/-	-3	upstream gene variant	modifier	75
		102,544	102,550	CCGCTCG/-	-7	upstream gene variant	modifier	15
		102,544	102,556	CCGCTCGCAGAAT/-	-13	upstream gene variant	modifier	7
		102,545	102,544	-/A	1	upstream gene variant	modifier	120
		102,545	102,546	CG/-	-2	upstream gene variant	modifier	3
		102,545	102,546	CG/TT	0	upstream gene variant	modifier	120
ldlrb	6	102,545	102,548	CGCT/-	-4	upstream gene variant	modifier	140
		102,546	102,546	G/T	0	upstream gene variant	modifier	7
		102,546	102,612	GCTCGCAGAATCCGCTCCCGGTA CAGAACAGCATCTCTATCCGCCC TCAGAGCTCTAACGTGACGCT/-	-67	upstream gene variant	modifier	5
		102,547	102,546	-/AAGAATCGCAGAATCCGAGA	20	upstream gene variant	modifier	9
		102,547	102,546	-/CAGGGAGAATCTCT	14	upstream gene variant	modifier	9
		102,547	102,547	C/A	0	upstream gene variant	modifier	9
		102,548	102,547	-/CA	2	upstream gene variant	modifier	40
		102,548	102,547	-/ATTCTGT	7	upstream gene variant	modifier	1

VEP: Ensembl's variant effect predictor; $n_{affected\ alleles}$: the number of alleles across the 384 sequenced larvae in which the variant was observed (possible range 0 to 768)

Supplementary Table 15 - Sequencing results expressed in number of mutated alleles for proof-of-concept genes

Zebrafish orthologue	Number of affected alleles			Missing genotypes	Total	Non-missing	Mutant allele freq	P_{HWE_LR}
	0	1	2					
apoea	112	202	66	1	381	380	0.439	1.45E-01
apoeb	37	11	315	18	381	363	0.883	2.53E-35
apoba	0	0	377	4	381	377	1.000	-
apobb.1	149	166	34	32	381	349	0.335	1.89E-01
apobb.2	0	22	332	27	381	354	0.969	-
ldlra	120	63	197	1	381	380	0.601	8.60E-40
ldlrb	1	0	327	25	353	328	0.997	-

The number of affected alleles located in a ±30 base pair window around the CRISPR cut site, without taking into account the variants' probability of affecting protein function. P_{HWE_LR}: *P*- value for a Hardy-Weinberg equilibrium (HWE) likelihood-ratio chi-squared statistic (*P* <2.9E-3 is significant after Bonferroni correction). For both *apoeb* and *ldlra* , there were more larvae carrying two mutated alleles than expected under HWE.

Supplementary Table 16 - The effect of a genetic burden score on body size

		Body length (n=339)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	-0.047	0.028	9.33E-02	-0.103	0.008
	apoba	0.022	0.231	9.24E-01	-0.431	0.475
	apobb.2	0.455	0.167	6.58E-03	0.127	0.783
	ldlrb	2.135	1.852	2.49E-01	-1.495	5.766
	time of day (in hours since 9AM)	-0.022	0.037	5.54E-01	-0.095	0.051
	intercept	-1.439	0.914	1.15E-01	-3.230	0.351
random factors	***variance by batch***	*0.469*	*0.129*	-	*0.274*	*0.804*
	residual	*0.724*	*0.028*	-	*0.671*	*0.781*

		Dorsal body surface area (n=339)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	0.001	0.033	9.76E-01	-0.063	0.065
	apoba	0.165	0.267	5.36E-01	-0.358	0.689
	apobb.2	-0.459	0.194	1.78E-02	-0.838	-0.079
	ldlrb	-2.781	2.142	1.94E-01	-6.979	1.417
	time of day (in hours since 9AM)	0.028	0.043	5.21E-01	-0.057	0.112
	intercept	1.335	1.054	2.05E-01	-0.731	3.400
random factors	***variance by batch***	*0.503*	*0.140*	-	*0.291*	*0.868*
	residual	*0.837*	*0.033*	-	*0.776*	*0.904*

		Lateral body surface area (n=335)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	0.005	0.034	8.79E-01	-0.061	0.071
	apoba	0.153	0.276	5.79E-01	-0.387	0.693
	apobb.2	-0.221	0.198	2.63E-01	-0.609	0.166
	ldlrb	-2.306	2.189	2.92E-01	-6.595	1.983
	time of day (in hours since 9AM)	0.020	0.044	6.52E-01	-0.066	0.106
	intercept	0.814	1.078	4.50E-01	-1.299	2.927
random factors	***variance by batch***	*0.483*	*0.135*	-	*0.279*	*0.835*
	residual	*0.854*	*0.033*	-	*0.791*	*0.922*

		Body volume (n=328)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	0.009	0.033	7.93E-01	-0.056	0.074
	apoba	0.152	0.270	5.75E-01	-0.378	0.682
	apobb.2	-0.309	0.196	1.15E-01	-0.694	0.075
	ldlrb	-2.617	2.141	2.21E-01	-6.814	1.579
	time of day (in hours since 9AM)	0.041	0.044	3.46E-01	-0.045	0.128
	intercept	1.000	1.060	3.46E-01	-1.078	3.078
random factors	***variance by batch***	*0.494*	*0.137*	-	*0.287*	*0.851*
	residual	*0.834*	*0.033*	-	*0.772*	*0.902*

A genetic burden score was calculated by summing the dosage scores for *apoea* , *apoeb* , *apobb.1* and *ldlra.* Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models and were adjusted for mutations in *apoba* , *apobb.2* and *ldlrb* , time of day and batch. Effects shown for the genetic burden score are for each additional mutated allele. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 17 - The effect of a genetic burden score on whole-body lipid and glucose levels

		LDL cholesterol levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	0.052	0.035	1.35E-01	-0.016	0.120
	apoba	0.019	0.290	9.47E-01	-0.549	0.588
	apobb.2	0.302	0.211	1.52E-01	-0.111	0.715
	ldlrb	-3.424	2.424	1.58E-01	-8.175	1.327
	time of day (in hours since 9AM)	0.055	0.043	1.97E-01	-0.029	0.139
	intercept	0.595	1.167	6.10E-01	-1.693	2.883
random factors	***variance by batch***	*0.355*	*0.123*	-	*0.181*	*0.699*
	residual	*0.951*	*0.035*	-	*0.885*	*1.022*

		HDL cholesterol levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	0.067	0.032	3.40E-02	0.005	0.129
	apoba	0.050	0.263	8.49E-01	-0.465	0.565
	apobb.2	0.312	0.190	1.01E-01	-0.061	0.685
	ldlrb	0.841	2.192	7.01E-01	-3.455	5.136
	time of day (in hours since 9AM)	-0.028	0.040	4.77E-01	-0.107	0.050
	intercept	-1.071	1.070	3.17E-01	-3.168	1.027
random factors	***variance by batch***	*0.589*	*0.159*	-	*0.346*	*1.001*
	residual	*0.857*	*0.031*	-	*0.798*	*0.921*

		Triglyceride levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	0.014	0.025	5.72E-01	-0.035	0.064
	apoba	-0.098	0.210	6.43E-01	-0.510	0.315
	apobb.2	-0.326	0.152	3.25E-02	-0.625	-0.027
	ldlrb	-0.351	1.754	8.41E-01	-3.790	3.088
	time of day (in hours since 9AM)	-0.146	0.032	5.92E-06	-0.210	-0.083
	intercept	0.987	0.885	2.64E-01	-0.747	2.721
random factors	***variance by batch***	*0.781*	*0.200*	-	*0.473*	*1.290*
	residual	*0.686*	*0.025*	-	*0.638*	*0.737*

		Total cholesterol levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	-0.031	0.030	3.01E-01	-0.091	0.028
	apoba	0.165	0.252	5.13E-01	-0.329	0.659
	apobb.2	-0.064	0.183	7.28E-01	-0.422	0.294
	ldlrb	-0.850	2.102	6.86E-01	-4.970	3.269
	time of day (in hours since 9AM)	0.083	0.039	3.24E-02	0.007	0.158
	intercept	0.109	1.042	9.17E-01	-1.933	2.150
random factors	***variance by batch***	*0.754*	*0.199*	-	*0.449*	*1.267*
	residual	*0.822*	*0.030*	-	*0.765*	*0.883*

continued **Supplementary Table 17**

		Glucose levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	-0.047	0.035	1.74E-01	-0.116	0.021
	apoba	-0.080	0.290	7.82E-01	-0.649	0.489
	apobb.2	-0.364	0.211	8.44E-02	-0.777	0.049
	ldlrb	-1.790	2.424	4.60E-01	-6.542	2.961
	time of day (in hours since 9AM)	0.044	0.043	3.06E-01	-0.040	0.129
	intercept	1.458	1.169	2.12E-01	-0.833	3.748
random factors	***variance by batch***	*0.380*	*0.120*	-	*0.204*	*0.706*
	residual	*0.951*	*0.035*		*0.885*	*1.022*

A genetic burden score was calculated by summing the dosage scores for *apoea* , *apoeb* , *apobb.1* and *ldlra.* Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models and were adjusted for mutations in *apoba* , *apobb.2* and *ldlrb* , time of day and batch. Effects shown for the genetic burden score are for each additional mutated allele. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 18 - The effect of a genetic burden score on vascular atherogenic traits

		Vascular lipid deposition														
		Model 1 (n=306)					Model 2 (n=272)					Model 3 (n=272)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	genetic burden score	0.233	0.064	2.81E-04	0.107	0.359	0.202	0.073	5.81E-03	0.059	0.346	0.176	0.077	2.29E-02	0.024	0.327
	apoba	-0.075	0.556	8.93E-01	-1.165	1.016	-0.147	0.572	7.98E-01	-1.267	0.974	0.187	0.549	7.34E-01	-0.890	1.263
	apobb.2	-0.693	0.506	1.70E-01	-1.684	0.297	-0.666	0.471	1.57E-01	-1.589	0.257	-0.371	0.418	3.75E-01	-1.191	0.448
	ldlrb	18.109	3.317	4.76E-08	11.608	24.609	19.711	3.363	4.61E-09	13.119	26.303	18.757	3.209	5.08E-09	12.466	25.047
	time of day (in hours since 9AM)	-0.118	0.094	2.08E-01	-0.302	0.066	-0.198	0.107	6.37E-02	-0.408	0.011	-0.163	0.110	1.38E-01	-0.379	0.052
	body length (in SD)	-	-	-	-	-	-0.285	0.144	4.72E-02	-0.567	-0.004	-0.207	0.153	1.77E-01	-0.508	0.094
	dorsal body surface area (in SD)	-	-	-	-	-	0.150	0.129	2.43E-01	-0.102	0.403	0.183	0.130	1.58E-01	-0.071	0.438
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.088	0.092	3.38E-01	-0.270	0.093
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.035	0.129	7.87E-01	-0.287	0.218
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.318	0.182	8.06E-02	-0.039	0.674
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.120	0.107	2.60E-01	-0.330	0.089
	batch 1	2.442	0.485	4.84E-07	1.491	3.394	2.791	0.557	5.35E-07	1.700	3.882	2.808	0.611	4.29E-06	1.611	4.005
	batch 2	0.979	0.560	8.05E-02	-0.119	2.076	1.060	0.596	7.52E-02	-0.108	2.227	1.363	0.692	4.90E-02	0.006	2.719
	batch 3	1.114	0.510	2.89E-02	0.115	2.113	1.411	0.553	1.07E-02	0.327	2.495	1.363	0.568	1.64E-02	0.250	2.476
	batch 4	1.555	0.585	7.87E-03	0.408	2.702	1.548	0.583	7.97E-03	0.404	2.691	1.627	0.584	5.32E-03	0.483	2.771
	batch 5	2.749	0.595	3.76E-06	1.584	3.915	2.987	0.648	4.01E-06	1.718	4.257	2.541	0.703	3.01E-04	1.163	3.919
	batch 6	2.541	0.509	5.95E-07	1.543	3.538	3.058	0.609	5.12E-07	1.864	4.251	2.488	0.654	1.42E-04	1.206	3.769
	batch 7	1.695	0.564	2.64E-03	0.590	2.799	2.100	0.689	2.30E-03	0.750	3.450	1.791	0.697	1.02E-02	0.425	3.157
	intercept	-3.897	1.815	3.18E-02	-7.454	-0.339	-4.338	1.729	1.21E-02	-7.728	-0.949	-4.795	1.685	4.44E-03	-8.098	-1.492

		Vascular infiltration by macrophages														
		Model 1 (n=368)					Model 2 (n=328)					Model 3 (n=328)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	genetic burden score	-0.076	0.032	1.76E-02	-0.139	-0.013	-0.087	0.035	1.22E-02	-0.155	-0.019	-0.099	0.035	5.04E-03	-0.168	-0.030
	apoba	-0.115	0.267	6.68E-01	-0.639	0.409	-0.089	0.284	7.54E-01	-0.645	0.467	-0.101	0.283	7.20E-01	-0.655	0.453
	apobb.2	-0.264	0.194	1.73E-01	-0.645	0.116	-0.371	0.210	7.71E-02	-0.782	0.040	-0.427	0.212	4.38E-02	-0.842	-0.012
	ldlrb	-0.253	2.213	9.09E-01	-4.591	4.085	-0.537	2.267	8.13E-01	-4.980	3.906	-0.522	2.266	8.18E-01	-4.963	3.919
	time of day (in hours since 9AM)	0.036	0.041	3.82E-01	-0.044	0.116	0.036	0.046	4.33E-01	-0.054	0.126	0.038	0.046	4.16E-01	-0.053	0.128
	body length (in SD)	-	-	-	-	-	0.072	0.071	3.09E-01	-0.067	0.211	0.075	0.072	2.92E-01	-0.065	0.216
	dorsal body surface area (in SD)	-	-	-	-	-	-0.049	0.061	4.22E-01	-0.167	0.070	-0.046	0.061	4.47E-01	-0.166	0.073
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.055	0.055	3.11E-01	-0.052	0.162
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.086	0.061	1.60E-01	-0.034	0.205
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.021	0.074	7.80E-01	-0.124	0.165
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.040	0.054	4.62E-01	-0.146	0.066
	intercept	0.932	1.078	3.87E-01	-1.181	3.045	1.214	1.119	2.78E-01	-0.980	3.408	1.358	1.119	2.25E-01	-0.835	3.551
random factors	*variance by batch*	*0.506*	*0.138*	-	*0.296*	*0.865*	*0.510*	*0.144*	-	*0.293*	*0.887*	*0.475*	*0.138*	-	*0.269*	*0.839*
	residual	*0.866*	*0.032*	-	*0.805*	*0.932*	*0.883*	*0.035*	-	*0.817*	*0.954*	*0.879*	*0.035*	-	*0.813*	*0.950*

continued **Supplementary Table 18**

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=301)					Model 2 (n=269)					Model 3 (n=269)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**genetic burden score**	0.066	0.092	4.71E-01	-0.114	0.247	0.029	0.095	7.59E-01	-0.158	0.216	0.010	0.103	9.25E-01	-0.192	0.211
	apoba	0.259	0.869	7.65E-01	-1.443	1.962	0.072	0.832	9.31E-01	-1.559	1.703	0.481	0.875	5.82E-01	-1.233	2.196
	apobb.2	-0.765	0.587	1.92E-01	-1.917	0.386	-0.754	0.557	1.76E-01	-1.846	0.338	-0.360	0.493	4.65E-01	-1.327	0.607
	ldlrb	15.180	3.761	5.43E-05	7.809	22.551	17.068	3.698	3.93E-06	9.819	24.316	15.483	3.640	2.10E-05	8.350	22.616
	time of day (in hours since 9AM)	0.022	0.101	8.24E-01	-0.175	0.219	-0.041	0.113	7.16E-01	-0.262	0.180	0.042	0.123	7.36E-01	-0.200	0.283
	body length (in SD)	-	-	-	-	-	-0.397	0.204	5.16E-02	-0.796	0.003	-0.338	0.230	1.42E-01	-0.789	0.113
	dorsal body surface area (in SD)	-	-	-	-	-	0.067	0.148	6.52E-01	-0.223	0.357	0.061	0.149	6.81E-01	-0.231	0.354
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.119	0.150	4.29E-01	-0.414	0.176
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.182	0.153	2.35E-01	-0.118	0.482
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.482	0.241	4.59E-02	0.009	0.955
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.128	0.139	3.56E-01	-0.400	0.144
	batch 1	1.324	0.750	7.74E-02	-0.146	2.793	1.525	0.835	6.76E-02	-0.110	3.161	1.415	0.877	1.07E-01	-0.303	3.133
	batch 2	0.132	0.926	8.87E-01	-1.683	1.946	0.012	0.969	9.90E-01	-1.887	1.912	0.018	0.994	9.86E-01	-1.931	1.967
	batch 3	0.273	0.753	7.17E-01	-1.203	1.748	0.252	0.781	7.46E-01	-1.278	1.782	0.152	0.771	8.44E-01	-1.360	1.663
	batch 4	1.378	0.834	9.84E-02	-0.256	3.011	0.986	0.849	2.46E-01	-0.679	2.650	0.851	0.818	2.98E-01	-0.752	2.454
	batch 5	1.816	0.868	3.65E-02	0.114	3.517	1.766	0.917	5.43E-02	-0.033	3.564	1.203	0.969	2.14E-01	-0.696	3.102
	batch 6	0.740	0.789	3.48E-01	-0.806	2.286	1.264	0.933	1.76E-01	-0.565	3.094	0.589	1.029	5.67E-01	-1.427	2.606
	batch 7	-0.383	0.915	6.76E-01	-2.176	1.411	-0.144	1.066	8.92E-01	-2.234	1.945	-0.449	1.121	6.89E-01	-2.645	1.748
	intercept	-4.162	2.165	5.46E-02	-8.406	0.082	-4.308	2.087	3.90E-02	-8.399	-0.217	-4.870	2.132	2.23E-02	-9.049	-0.692

		Vascular infiltration by neutrophils														
		Model 1 (n=371)					Model 2 (n=330)					Model 3 (n=330)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	**genetic burden score**	-0.018	0.033	5.78E-01	-0.082	0.046	-0.026	0.035	4.57E-01	-0.094	0.042	-0.029	0.035	4.10E-01	-0.098	0.040
	apoba	0.096	0.272	7.24E-01	-0.436	0.628	0.144	0.284	6.11E-01	-0.412	0.701	0.140	0.283	6.20E-01	-0.414	0.695
	apobb.2	-0.084	0.198	6.71E-01	-0.472	0.304	0.016	0.211	9.40E-01	-0.397	0.429	0.003	0.213	9.90E-01	-0.414	0.420
	ldlrb	-2.023	2.259	3.71E-01	-6.451	2.405	-1.483	2.282	5.16E-01	-5.955	2.990	-1.459	2.286	5.23E-01	-5.940	3.021
	time of day (in hours since 9AM)	0.012	0.041	7.65E-01	-0.067	0.092	-0.020	0.045	6.55E-01	-0.107	0.067	-0.022	0.045	6.20E-01	-0.110	0.065
	body length (in SD)	-	-	-	-	-	-0.122	0.070	7.94E-02	-0.258	0.014	-0.114	0.070	1.04E-01	-0.252	0.023
	dorsal body surface area (in SD)	-	-	-	-	-	0.060	0.059	3.12E-01	-0.056	0.176	0.075	0.060	2.11E-01	-0.043	0.193
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.002	0.053	9.65E-01	-0.103	0.107
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.081	0.060	1.79E-01	-0.037	0.200
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.042	0.071	5.50E-01	-0.181	0.097
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.060	0.054	2.71E-01	-0.046	0.166
	intercept	0.845	1.091	4.38E-01	-1.293	2.983	0.536	1.116	6.31E-01	-1.651	2.723	0.570	1.117	6.10E-01	-1.619	2.759
random factors	***variance by batch***	*0.356*	*0.101*	-	*0.204*	*0.622*	*0.323*	*0.097*	-	*0.179*	*0.582*	*0.297*	*0.092*	-	*0.162*	*0.545*
	residual	*0.885*	*0.033*	-	*0.823*	*0.952*	*0.890*	*0.035*	-	*0.824*	*0.962*	*0.888*	*0.035*	-	*0.822*	*0.959*

continued **Supplementary Table 18**

		Vascular co-localization of lipids with neutrophils														
		Model 1 (n=304)					Model 2 (n=271)					Model 3 (n=271)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**genetic burden score**	0.454	0.100	5.63E-06	0.258	0.650	0.383	0.122	1.73E-03	0.144	0.623	0.276	0.143	5.37E-02	-0.004	0.556
	apoba	0.301	1.127	7.90E-01	-1.908	2.510	0.098	1.173	9.33E-01	-2.201	2.397	1.046	1.072	3.29E-01	-1.055	3.147
	apobb.2	0.231	0.553	6.76E-01	-0.854	1.316	0.185	0.608	7.61E-01	-1.006	1.376	0.909	0.674	1.78E-01	-0.412	2.230
	ldlrb	9.320	3.741	1.27E-02	1.987	16.653	10.263	3.782	6.66E-03	2.850	17.677	11.151	3.863	3.89E-03	3.580	18.722
	time of day (in hours since 9AM)	-0.074	0.165	6.54E-01	-0.398	0.250	-0.176	0.187	3.46E-01	-0.542	0.190	-0.198	0.169	2.43E-01	-0.529	0.134
	body length (in SD)	-	-	-	-	-	-0.513	0.274	6.16E-02	-1.051	0.025	-0.632	0.269	1.88E-02	-1.159	-0.105
	dorsal body surface area (in SD)	-	-	-	-	-	-0.004	0.224	9.87E-01	-0.443	0.436	-0.074	0.208	7.23E-01	-0.482	0.334
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.540	0.255	3.42E-02	0.040	1.040
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.627	0.304	3.93E-02	0.031	1.224
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.083	0.290	1.93E-04	0.513	1.652
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.095	0.204	6.40E-01	-0.304	0.495
	batch 1	3.896	0.963	5.19E-05	2.009	5.782	4.110	1.000	3.93E-05	2.151	6.069	5.318	1.174	5.95E-06	3.016	7.620
	batch 2	1.723	1.095	1.16E-01	-0.423	3.870	1.735	1.136	1.27E-01	-0.492	3.961	4.159	1.448	4.08E-03	1.320	6.997
	batch 3	2.330	1.086	3.19E-02	0.201	4.459	2.510	1.103	2.29E-02	0.348	4.672	3.085	1.143	6.97E-03	0.844	5.327
	batch 4	3.533	1.056	8.17E-04	1.464	5.603	3.288	1.086	2.47E-03	1.159	5.416	4.296	1.067	5.67E-05	2.205	6.388
	batch 5	4.590	1.077	2.01E-05	2.480	6.700	4.720	1.103	1.86E-05	2.559	6.881	4.782	1.145	2.98E-05	2.537	7.027
	batch 6	3.473	1.027	7.17E-04	1.461	5.485	3.780	1.064	3.79E-04	1.695	5.865	4.115	1.142	3.15E-04	1.876	6.353
	batch 7	1.922	1.340	1.51E-01	-0.704	4.549	2.988	1.521	4.95E-02	0.007	5.969	3.253	1.429	2.29E-02	0.451	6.054
	intercept	-8.759	2.629	8.62E-04	-13.911	-3.607	-8.322	2.696	2.03E-03	-13.606	-3.037	-11.768	2.659	9.61E-06	-16.980	-6.557

		Vascular co-localization of macrophages with neutrophils														
		Model 1 (n=367)					Model 2 (n=327)					Model 3 (n=327)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	**genetic burden score**	-0.034	0.051	5.09E-01	-0.135	0.067	-0.038	0.054	4.75E-01	-0.143	0.067	-0.031	0.054	5.64E-01	-0.137	0.075
	apoba	0.113	0.404	7.80E-01	-0.679	0.904	0.332	0.399	4.05E-01	-0.450	1.115	0.379	0.398	3.41E-01	-0.401	1.159
	apobb.2	-0.264	0.319	4.07E-01	-0.888	0.360	-0.414	0.358	2.47E-01	-1.116	0.287	-0.319	0.341	3.50E-01	-0.988	0.350
	ldlrb	0.251	0.678	7.11E-01	-1.077	1.580	0.266	0.795	7.38E-01	-1.293	1.824	0.856	0.918	3.51E-01	-0.944	2.656
	time of day (in hours since 9AM)	0.069	0.067	2.98E-01	-0.061	0.200	0.085	0.071	2.29E-01	-0.053	0.223	0.069	0.074	3.50E-01	-0.076	0.214
	body length (in SD)	-	-	-	-	-	0.304	0.112	6.88E-03	0.083	0.524	0.252	0.121	3.66E-02	0.016	0.489
	dorsal body surface area (in SD)	-	-	-	-	-	0.261	0.110	1.83E-02	0.044	0.477	0.253	0.116	2.90E-02	0.026	0.479
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.086	0.094	3.62E-01	-0.098	0.270
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.035	0.102	7.33E-01	-0.235	0.165
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.037	0.127	7.72E-01	-0.285	0.211
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.106	0.083	2.04E-01	-0.058	0.270
	batch 1	0.408	0.310	1.87E-01	-0.199	1.015	0.202	0.333	5.44E-01	-0.450	0.854	0.379	0.391	3.33E-01	-0.388	1.147
	batch 2	0.285	0.518	5.82E-01	-0.730	1.301	0.309	0.482	5.21E-01	-0.636	1.254	0.488	0.498	3.27E-01	-0.488	1.464
	batch 3	-0.610	0.376	1.04E-01	-1.346	0.126	-0.727	0.373	5.13E-02	-1.459	0.004	-0.553	0.403	1.69E-01	-1.343	0.236
	batch 4	0.938	0.390	1.60E-02	0.175	1.702	1.045	0.410	1.07E-02	0.242	1.849	1.091	0.443	1.39E-02	0.222	1.960
	batch 5	0.216	0.351	5.38E-01	-0.472	0.903	-0.098	0.362	7.88E-01	-0.807	0.612	0.113	0.419	7.88E-01	-0.709	0.935
	batch 6	-1.562	0.358	1.27E-05	-2.263	-0.861	-2.156	0.413	1.80E-07	-2.966	-1.346	-2.009	0.434	3.73E-06	-2.860	-1.158
	batch 7	-0.454	0.460	3.24E-01	-1.355	0.448	-1.079	0.517	3.67E-02	-2.092	-0.067	-0.986	0.599	9.96E-02	-2.160	0.188
	intercept	3.911	0.862	5.66E-06	2.222	5.600	3.929	0.927	2.24E-05	2.113	5.746	3.325	0.975	6.47E-04	1.415	5.236

A genetic burden score was calculated by summing the dosage scores for *apoea* , *apoeb* , *apobb.1* and *ldlra* . Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models and were adjusted for mutations in *apoba* , *apobb.2* and *ldlrb* , time of day and batch. Effects shown for the genetic burden score are for each additional mutated allele. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 19 - The effect of two vs. zero mutated alleles in apoea, apoeb, apobb.1 or ldlra on body size

		Body length																			
		apoea					*apoeb*					*apobb.1*					*ldlra*				
		44 vs. 96 larvae with 2 vs 0 mutated alleles					212 vs. 34 larvae with 2 vs 0 mutated alleles					30 vs. 130 larvae with 2 vs 0 mutated alleles					165 vs. 105 larvae with 2 vs 0 mutated				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	**2 vs. 0 mutated alleles**	0.057	0.146	6.95E-01	-0.229	0.343	-0.086	0.157	5.84E-01	-0.394	0.222	-1.071	0.149	7.19E-13	-1.364	-0.779	0.155	0.114	1.73E-01	-0.068	0.379
	apoea	-	-	-	-	-	0.036	0.074	6.27E-01	-0.109	0.181	-0.013	0.089	8.80E-01	-0.187	0.160	-0.002	0.071	9.77E-01	-0.141	0.137
	apoeb	-0.035	0.107	7.40E-01	-0.244	0.174	-	-	-	-	-	0.012	0.084	8.84E-01	-0.152	0.177	0.014	0.075	8.49E-01	-0.133	0.162
	apobb.1	-0.460	0.096	1.67E-06	-0.648	-0.272	-0.221	0.081	6.38E-03	-0.380	-0.062	-	-	-	-	-	-0.397	0.075	1.19E-07	-0.544	-0.250
	ldlra	0.044	0.078	5.69E-01	-0.108	0.197	0.022	0.065	7.36E-01	-0.106	0.150	0.081	0.080	3.08E-01	-0.075	0.238	-	-	-	-	-
	time of day (in hours since 9AM)	0.006	0.054	9.15E-01	-0.101	0.112	-0.026	0.044	5.56E-01	-0.111	0.060	0.077	0.047	1.02E-01	-0.015	0.168	-0.057	0.040	1.58E-01	-0.136	0.022
	intercept	-4.855	59.467	9.35E-01	-121.409	111.699	15.036	51.182	7.69E-01	-85.278	115.351	104.827	63.695	9.98E-02	-20.013	229.667	-1.214	0.932	1.93E-01	-3.041	0.614
	apoba	0.041	0.370	9.13E-01	-0.685	0.766	0.266	0.291	3.60E-01	-0.304	0.835	-0.408	0.320	2.02E-01	-1.035	0.219	-0.046	0.278	8.69E-01	-0.590	0.499
	apobb.2	0.404	0.247	1.02E-01	-0.081	0.889	0.423	0.183	2.12E-02	0.063	0.782	0.526	0.196	7.37E-03	0.141	0.911	0.359	0.178	4.39E-02	0.010	0.708
	ldlrb	10.731	148.645	9.42E-01	-280.607	302.069	-40.149	128.002	7.54E-01	-291.028	210.729	-263.194	159.306	9.85E-02	-575.428	49.041	2.336	1.790	1.92E-01	-1.172	5.844
random factors	***variance by batch***	*0.445*	*0.136*	-	*0.245*	*0.810*	*0.508*	*0.142*	-	*0.294*	*0.879*	*0.454*	*0.136*	-	*0.252*	*0.815*	*0.472*	*0.131*	-	*0.274*	*0.812*
	residual	*0.666*	*0.041*	-	*0.590*	*0.752*	*0.695*	*0.032*	-	*0.635*	*0.760*	*0.633*	*0.036*	-	*0.566*	*0.709*	*0.694*	*0.030*	-	*0.637*	*0.756*

		Dorsal body surface area																			
		apoea					*apoeb*					*apobb.1*					*ldlra*				
		44 vs. 96 larvae with 2 vs 0 mutated alleles					212 vs. 34 larvae with 2 vs 0 mutated alleles					30 vs. 130 larvae with 2 vs 0 mutated alleles					165 vs. 105 larvae with 2 vs 0 mutated				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	**2 vs. 0 mutated alleles**	-0.138	0.162	3.93E-01	-0.456	0.179	0.261	0.181	1.50E-01	-0.094	0.615	0.215	0.190	2.58E-01	-0.158	0.588	-0.166	0.139	2.32E-01	-0.439	0.106
	apoea	-	-	-	-	-	-0.126	0.085	1.39E-01	-0.293	0.041	-0.257	0.112	2.20E-02	-0.478	-0.037	-0.117	0.087	1.77E-01	-0.287	0.053
	apoeb	-0.015	0.119	8.98E-01	-0.248	0.218	-	-	-	-	-	-0.006	0.107	9.56E-01	-0.216	0.204	0.064	0.092	4.87E-01	-0.116	0.244
	apobb.1	0.287	0.107	7.43E-03	0.077	0.498	0.037	0.093	6.96E-01	-0.147	0.220	-	-	-	-	-	0.137	0.092	1.34E-01	-0.042	0.317
	ldlra	-0.078	0.087	3.72E-01	-0.249	0.093	-0.081	0.075	2.80E-01	-0.229	0.066	0.048	0.101	6.36E-01	-0.151	0.247	-	-	-	-	-
	time of day (in hours since 9AM)	0.106	0.059	7.53E-02	-0.011	0.222	0.044	0.050	3.79E-01	-0.053	0.141	0.000	0.058	9.95E-01	-0.114	0.115	0.066	0.049	1.76E-01	-0.029	0.161
	intercept	13.639	66.393	8.37E-01	-116.489	143.766	73.698	58.862	2.11E-01	-41.669	189.065	-102.710	81.214	2.06E-01	-261.885	56.466	0.913	1.132	4.20E-01	-1.306	3.131
	apoba	0.509	0.414	2.19E-01	-0.302	1.321	-0.089	0.334	7.90E-01	-0.745	0.567	-0.083	0.406	8.38E-01	-0.880	0.714	0.273	0.339	4.21E-01	-0.392	0.938
	apobb.2	-0.305	0.277	2.70E-01	-0.847	0.237	-0.372	0.211	7.87E-02	-0.786	0.043	-0.542	0.250	3.04E-02	-1.032	-0.051	-0.400	0.218	6.65E-02	-0.826	0.027
	ldlrb	-36.318	165.957	8.27E-01	-361.589	288.952	-183.074	147.212	2.14E-01	-471.605	105.458	259.291	203.127	2.02E-01	-138.832	657.413	-2.739	2.185	2.10E-01	-7.021	1.544
random factors	***variance by batch***	*0.403*	*0.146*	-	*0.199*	*0.818*	*0.451*	*0.135*	-	*0.251*	*0.812*	*0.425*	*0.133*	-	*0.230*	*0.783*	*0.453*	*0.131*	-	*0.256*	*0.800*
	residual	*0.745*	*0.046*	-	*0.660*	*0.842*	*0.801*	*0.037*	-	*0.732*	*0.877*	*0.808*	*0.046*	-	*0.722*	*0.905*	*0.849*	*0.037*	-	*0.779*	*0.925*

		Lateral body surface area																			
		apoea					*apoeb*					*apobb.1*					*ldlra*				
		43 vs. 95 larvae with 2 vs 0 mutated alleles					211 vs. 33 larvae with 2 vs 0 mutated alleles					30 vs. 128 larvae with 2 vs 0 mutated alleles					164 vs. 103 larvae with 2 vs 0 mutated				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	**2 vs. 0 mutated alleles**	-0.260	0.167	1.20E-01	-0.587	0.068	0.337	0.193	8.04E-02	-0.041	0.714	0.041	0.195	8.35E-01	-0.341	0.422	-0.027	0.141	8.46E-01	-0.305	0.250
	apoea	-	-	-	-	-	-0.150	0.089	9.23E-02	-0.324	0.025	-0.343	0.116	3.02E-03	-0.570	-0.116	-0.143	0.088	1.02E-01	-0.315	0.029
	apoeb	0.091	0.123	4.63E-01	-0.151	0.332	-	-	-	-	-	0.037	0.110	7.35E-01	-0.178	0.252	0.128	0.094	1.72E-01	-0.056	0.313
	apobb.1	0.259	0.112	2.05E-02	0.040	0.479	0.000	0.098	9.99E-01	-0.191	0.192	-	-	-	-	-	0.041	0.093	6.58E-01	-0.141	0.223
	ldlra	-0.020	0.091	8.25E-01	-0.199	0.159	-0.058	0.080	4.64E-01	-0.214	0.098	0.054	0.105	6.08E-01	-0.152	0.259	-	-	-	-	-
	time of day (in hours since 9AM)	0.072	0.061	2.40E-01	-0.048	0.191	0.067	0.052	1.95E-01	-0.034	0.168	-0.017	0.060	7.73E-01	-0.135	0.100	0.034	0.049	4.92E-01	-0.062	0.130
	intercept	2.580	68.557	9.70E-01	-131.789	136.950	66.633	61.642	2.80E-01	-54.183	187.448	-95.130	82.967	2.52E-01	-257.743	67.483	0.881	1.146	4.42E-01	-1.364	3.126
	apoba	0.228	0.430	5.97E-01	-0.616	1.071	-0.071	0.355	8.42E-01	-0.766	0.624	-0.171	0.418	6.82E-01	-0.989	0.647	-0.040	0.345	9.08E-01	-0.717	0.637
	apobb.2	0.181	0.286	5.27E-01	-0.380	0.742	-0.066	0.221	7.64E-01	-0.498	0.366	-0.345	0.256	1.77E-01	-0.847	0.156	-0.198	0.220	3.67E-01	-0.629	0.232
	ldlrb	-9.404	171.364	9.56E-01	-345.272	326.464	-166.932	154.152	2.79E-01	-469.064	135.199	240.229	207.510	2.47E-01	-166.484	646.941	-1.960	2.207	3.74E-01	-6.287	2.366
random factors	***variance by batch***	*0.382*	*0.141*	-	*0.185*	*0.787*	*0.455*	*0.135*	-	*0.254*	*0.812*	*0.432*	*0.137*	-	*0.231*	*0.805*	*0.442*	*0.127*	-	*0.252*	*0.776*
	residual	*0.770*	*0.048*	-	*0.681*	*0.870*	*0.836*	*0.039*	-	*0.764*	*0.915*	*0.826*	*0.048*	-	*0.737*	*0.925*	*0.855*	*0.038*	-	*0.784*	*0.932*

continued **Supplementary Table 19**

		Body volume																			
		apoea					***apoeb***					***apobb.1***					***ldlra***				
		43 vs. 90 larvae with 2 vs 0 mutated alleles					**206 vs. 32 larvae with 2 vs 0 mutated alleles**					**29 vs. 125 larvae with 2 vs 0 mutated alleles**					**161 vs. 100 larvae with 2 vs 0 mutated**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.209	0.161	1.94E-01	-0.525	0.107	0.352	0.191	6.49E-02	-0.022	0.726	0.074	0.193	7.02E-01	-0.304	0.452	-0.086	0.142	5.44E-01	-0.365	0.193
	apoea	-	-	-	-	-	-0.126	0.089	1.56E-01	-0.299	0.048	-0.288	0.115	1.24E-02	-0.514	-0.062	-0.108	0.089	2.24E-01	-0.281	0.066
	apoeb	0.058	0.121	6.29E-01	-0.178	0.295	-	-	-	-	-	0.042	0.107	6.93E-01	-0.168	0.253	0.111	0.095	2.41E-01	-0.075	0.298
	apobb.1	0.282	0.110	1.02E-02	0.067	0.497	0.009	0.097	9.23E-01	-0.182	0.200	-	-	-	-	-	0.063	0.094	5.07E-01	-0.122	0.247
	ldlra	-0.014	0.088	8.72E-01	-0.188	0.159	-0.059	0.078	4.47E-01	-0.213	0.094	0.086	0.104	4.10E-01	-0.118	0.289	-	-	-	-	-
	time of day (in hours since 9AM)	0.123	0.060	4.13E-02	0.005	0.242	0.078	0.052	1.30E-01	-0.023	0.180	0.006	0.060	9.25E-01	-0.112	0.124	0.062	0.050	2.16E-01	-0.036	0.159
	intercept	13.835	65.406	8.32E-01	-114.357	142.028	56.403	61.175	3.57E-01	-63.497	176.303	-92.716	81.151	2.53E-01	-251.770	66.338	0.730	1.147	5.25E-01	-1.518	2.978
	apoba	0.332	0.411	4.19E-01	-0.474	1.138	-0.167	0.346	6.30E-01	-0.845	0.512	-0.234	0.409	5.68E-01	-1.034	0.567	0.167	0.346	6.30E-01	-0.511	0.844
	apobb.2	0.022	0.285	9.39E-01	-0.536	0.579	-0.182	0.219	4.06E-01	-0.611	0.247	-0.424	0.253	9.33E-02	-0.920	0.071	-0.269	0.223	2.27E-01	-0.707	0.168
	ldlrb	-37.762	163.498	8.17E-01	-358.212	282.688	-140.614	152.985	3.58E-01	-440.459	159.231	234.401	202.978	2.48E-01	-163.428	632.231	-2.413	2.199	2.73E-01	-6.723	1.898
random factors	***variance by batch***	*0.368*	*0.134*	-	*0.181*	*0.750*	*0.449*	*0.134*	-	*0.251*	*0.805*	*0.434*	*0.134*	-	*0.237*	*0.796*	*0.468*	*0.133*	-	*0.269*	*0.817*
	residual	*0.732*	*0.047*	-	*0.646*	*0.829*	*0.814*	*0.038*	-	*0.742*	*0.892*	*0.804*	*0.047*	-	*0.717*	*0.902*	*0.850*	*0.038*	-	*0.779*	*0.927*

Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis and examined using hierarchical linear models. Effects shown are for larvae with two mutated alleles that are highly likely to affect protein function as predicted by Ensembl's Varient Effect Predictor (VEP) compared with larvae with zero CRISPR-mutated alleles. Associations were adjusted for the number of mutated alleles in the other six orthologues, weighted by their predicted effect on protein function, as well as for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 20 - The effect of two vs. zero mutated alleles in *apoea* , *apoeb* , *apobb.1* or *ldlra* on whole-body lipid and glucose levels

		LDL cholesterol levels																			
		apoea					***apoeb***					***apobb.1***					***ldlra***				
		44 vs. 96 larvae with 2 vs 0 mutated alleles					**212 vs. 34 larvae with 2 vs 0 mutated alleles**					**30 vs. 130 larvae with 2 vs 0 mutated alleles**					**165 vs. 105 larvae with 2 vs 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.494	0.194	1.08E-02	0.114	0.873	0.164	0.206	4.25E-01	-0.239	0.567	-0.205	0.218	3.48E-01	-0.632	0.223	-0.080	0.147	5.87E-01	-0.367	0.208
	apoea	-	-	-	-	-	0.242	0.097	1.21E-02	0.053	0.431	0.163	0.123	1.85E-01	-0.078	0.404	0.133	0.094	1.57E-01	-0.051	0.317
	apoeb	0.030	0.141	8.31E-01	-0.247	0.307	-	-	-	-	-	0.040	0.118	7.32E-01	-0.191	0.272	0.075	0.099	4.47E-01	-0.118	0.268
	apobb.1	-0.026	0.134	8.46E-01	-0.288	0.236	0.014	0.108	8.95E-01	-0.197	0.225	-	-	-	-	-	0.003	0.101	9.74E-01	-0.195	0.201
	ldlra	-0.087	0.109	4.22E-01	-0.301	0.126	-0.015	0.083	8.62E-01	-0.178	0.149	-0.022	0.111	8.44E-01	-0.240	0.196	-	-	-	-	-
	time of day (in hours since 9AM)	-0.051	0.063	4.20E-01	-0.175	0.073	0.068	0.051	1.83E-01	-0.032	0.168	0.046	0.060	4.42E-01	-0.072	0.164	0.047	0.050	3.45E-01	-0.050	0.144
	intercept	27.315	78.833	7.29E-01	-127.196	181.825	42.957	64.470	5.05E-01	-83.401	169.315	96.277	89.628	2.83E-01	-79.391	271.946	0.132	1.258	9.16E-01	-2.332	2.597
	apoba	0.466	0.525	3.75E-01	-0.563	1.496	0.042	0.378	9.11E-01	-0.698	0.782	0.044	0.459	9.24E-01	-0.855	0.942	0.364	0.368	3.22E-01	-0.356	1.085
	apobb.2	0.557	0.350	1.11E-01	-0.128	1.242	0.412	0.243	9.00E-02	-0.064	0.888	0.326	0.281	2.46E-01	-0.224	0.876	0.265	0.238	2.66E-01	-0.202	0.731
	ldlrb	-72.128	197.119	7.14E-01	-458.474	314.217	-110.280	161.325	4.94E-01	-426.471	205.911	-243.081	224.383	2.79E-01	-682.863	196.702	-3.696	2.490	1.38E-01	-8.576	1.184
random factors	***variance by batch***	*0.202*	*0.140*	-	*0.052*	*0.787*	*0.315*	*0.126*	-	*0.144*	*0.689*	*0.203*	*0.383*	-	*0.005*	*8.145*	*0.356*	*0.136*		*0.168*	*0.753*
	residual	*0.977*	*0.057*	-	*0.871*	*1.094*	*0.967*	*0.042*	-	*0.889*	*1.052*	*0.958*	*0.063*	-	*0.842*	*1.090*	*0.972*	*0.040*		*0.896*	*1.054*

		HDL cholesterol levels																			
		apoea					***apoeb***					***apobb.1***					***ldlra***				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.123	0.190	5.15E-01	-0.248	0.495	0.223	0.180	2.16E-01	-0.130	0.577	0.253	0.189	1.79E-01	-0.116	0.623	0.072	0.132	5.85E-01	-0.187	0.331
	apoea	-	-	-	-	-	0.035	0.086	6.80E-01	-0.132	0.203	-0.040	0.109	7.12E-01	-0.254	0.174	-0.010	0.085	9.02E-01	-0.177	0.156
	apoeb	-0.058	0.132	6.59E-01	-0.317	0.200	-	-	-	-	-	0.148	0.102	1.47E-01	-0.052	0.347	0.073	0.088	4.08E-01	-0.100	0.246
	apobb.1	0.011	0.124	9.29E-01	-0.233	0.255	0.037	0.095	6.93E-01	-0.148	0.223	-	-	-	-	-	0.118	0.090	1.90E-01	-0.059	0.296
	ldlra	0.130	0.101	1.99E-01	-0.068	0.328	0.104	0.073	1.56E-01	-0.040	0.248	0.090	0.098	3.60E-01	-0.103	0.283	-	-	-	-	-
	time of day (in hours since 9AM)	-0.077	0.066	2.42E-01	-0.206	0.052	-0.065	0.047	1.66E-01	-0.157	0.027	-0.109	0.056	5.18E-02	-0.219	0.001	-0.014	0.046	7.59E-01	-0.105	0.076
	intercept	79.225	73.332	2.80E-01	-64.504	222.954	-2.809	57.043	9.61E-01	-114.611	108.993	-22.711	77.230	7.69E-01	-174.080	128.657	-0.979	1.141	3.91E-01	-3.216	1.257
	apoba	0.053	0.489	9.13E-01	-0.905	1.012	-0.412	0.333	2.16E-01	-1.065	0.240	0.014	0.404	9.73E-01	-0.777	0.805	0.088	0.330	7.89E-01	-0.558	0.735
	apobb.2	0.444	0.324	1.70E-01	-0.191	1.078	0.196	0.214	3.60E-01	-0.223	0.614	0.210	0.243	3.88E-01	-0.266	0.686	0.229	0.213	2.84E-01	-0.189	0.646
	ldlrb	-199.333	183.370	2.77E-01	-558.731	160.065	7.909	142.733	9.56E-01	-271.843	287.661	55.951	193.319	7.72E-01	-322.947	434.849	0.810	2.237	7.17E-01	-3.574	5.194
random factors	***variance by batch***	*0.570*	*0.172*	-	*0.316*	*1.029*	*0.579*	*0.160*	-	*0.336*	*0.997*	*0.528*	*0.161*	-	*0.290*	*0.958*	*0.584*	*0.162*	-	*0.340*	*1.005*
	residual	*0.901*	*0.052*	-	*0.804*	*1.008*	*0.847*	*0.036*	-	*0.779*	*0.921*	*0.822*	*0.045*	-	*0.739*	*0.914*	*0.869*	*0.036*	-	*0.801*	*0.942*

		Triglyceride levels																			
		apoea					***apoeb***					***apobb.1***					***ldlra***				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.265	0.141	6.00E-02	-0.541	0.011	-0.052	0.145	7.21E-01	-0.336	0.233	0.251	0.139	7.06E-02	-0.021	0.522	0.034	0.104	7.41E-01	-0.169	0.238
	apoea	-	-	-	-	-	-0.075	0.069	2.77E-01	-0.210	0.060	-0.093	0.081	2.51E-01	-0.251	0.066	-0.037	0.067	5.80E-01	-0.168	0.094
	apoeb	-0.021	0.097	8.26E-01	-0.210	0.168	-	-	-	-	-	-0.057	0.075	4.44E-01	-0.204	0.089	-0.037	0.069	5.93E-01	-0.173	0.099
	apobb.1	0.012	0.091	8.93E-01	-0.166	0.190	0.115	0.076	1.30E-01	-0.034	0.265	-	-	-	-	-	0.078	0.071	2.75E-01	-0.062	0.217
	ldlra	0.034	0.074	6.46E-01	-0.111	0.179	0.022	0.059	7.15E-01	-0.094	0.138	0.045	0.073	5.33E-01	-0.097	0.188	-	-	-	-	-
	time of day (in hours since 9AM)	-0.146	0.050	3.27E-03	-0.244	-0.049	-0.126	0.038	9.97E-04	-0.201	-0.051	-0.145	0.042	5.90E-04	-0.228	-0.062	-0.181	0.037	8.37E-07	-0.253	-0.109
	intercept	43.986	53.653	4.12E-01	-61.173	149.145	21.252	46.003	6.44E-01	-68.911	111.415	36.478	56.734	5.20E-01	-74.719	147.675	0.872	0.924	3.46E-01	-0.940	2.684
	apoba	0.079	0.358	8.25E-01	-0.622	0.780	-0.091	0.268	7.35E-01	-0.616	0.435	0.025	0.298	9.32E-01	-0.558	0.609	-0.012	0.259	9.64E-01	-0.520	0.497
	apobb.2	-0.401	0.236	8.97E-02	-0.865	0.062	-0.402	0.172	1.96E-02	-0.739	-0.064	-0.538	0.179	2.59E-03	-0.889	-0.188	-0.246	0.167	1.42E-01	-0.574	0.082
	ldlrb	-108.252	134.160	4.20E-01	-371.202	154.697	-50.755	115.105	6.59E-01	-276.357	174.846	-88.498	142.009	5.33E-01	-366.830	189.835	-0.338	1.759	8.48E-01	-3.786	3.110
random factors	***variance by batch***	*0.789*	*0.209*	-	*0.470*	*1.326*	*0.810*	*0.209*	-	*0.489*	*1.342*	0.720	0.188	-	0.431	1.203	*0.784*	*0.202*	-	*0.473*	*1.299*
	residual	*0.657*	*0.038*	-	*0.587*	*0.736*	*0.681*	*0.029*	-	*0.626*	*0.741*	0.603	0.033	-	0.543	0.671	*0.682*	*0.028*	-	*0.629*	*0.740*

continued **Supplementary Table 20**

		Total cholesterol levels																			
		apoea					***apoeb***					***apobb.1***					***ldlra***				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.204	0.168	2.25E-01	-0.126	0.534	0.049	0.178	7.82E-01	-0.300	0.399	-0.881	0.184	1.63E-06	-1.241	-0.521	-0.084	0.116	4.70E-01	-0.311	0.144
	apoea	-	-	-	-	-	0.135	0.085	1.11E-01	-0.031	0.301	0.074	0.107	4.88E-01	-0.135	0.283	0.066	0.075	3.80E-01	-0.081	0.212
	apoeb	0.076	0.116	5.09E-01	-0.150	0.303	-	-	-	-	-	0.007	0.099	9.47E-01	-0.188	0.201	0.031	0.077	6.89E-01	-0.121	0.183
	apobb.1	-0.351	0.109	1.29E-03	-0.565	-0.137	-0.221	0.094	1.84E-02	-0.404	-0.037	-	-	-	-	-	-0.171	0.079	3.09E-02	-0.327	-0.016
	ldlra	-0.018	0.089	8.43E-01	-0.191	0.156	-0.007	0.073	9.21E-01	-0.150	0.135	0.070	0.096	4.64E-01	-0.118	0.259	-	-	-	-	-
	time of day (in hours since 9AM)	0.133	0.059	2.44E-02	0.017	0.249	0.094	0.047	4.32E-02	0.003	0.186	0.097	0.055	8.01E-02	-0.012	0.205	0.088	0.041	3.17E-02	0.008	0.168
	intercept	28.011	64.334	6.63E-01	-98.081	154.104	17.441	56.457	7.57E-01	-93.213	128.096	108.667	75.188	1.48E-01	-38.698	256.031	0.097	1.023	9.24E-01	-1.908	2.102
	apoba	0.657	0.429	1.26E-01	-0.184	1.498	0.071	0.329	8.30E-01	-0.575	0.716	0.042	0.394	9.16E-01	-0.730	0.814	0.196	0.290	4.98E-01	-0.371	0.764
	apobb.2	-0.009	0.284	9.74E-01	-0.565	0.547	-0.176	0.211	4.04E-01	-0.591	0.238	-0.248	0.237	2.95E-01	-0.712	0.216	-0.145	0.187	4.40E-01	-0.511	0.222
	ldlrb	-73.671	160.868	6.47E-01	-388.966	241.625	-43.732	141.267	7.57E-01	-320.610	233.145	-271.674	188.202	1.49E-01	-640.542	97.195	-0.969	1.965	6.22E-01	-4.821	2.882
random factors	***variance by batch***	*0.761*	*0.209*	-	*0.444*	*1.304*	*0.721*	*0.196*	-	*0.424*	*1.228*	*0.695*	*0.206*	-	*0.388*	*1.243*	*0.780*	*0.206*	-	*0.464*	*1.310*
	residual	*0.789*	*0.045*	-	*0.704*	*0.883*	*0.837*	*0.036*	-	*0.770*	*0.910*	*0.800*	*0.043*	-	*0.719*	*0.890*	*0.762*	*0.032*	-	*0.703*	*0.826*

		Glucose levels																			
		apoea					***apoeb***					***apobb.1***					***ldlra***				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.270	0.199	1.74E-01	-0.659	0.120	0.202	0.205	3.24E-01	-0.199	0.603	-0.485	0.210	2.10E-02	-0.897	-0.073	-0.153	0.140	2.73E-01	-0.427	0.121
	apoea	-	-	-	-	-	-0.045	0.096	6.42E-01	-0.234	0.144	-0.009	0.120	9.37E-01	-0.245	0.226	-0.055	0.089	5.41E-01	-0.230	0.121
	apoeb	0.065	0.140	6.42E-01	-0.210	0.340	-	-	-	-	-	-0.001	0.114	9.90E-01	-0.224	0.221	0.112	0.094	2.33E-01	-0.072	0.295
	apobb.1	-0.226	0.132	8.73E-02	-0.486	0.033	-0.137	0.107	2.00E-01	-0.347	0.073	-	-	-	-	-	-0.138	0.096	1.50E-01	-0.326	0.050
	ldlra	-0.130	0.108	2.26E-01	-0.341	0.081	-0.007	0.083	9.35E-01	-0.170	0.156	-0.091	0.108	4.00E-01	-0.304	0.121	-	-	-	-	-
	time of day (in hours since 9AM)	-0.018	0.068	7.89E-01	-0.151	0.115	0.046	0.052	3.72E-01	-0.055	0.147	0.046	0.060	4.41E-01	-0.071	0.163	0.028	0.047	5.51E-01	-0.065	0.121
	intercept	-13.418	78.005	8.63E-01	-166.306	139.469	35.006	64.294	5.86E-01	-91.008	161.019	7.275	86.223	9.33E-01	-161.719	176.269	1.685	1.197	1.59E-01	-0.661	4.031
	apoba	0.100	0.520	8.47E-01	-0.920	1.120	-0.202	0.376	5.92E-01	-0.939	0.536	0.130	0.446	7.70E-01	-0.743	1.004	-0.207	0.350	5.54E-01	-0.892	0.478
	apobb.2	-0.790	0.345	2.19E-02	-1.466	-0.114	-0.376	0.242	1.20E-01	-0.850	0.098	-0.523	0.271	5.36E-02	-1.053	0.008	-0.357	0.226	1.15E-01	-0.800	0.087
	ldlrb	36.552	195.054	8.51E-01	-345.747	418.850	-85.721	160.882	5.94E-01	-401.044	229.602	-16.791	215.844	9.38E-01	-439.838	406.255	-2.133	2.369	3.68E-01	-6.776	2.510
random factors	***variance by batch***	*0.414*	*0.152*	-	*0.201*	*0.851*	*0.379*	*0.129*	-	*0.194*	*0.740*	*0.302*	*0.159*	-	*0.107*	*0.849*	*0.360*	*0.120*	-	*0.187*	*0.693*
	residual	*0.960*	*0.056*	-	*0.857*	*1.076*	*0.961*	*0.041*	-	*0.884*	*1.046*	*0.920*	*0.051*	-	*0.826*	*1.025*	*0.924*	*0.038*	-	*0.852*	*1.002*

Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis and examined using hierarchical linear models. Effects shown are for larvae with two mutated alleles that are highly likely to affect protein function as predicted by Ensembl's Varient Effect Predictor (VEP) compared with larvae with zero CRISPR-mutated alleles. Associations were adjusted for the number of mutated alleles in the other six orthologues, weighted by their predicted effect on protein function, as well as for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 21 - The effect of two vs. zero mutated alleles in *apoea* , *apoeb* , *apobb.1* or *ldlra* on vascular atherogenic traits

		apoea														
		Vascular lipid deposition														
		Model 1					Model 2					Model 3				
		31 vs. 83 larvae with 2 vs. 0 mutated alleles (n=114)					30 vs. 67 larvae with 2 vs. 0 mutated alleles (n=97)					30 vs. 67 larvae with 2 vs. 0 mutated alleles (n=97)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	-0.773	0.419	6.55E-02	-1.595	0.050	-0.802	0.471	8.88E-02	-1.725	0.122	-0.491	0.655	4.54E-01	-1.776	0.793
	apoeb	0.365	0.195	6.08E-02	-0.017	0.747	0.500	0.269	6.28E-02	-0.027	1.027	0.466	0.282	9.80E-02	-0.086	1.018
	apobb.1	1.007	0.233	1.59E-05	0.550	1.464	0.930	0.340	6.26E-03	0.263	1.597	0.875	0.349	1.22E-02	0.191	1.560
	ldlra	0.244	0.174	1.61E-01	-0.098	0.586	0.229	0.201	2.54E-01	-0.165	0.622	0.187	0.227	4.10E-01	-0.258	0.632
	body length (in SD)	-	-	-	-	-	0.101	0.275	7.12E-01	-0.437	0.640	0.205	0.280	4.64E-01	-0.343	0.753
	dorsal body surface area (in SD)	-	-	-	-	-	0.470	0.274	8.59E-02	-0.066	1.007	0.529	0.322	9.99E-02	-0.101	1.160
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.156	0.176	3.76E-01	-0.501	0.189
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.051	0.251	8.39E-01	-0.442	0.544
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.423	0.172	1.39E-02	0.086	0.761
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.133	0.224	5.52E-01	-0.306	0.573
	time of day (in hours since 9AM)	0.148	0.116	1.99E-01	-0.078	0.375	0.029	0.179	8.72E-01	-0.323	0.381	0.046	0.193	8.11E-01	-0.331	0.424
	batch 2	0.070	0.527	8.94E-01	-0.963	1.104	0.485	0.670	4.69E-01	-0.829	1.799	0.913	0.828	2.70E-01	-0.709	2.535
	batch 3	-0.101	0.715	8.88E-01	-1.502	1.301	0.264	0.737	7.20E-01	-1.182	1.709	0.069	1.177	9.54E-01	-2.239	2.376
	batch 4	-0.760	0.525	1.48E-01	-1.789	0.270	-0.268	0.679	6.93E-01	-1.599	1.063	-0.372	0.785	6.35E-01	-1.910	1.166
	batch 5	0.164	0.449	7.15E-01	-0.716	1.045	0.462	0.602	4.42E-01	-0.717	1.642	-0.118	0.910	8.97E-01	-1.903	1.666
	batch 6	0.086	0.415	8.36E-01	-0.727	0.899	-0.073	0.568	8.97E-01	-1.187	1.040	-0.803	0.874	3.59E-01	-2.516	0.911
	batch 7	-0.961	0.462	3.74E-02	-1.866	-0.056	-1.047	0.624	9.33E-02	-2.270	0.176	-1.468	1.048	1.61E-01	-3.522	0.586
	intercept	-91.057	172.280	5.97E-01	-428.720	246.607	-109.553	223.730	6.24E-01	-548.056	328.950	-88.167	263.319	7.38E-01	-604.262	427.928
	apoba	-1.053	1.031	3.07E-01	-3.074	0.968	-1.141	1.295	3.78E-01	-3.680	1.397	-1.129	1.312	3.89E-01	-3.699	1.442
	apobb.2	-0.319	0.517	5.37E-01	-1.333	0.694	-0.360	0.594	5.44E-01	-1.525	0.804	0.074	0.699	9.16E-01	-1.296	1.443
	ldlrb	241.106	431.619	5.76E-01	-604.850	1087.063	287.842	559.627	6.07E-01	-809.006	1384.690	233.629	658.235	7.23E-01	-1100.000	1523.746

							Vascular infiltration by macrophages									
		47 vs. 104 larvae with 2 vs. 0 mutated alleles (n=151)					44 vs. 89 larvae with 2 vs. 0 mutated alleles (n=133)					44 vs. 89 larvae with 2 vs. 0 mutated alleles (n=133)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	2 vs. 0 mutated alleles	-0.063	0.177	7.23E-01	-0.410	0.284	-0.162	0.184	3.80E-01	-0.524	0.200	-0.187	0.187	3.18E-01	-0.552	0.179
	apoeb	-0.013	0.126	9.18E-01	-0.260	0.234	-0.006	0.139	9.67E-01	-0.277	0.266	0.027	0.138	8.47E-01	-0.244	0.297
	apobb.1	-0.240	0.123	5.12E-02	-0.481	0.001	-0.294	0.137	3.17E-02	-0.563	-0.026	-0.315	0.137	2.13E-02	-0.583	-0.047
	ldlra	0.088	0.097	3.64E-01	-0.102	0.278	0.073	0.103	4.76E-01	-0.128	0.274	0.048	0.102	6.39E-01	-0.152	0.249
	body length (in SD)	-	-	-	-	-	-0.193	0.110	7.85E-02	-0.409	0.022	-0.187	0.111	9.15E-02	-0.403	0.030
	dorsal body surface area (in SD)	-	-	-	-	-	-0.118	0.100	2.39E-01	-0.313	0.078	-0.109	0.101	2.83E-01	-0.307	0.090
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.057	0.083	4.92E-01	-0.105	0.219
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.108	0.089	2.27E-01	-0.067	0.282
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.105	0.112	3.47E-01	-0.114	0.324
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.123	0.084	1.44E-01	-0.289	0.042
	time of day (in hours since 9AM)	0.049	0.062	4.29E-01	-0.073	0.171	0.064	0.069	3.53E-01	-0.071	0.200	0.075	0.068	2.71E-01	-0.059	0.209
	intercept_random	-9.339	69.740	8.93E-01	-146.027	127.350	14.432	77.040	8.51E-01	-136.563	165.427	8.768	76.105	9.08E-01	-140.396	157.931
	apoba	0.070	0.463	8.80E-01	-0.837	0.977	0.225	0.478	6.39E-01	-0.713	1.162	0.150	0.473	7.51E-01	-0.778	1.078
	apobb.2	-0.383	0.303	2.06E-01	-0.977	0.211	-0.392	0.319	2.19E-01	-1.017	0.233	-0.547	0.327	9.47E-02	-1.189	0.095
	ldlrb	24.231	174.423	8.90E-01	-317.631	366.094	-35.876	192.602	8.52E-01	-413.370	341.618	-20.891	190.282	9.13E-01	-393.836	352.054
random factors	*variance by batch*	*0.463*	*0.149*	-	*0.247*	*0.869*	*0.407*	*0.141*	-	*0.206*	*0.803*	*0.373*	*0.140*	-	*0.178*	*0.779*
	residual	*0.840*	*0.050*	-	*0.747*	*0.944*	*0.844*	*0.054*	-	*0.745*	*0.957*	*0.833*	*0.053*	-	*0.735*	*0.944*

continued **Supplementary Table 21**

		Vascular co-localization of lipids with macrophages														
		31 vs. 80 larvae with 2 vs. 0 mutated alleles (n=111)					30 vs. 65 larvae with 2 vs. 0 mutated alleles (n=95)					30 vs. 65 larvae with 2 vs. 0 mutated alleles (n=95)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.387	0.699	5.80E-01	-1.758	0.984	-0.748	0.875	3.93E-01	-2.463	0.967	-0.531	0.976	5.86E-01	-2.444	1.381
	apoeb	0.021	0.295	9.43E-01	-0.558	0.600	0.251	0.314	4.24E-01	-0.365	0.868	0.337	0.345	3.29E-01	-0.339	1.014
	apobb.1	1.362	0.326	2.93E-05	0.723	2.001	1.142	0.513	2.61E-02	0.136	2.148	0.694	0.859	4.19E-01	-0.990	2.378
	ldlra	0.166	0.351	6.35E-01	-0.521	0.854	0.195	0.454	6.68E-01	-0.696	1.086	-0.096	0.468	8.37E-01	-1.014	0.821
	body length (in SD)	-	-	-	-	-	0.078	0.479	8.70E-01	-0.860	1.016	0.023	0.611	9.71E-01	-1.174	1.219
	dorsal body surface area (in SD)	-	-	-	-	-	0.481	0.297	1.05E-01	-0.101	1.062	0.426	0.645	5.09E-01	-0.838	1.689
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.081	0.327	8.03E-01	-0.722	0.559
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.016	0.498	9.74E-01	-0.993	0.960
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.035	0.501	3.89E-02	0.053	2.018
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.228	0.522	6.62E-01	-1.250	0.794
	time of day (in hours since 9AM)	0.215	0.140	1.25E-01	-0.060	0.489	0.183	0.237	4.39E-01	-0.281	0.648	0.327	0.361	3.65E-01	-0.380	1.034
	batch 2	1.037	1.056	3.26E-01	-1.033	3.107	0.982	1.145	3.91E-01	-1.263	3.227	0.438	1.648	7.90E-01	-2.792	3.668
	batch 3	-1.382	0.712	5.22E-02	-2.777	0.013	-1.267	0.862	1.42E-01	-2.956	0.423	-1.449	1.537	3.46E-01	-4.460	1.563
	batch 4	-0.418	0.699	5.50E-01	-1.789	0.952	-0.393	0.911	6.66E-01	-2.179	1.393	-0.693	1.405	6.22E-01	-3.447	2.061
	batch 5	0.438	0.619	4.80E-01	-0.776	1.651	0.017	0.789	9.83E-01	-1.529	1.563	-1.515	1.427	2.89E-01	-4.312	1.283
	batch 6	-0.877	0.644	1.73E-01	-2.139	0.386	-1.652	0.760	2.98E-02	-3.142	-0.162	-3.576	1.802	4.72E-02	-7.107	-0.044
	batch 7	-2.995	0.769	9.76E-05	-4.501	-1.488	-3.887	0.920	2.40E-05	-5.691	-2.084	-4.793	2.075	2.09E-02	-8.859	-0.726
	intercept	-233.734	227.970	3.05E-01	-680.548	213.080	-196.479	316.933	5.35E-01	-817.657	424.699	-194.514	380.442	6.09E-01	-940.167	551.139
	apoba	-1.350	1.667	4.18E-01	-4.617	1.916	-1.213	1.698	4.75E-01	-4.540	2.115	-0.244	2.329	9.16E-01	-4.809	4.320
	apobb.2	-0.885	0.700	2.06E-01	-2.256	0.486	-0.837	0.713	2.41E-01	-2.235	0.561	-0.087	1.485	9.53E-01	-2.997	2.824
	ldlrb	596.038	572.764	2.98E-01	-526.558	1718.634	502.398	792.141	5.26E-01	-1100.000	2054.967	492.382	952.213	6.05E-01	-1400.000	2358.685

		Vascular infiltration by neutrophils														
		47 vs. 106 larvae with 2 vs. 0 mutated alleles (n=153)					44 vs. 91 larvae with 2 vs. 0 mutated alleles (n=135)					44 vs. 91 larvae with 2 vs. 0 mutated alleles (n=135)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.064	0.179	7.20E-01	-0.416	0.287	-0.080	0.176	6.48E-01	-0.426	0.265	-0.138	0.179	4.40E-01	-0.489	0.213
	apoeb	-0.108	0.128	3.98E-01	-0.359	0.142	-0.086	0.131	5.12E-01	-0.344	0.171	-0.083	0.131	5.30E-01	-0.340	0.175
	apobb.1	0.140	0.125	2.65E-01	-0.106	0.386	-0.113	0.131	3.89E-01	-0.369	0.144	-0.112	0.132	3.95E-01	-0.370	0.146
	ldlra	-0.008	0.099	9.33E-01	-0.202	0.185	0.069	0.098	4.84E-01	-0.124	0.261	0.063	0.098	5.19E-01	-0.129	0.256
	body length (in SD)	-	-	-	-	-	-0.315	0.103	2.28E-03	-0.517	-0.113	-0.325	0.103	1.59E-03	-0.527	-0.123
	dorsal body surface area (in SD)	-	-	-	-	-	0.191	0.094	4.25E-02	0.006	0.376	0.216	0.096	2.41E-02	0.028	0.404
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.130	0.077	9.08E-02	-0.021	0.282
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.091	0.085	2.85E-01	-0.076	0.257
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.047	0.103	6.48E-01	-0.155	0.249
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.008	0.080	9.18E-01	-0.149	0.165
	time of day (in hours since 9AM)	0.006	0.062	9.22E-01	-0.115	0.128	-0.030	0.065	6.45E-01	-0.158	0.098	-0.017	0.064	7.90E-01	-0.142	0.108
	intercept_random	-120.289	71.401	9.20E-02	-260.231	19.654	-125.307	73.902	9.00E-02	-270.152	19.539	-134.596	73.421	6.68E-02	-278.498	9.306
	apoba	0.345	0.471	4.63E-01	-0.577	1.268	0.182	0.456	6.89E-01	-0.711	1.076	0.087	0.455	8.49E-01	-0.805	0.978
	apobb.2	-0.028	0.310	9.29E-01	-0.636	0.580	0.174	0.306	5.71E-01	-0.426	0.773	0.103	0.315	7.45E-01	-0.515	0.721
	ldlrb	299.596	178.573	9.34E-02	-50.401	649.593	312.556	184.759	9.07E-02	-49.565	674.677	336.427	183.574	6.69E-02	-23.371	696.226
random factors	***variance by batch***	*0.375*	*0.121*	-	*0.199*	*0.706*	*0.334*	*0.121*	-	*0.164*	*0.681*	*0.271*	*0.117*	-	*0.116*	*0.632*
	residual	*0.861*	*0.051*	-	*0.768*	*0.967*	*0.812*	*0.051*	-	*0.717*	*0.919*	*0.807*	*0.051*	-	*0.713*	*0.913*

continued **Supplementary Table 21**

		Vascular co-localization of lipids with neutrophils														
		31 vs. 75 larvae with 2 vs. 0 mutated alleles (n=106)					30 vs. 60 larvae with 2 vs. 0 mutated alleles (n=90)					30 vs. 60 larvae with 2 vs. 0 mutated alleles (n=90)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.823	0.679	2.25E-01	-2.154	0.507	-0.243	0.568	6.69E-01	-1.355	0.870	-0.523	0.644	4.17E-01	-1.786	0.740
	apoeb	0.219	0.437	6.17E-01	-0.638	1.075	0.780	0.294	7.90E-03	0.204	1.355	0.770	0.322	1.67E-02	0.140	1.401
	apobb.1	1.968	0.327	1.80E-09	1.327	2.610	2.615	0.502	1.90E-07	1.631	3.599	2.243	0.549	4.37E-05	1.167	3.319
	ldlra	0.702	0.327	3.20E-02	0.061	1.343	0.724	0.372	5.17E-02	-0.005	1.452	0.562	0.354	1.13E-01	-0.132	1.256
	body length (in SD)	-	-	-	-	-	0.073	0.477	8.79E-01	-0.862	1.008	0.181	0.533	7.34E-01	-0.863	1.225
	dorsal body surface area (in SD)	-	-	-	-	-	-0.512	0.503	3.08E-01	-1.497	0.473	-0.284	0.538	5.98E-01	-1.338	0.770
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.033	0.332	9.22E-01	-0.617	0.683
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.646	0.379	8.87E-02	-0.098	1.389
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.655	0.340	5.43E-02	-0.012	1.322
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.106	0.262	6.85E-01	-0.407	0.620
	time of day (in hours since 9AM)	0.469	0.179	9.00E-03	0.117	0.821	0.784	0.279	4.96E-03	0.237	1.331	0.642	0.305	3.50E-02	0.045	1.239
	batch 2	0.551	1.161	6.35E-01	-1.725	2.827	1.792	1.096	1.02E-01	-0.356	3.940	2.003	1.165	8.55E-02	-0.280	4.286
	batch 3	-1.322	1.155	2.52E-01	-3.586	0.941	-0.854	1.017	4.01E-01	-2.847	1.139	-0.100	1.270	9.38E-01	-2.589	2.390
	batch 4	-0.266	0.953	7.80E-01	-2.134	1.603	0.286	0.971	7.68E-01	-1.616	2.189	0.975	1.147	3.95E-01	-1.273	3.223
	batch 5	-0.247	0.830	7.66E-01	-1.874	1.380	0.722	0.745	3.32E-01	-0.738	2.182	0.661	1.019	5.16E-01	-1.336	2.659
	batch 6	-2.620	0.959	6.28E-03	-4.499	-0.741	-1.984	0.865	2.19E-02	-3.680	-0.288	-2.230	1.129	4.83E-02	-4.443	-0.017
	intercept	-791.606	250.244	1.56E-03	-1300.000	-301.137	-918.003	298.459	2.10E-03	-1500.000	-333.034	-853.180	303.486	4.93E-03	-1400.000	-258.358
	apoba	-3.117	1.464	3.32E-02	-5.987	-0.248	-2.355	1.211	5.17E-02	-4.728	0.017	-2.021	1.458	1.66E-01	-4.879	0.837
	apobb.2	1.520	0.907	9.38E-02	-0.258	3.298	-0.202	0.809	8.02E-01	-1.787	1.383	0.105	0.976	9.14E-01	-1.808	2.018
	ldlrb	1982.551	626.570	1.56E-03	754.497	3210.604	2291.772	746.022	2.13E-03	829.596	3753.949	2128.907	756.916	4.91E-03	645.379	3612.435

		Vascular co-localization of macrophages with neutrophils														
		47 vs. 104 larvae with 2 vs. 0 mutated alleles (n=151)					44 vs. 89 larvae with 2 vs. 0 mutated alleles (n=133)					44 vs. 89 larvae with 2 vs. 0 mutated alleles (n=133)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.335	0.255	1.88E-01	-0.834	0.164	-0.252	0.247	3.07E-01	-0.735	0.231	-0.218	0.245	3.75E-01	-0.699	0.263
	apoeb	-0.434	0.195	2.61E-02	-0.816	-0.052	-0.336	0.200	9.26E-02	-0.728	0.056	-0.367	0.197	6.30E-02	-0.754	0.020
	apobb.1	-0.105	0.162	5.18E-01	-0.422	0.213	-0.416	0.205	4.26E-02	-0.818	-0.014	-0.427	0.201	3.36E-02	-0.821	-0.033
	ldlra	0.198	0.138	1.50E-01	-0.071	0.468	0.203	0.143	1.57E-01	-0.078	0.483	0.177	0.145	2.22E-01	-0.107	0.462
	body length (in SD)	-	-	-	-	-	0.009	0.192	9.61E-01	-0.366	0.385	-0.019	0.190	9.18E-01	-0.391	0.352
	dorsal body surface area (in SD)	-	-	-	-	-	0.741	0.289	1.04E-02	0.174	1.308	0.701	0.287	1.47E-02	0.138	1.264
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.229	0.114	4.45E-02	0.006	0.451
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.176	0.146	2.29E-01	-0.110	0.461
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.293	0.146	4.49E-02	0.007	0.580
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.173	0.141	2.20E-01	-0.104	0.449
	time of day (in hours since 9AM)	0.062	0.109	5.65E-01	-0.150	0.275	-0.112	0.142	4.27E-01	-0.390	0.165	-0.104	0.135	4.43E-01	-0.368	0.161
	batch 1	-0.433	0.383	2.58E-01	-1.183	0.317	-0.120	0.550	8.28E-01	-1.199	0.959	0.085	0.667	8.99E-01	-1.223	1.393
	batch 2	-0.964	0.392	1.38E-02	-1.732	-0.197	-0.997	0.445	2.52E-02	-1.870	-0.124	-0.329	0.542	5.43E-01	-1.391	0.732
	batch 3	-1.324	0.485	6.36E-03	-2.276	-0.373	-1.012	0.547	6.45E-02	-2.085	0.061	-0.777	0.552	1.59E-01	-1.858	0.304
	batch 4	-0.112	0.466	8.09E-01	-1.025	0.800	0.237	0.546	6.63E-01	-0.832	1.307	0.430	0.558	4.40E-01	-0.663	1.524
	batch 5	0.030	0.469	9.48E-01	-0.890	0.951	0.003	0.489	9.95E-01	-0.956	0.962	0.060	0.535	9.10E-01	-0.989	1.109
	batch 6	-2.377	0.454	1.66E-07	-3.267	-1.487	-3.075	0.624	8.32E-07	-4.298	-1.852	-3.125	0.630	7.01E-07	-4.359	-1.890
	batch 7	-1.110	0.731	1.29E-01	-2.542	0.323	-1.873	0.731	1.04E-02	-3.306	-0.440	-1.714	0.733	1.93E-02	-3.151	-0.278
	intercept	-55.609	120.106	6.43E-01	-291.013	179.796	-196.032	143.724	1.73E-01	-477.726	85.662	-287.996	137.895	3.68E-02	-558.265	-17.727
	apoba	1.159	0.625	6.37E-02	-0.066	2.384	1.815	0.750	1.56E-02	0.344	3.286	1.848	0.744	1.30E-02	0.389	3.307
	apobb.2	-0.200	0.324	5.38E-01	-0.835	0.436	-0.270	0.373	4.69E-01	-1.002	0.461	-0.283	0.404	4.84E-01	-1.075	0.510
	ldlrb	146.298	300.491	6.26E-01	-442.654	735.250	495.866	359.236	1.67E-01	-208.223	1199.955	725.424	344.591	3.53E-02	50.039	1400.809

continued **Supplementary Table 21**

		apoeb														
		Vascular lipid deposition														
		Model 1					**Model 2**					**Model 3**				
		179 vs. 29 larvae with 2 vs. 0 mutated alleles (n=208)					**153 vs. 26 larvae with 2 vs. 0 mutated alleles (n=179)**					**153 vs. 26 larvae with 2 vs. 0 mutated alleles (n=179)**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.479	0.305	1.16E-01	-0.118	1.076	0.592	0.347	8.76E-02	-0.087	1.272	0.564	0.370	1.28E-01	-0.162	1.290
	apoea	-0.238	0.188	2.06E-01	-0.606	0.131	-0.331	0.210	1.15E-01	-0.742	0.081	-0.263	0.207	2.04E-01	-0.667	0.142
	apobb.1	0.730	0.174	2.64E-05	0.390	1.071	0.843	0.199	2.33E-05	0.452	1.234	0.671	0.201	8.13E-04	0.278	1.064
	ldlra	0.250	0.130	5.34E-02	-0.004	0.504	0.267	0.149	7.25E-02	-0.024	0.558	0.276	0.143	5.38E-02	-0.004	0.556
	body length (in SD)	-	-	-	-	-	0.238	0.159	1.34E-01	-0.074	0.550	0.336	0.158	3.36E-02	0.026	0.646
	dorsal body surface area (in SD)	-	-	-	-	-	0.217	0.148	1.43E-01	-0.073	0.507	0.282	0.145	5.25E-02	-0.003	0.567
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.136	0.104	1.94E-01	-0.340	0.069
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.055	0.168	7.43E-01	-0.384	0.274
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.435	0.167	9.32E-03	0.107	0.764
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.202	0.102	4.80E-02	-0.403	-0.002
	time of day (in hours since 9AM)	-0.044	0.086	6.12E-01	-0.213	0.125	-0.103	0.105	3.28E-01	-0.310	0.104	-0.018	0.110	8.68E-01	-0.233	0.197
	batch 2	-1.404	0.457	2.14E-03	-2.300	-0.508	-1.319	0.527	1.24E-02	-2.352	-0.285	-0.923	0.528	8.03E-02	-1.957	0.111
	batch 3	-1.085	0.389	5.31E-03	-1.847	-0.322	-1.113	0.409	6.48E-03	-1.914	-0.312	-1.198	0.414	3.85E-03	-2.010	-0.386
	batch 4	-1.068	0.442	1.56E-02	-1.934	-0.203	-0.943	0.476	4.73E-02	-1.876	-0.011	-0.826	0.435	5.74E-02	-1.677	0.026
	batch 5	-0.155	0.283	5.84E-01	-0.709	0.399	-0.238	0.325	4.64E-01	-0.875	0.399	-0.903	0.466	5.29E-02	-1.817	0.011
	batch 6	-0.217	0.295	4.63E-01	-0.796	0.362	-0.543	0.372	1.44E-01	-1.273	0.186	-1.323	0.550	1.62E-02	-2.402	-0.245
	batch 7	-0.867	0.388	2.55E-02	-1.628	-0.106	-1.179	0.401	3.24E-03	-1.965	-0.394	-1.622	0.595	6.37E-03	-2.787	-0.457
	intercept	58.235	136.197	6.69E-01	-208.706	325.175	41.113	152.198	7.87E-01	-257.191	339.416	31.011	152.088	8.38E-01	-267.075	329.097
	apoba	-0.199	0.608	7.43E-01	-1.391	0.992	-0.357	0.650	5.83E-01	-1.632	0.918	-0.180	0.646	7.81E-01	-1.447	1.087
	apobb.2	0.001	0.463	9.98E-01	-0.907	0.909	-0.029	0.491	9.52E-01	-0.992	0.933	0.336	0.478	4.82E-01	-0.601	1.274
	ldlrb	-133.537	341.561	6.96E-01	-802.985	535.911	-89.418	381.314	8.15E-01	-836.779	657.943	-66.125	381.349	8.62E-01	-813.556	681.305

							Vascular infiltration by macrophages									
		237 vs. 37 larvae with 2 vs. 0 mutated alleles (n=274)					**206 vs. 34 larvae with 2 vs. 0 mutated alleles (n=240)**					**206 vs. 34 larvae with 2 vs. 0 mutated alleles (n=240)**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.257	0.184	1.62E-01	-0.617	0.103	-0.218	0.203	2.83E-01	-0.616	0.180	-0.245	0.204	2.30E-01	-0.646	0.155
	apoea	-0.117	0.088	1.82E-01	-0.289	0.055	-0.148	0.096	1.24E-01	-0.336	0.041	-0.160	0.097	9.97E-02	-0.350	0.030
	apobb.1	-0.168	0.098	8.57E-02	-0.361	0.024	-0.173	0.107	1.05E-01	-0.383	0.036	-0.172	0.108	1.13E-01	-0.385	0.040
	ldlra	0.013	0.075	8.67E-01	-0.135	0.160	0.018	0.085	8.35E-01	-0.149	0.184	0.002	0.085	9.81E-01	-0.165	0.169
	body length (in SD)	-	-	-	-	-	0.023	0.086	7.91E-01	-0.146	0.192	0.024	0.088	7.85E-01	-0.148	0.195
	dorsal body surface area (in SD)	-	-	-	-	-	-0.037	0.075	6.27E-01	-0.184	0.111	-0.039	0.076	6.07E-01	-0.187	0.109
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.029	0.063	6.45E-01	-0.095	0.153
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.112	0.074	1.30E-01	-0.033	0.256
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.000	0.086	1.00E+00	-0.169	0.169
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.031	0.064	6.34E-01	-0.095	0.156
	time of day (in hours since 9AM)	0.020	0.048	6.72E-01	-0.074	0.114	0.018	0.056	7.43E-01	-0.091	0.128	0.023	0.056	6.79E-01	-0.086	0.133
	intercept_random	-49.906	57.788	3.88E-01	-163.168	63.355	-42.117	65.580	5.21E-01	-170.650	86.417	-34.466	65.536	5.99E-01	-162.914	93.982
	apoba	-0.187	0.340	5.82E-01	-0.853	0.479	-0.318	0.374	3.96E-01	-1.051	0.416	-0.283	0.374	4.49E-01	-1.017	0.450
	apobb.2	-0.359	0.217	9.75E-02	-0.783	0.066	-0.391	0.238	9.97E-02	-0.857	0.075	-0.416	0.242	8.58E-02	-0.891	0.059
	ldlrb	127.830	144.603	3.77E-01	-155.586	411.246	109.097	164.010	5.06E-01	-212.356	430.551	89.972	163.907	5.83E-01	-231.281	411.224
random factors	***variance by batch***	*0.510*	*0.143*	-	*0.295*	*0.883*	*0.492*	*0.143*	-	*0.278*	*0.870*	*0.452*	*0.136*	-	*0.250*	*0.816*
	residual	*0.857*	*0.037*	-	*0.787*	*0.933*	*0.886*	*0.041*	-	*0.809*	*0.971*	*0.884*	*0.041*	-	*0.806*	*0.968*

continued **Supplementary Table 21**

		Vascular co-localization of lipids with macrophages														
		174 vs. 29 larvae with 2 vs. 0 mutated alleles (n=203)					150 vs. 26 larvae with 2 vs. 0 mutated alleles (n=176)					150 vs. 26 larvae with 2 vs. 0 mutated alleles (n=176)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.468	0.389	2.29E-01	-1.231	0.295	-0.477	0.443	2.81E-01	-1.345	0.391	-0.283	0.464	5.41E-01	-1.192	0.625
	apoea	-0.247	0.253	3.28E-01	-0.742	0.248	-0.429	0.292	1.42E-01	-1.000	0.143	-0.402	0.343	2.41E-01	-1.074	0.271
	apobb.1	0.934	0.220	2.27E-05	0.502	1.366	1.015	0.287	3.99E-04	0.453	1.576	0.692	0.352	4.91E-02	0.003	1.382
	ldlra	0.242	0.185	1.91E-01	-0.121	0.606	0.306	0.221	1.65E-01	-0.126	0.739	0.368	0.220	9.40E-02	-0.063	0.799
	body length (in SD)	-	-	-	-	-	0.242	0.260	3.53E-01	-0.268	0.751	0.234	0.279	4.02E-01	-0.313	0.780
	dorsal body surface area (in SD)	-	-	-	-	-	0.471	0.184	1.07E-02	0.109	0.832	0.446	0.182	1.46E-02	0.088	0.804
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.307	0.232	1.87E-01	-0.762	0.149
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.051	0.279	8.56E-01	-0.496	0.597
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.467	0.265	7.77E-02	-0.052	0.986
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.139	0.163	3.92E-01	-0.459	0.180
	time of day (in hours since 9AM)	0.097	0.098	3.24E-01	-0.095	0.289	0.200	0.124	1.05E-01	-0.042	0.443	0.338	0.138	1.47E-02	0.067	0.609
	batch 2	-0.438	0.824	5.95E-01	-2.053	1.177	-0.016	0.967	9.87E-01	-1.911	1.880	-0.594	0.914	5.16E-01	-2.384	1.197
	batch 3	-1.015	0.444	2.21E-02	-1.885	-0.146	-0.976	0.490	4.65E-02	-1.936	-0.015	-1.036	0.648	1.10E-01	-2.305	0.234
	batch 4	-0.450	0.471	3.40E-01	-1.373	0.474	-0.505	0.568	3.74E-01	-1.619	0.608	-0.674	0.600	2.62E-01	-1.851	0.503
	batch 5	0.033	0.377	9.30E-01	-0.706	0.772	-0.486	0.464	2.95E-01	-1.396	0.424	-1.300	0.662	4.97E-02	-2.597	-0.002
	batch 6	-0.548	0.370	1.38E-01	-1.273	0.176	-0.968	0.532	6.91E-02	-2.011	0.076	-1.528	0.962	1.12E-01	-3.413	0.357
	batch 7	-1.275	0.742	8.58E-02	-2.729	0.180	-2.061	0.725	4.46E-03	-3.482	-0.640	-2.677	1.017	8.47E-03	-4.671	-0.684
	intercept	20.330	157.888	8.98E-01	-289.125	329.784	52.867	187.217	7.78E-01	-314.072	419.806	162.185	229.589	4.80E-01	-287.800	612.170
	apoba	-0.470	0.923	6.11E-01	-2.278	1.339	-0.523	1.012	6.06E-01	-2.507	1.461	-0.572	1.353	6.73E-01	-3.223	2.080
	apobb.2	-0.205	0.494	6.78E-01	-1.173	0.762	-0.180	0.536	7.38E-01	-1.229	0.870	0.175	0.536	7.45E-01	-0.876	1.225
	ldlrb	-42.152	396.237	9.15E-01	-818.763	734.458	-123.631	468.918	7.92E-01	-1000.000	795.432	-398.212	576.562	4.90E-01	-1500.000	731.829

		Vascular infiltration by neutrophils														
		240 vs. 37 larvae with 2 vs. 0 mutated alleles (n=277)					208 vs. 34 larvae with 2 vs. 0 mutated alleles (n=242)					208 vs. 34 larvae with 2 vs. 0 mutated alleles (n=242)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.100	0.179	5.77E-01	-0.251	0.451	0.163	0.192	3.96E-01	-0.214	0.540	0.128	0.192	5.06E-01	-0.249	0.505
	apoea	-0.032	0.085	7.08E-01	-0.199	0.135	-0.049	0.091	5.90E-01	-0.227	0.129	-0.073	0.091	4.22E-01	-0.253	0.106
	apobb.1	0.125	0.095	1.89E-01	-0.061	0.311	0.104	0.101	3.02E-01	-0.093	0.301	0.106	0.102	2.96E-01	-0.093	0.305
	ldlra	-0.083	0.073	2.58E-01	-0.227	0.061	-0.078	0.080	3.32E-01	-0.236	0.079	-0.099	0.080	2.18E-01	-0.256	0.058
	body length (in SD)	-	-	-	-	-	-0.027	0.081	7.42E-01	-0.186	0.132	-0.018	0.081	8.26E-01	-0.177	0.141
	dorsal body surface area (in SD)	-	-	-	-	-	0.070	0.070	3.17E-01	-0.068	0.209	0.076	0.070	2.80E-01	-0.062	0.213
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.071	0.058	2.22E-01	-0.043	0.185
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.138	0.069	4.47E-02	0.003	0.272
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.012	0.079	8.77E-01	-0.167	0.143
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.019	0.060	7.48E-01	-0.098	0.137
	time of day (in hours since 9AM)	0.041	0.046	3.69E-01	-0.049	0.132	0.002	0.052	9.72E-01	-0.100	0.104	0.006	0.052	9.02E-01	-0.095	0.108
	intercept_random	53.743	56.805	3.44E-01	-57.594	165.079	26.564	62.657	6.72E-01	-96.241	149.369	35.841	62.150	5.64E-01	-85.971	157.654
	apoba	0.077	0.330	8.15E-01	-0.570	0.725	0.102	0.353	7.73E-01	-0.590	0.794	0.131	0.351	7.09E-01	-0.557	0.820
	apobb.2	0.042	0.211	8.44E-01	-0.373	0.456	0.070	0.225	7.55E-01	-0.371	0.512	0.012	0.228	9.59E-01	-0.435	0.459
	ldlrb	-135.183	142.138	3.42E-01	-413.770	143.403	-67.148	156.701	6.68E-01	-374.276	239.980	-90.157	155.444	5.62E-01	-394.822	214.507
random factors	***variance by batch***	*0.407*	*0.115*	-	*0.234*	*0.708*	*0.395*	*0.118*	-	*0.220*	*0.709*	*0.343*	*0.108*	-	*0.186*	*0.634*
	residual	*0.838*	*0.036*	-	*0.770*	*0.912*	*0.842*	*0.039*	-	*0.768*	*0.922*	*0.834*	*0.039*	-	*0.762*	*0.914*

continued **Supplementary Table 21**

		Vascular co-localization of lipids with neutrophils														
		168 vs. 27 larvae with 2 vs. 0 mutated alleles (n=195)					143 vs. 24 larvae with 2 vs. 0 mutated alleles (n=167)					143 vs. 24 larvae with 2 vs. 0 mutated alleles (n=167)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.389	0.565	4.91E-01	-1.495	0.717	0.227	0.643	7.24E-01	-1.033	1.488	-0.109	0.648	8.67E-01	-1.379	1.162
	apoea	-0.241	0.339	4.77E-01	-0.906	0.423	0.048	0.373	8.99E-01	-0.684	0.779	-0.974	0.391	1.27E-02	-1.740	-0.208
	apobb.1	1.748	0.280	4.46E-10	1.198	2.297	1.812	0.380	1.90E-06	1.066	2.557	1.613	0.377	1.88E-05	0.874	2.351
	ldlra	0.240	0.315	4.46E-01	-0.377	0.858	0.092	0.322	7.76E-01	-0.540	0.723	0.074	0.272	7.85E-01	-0.459	0.607
	body length (in SD)	-	-	-	-	-	0.071	0.504	8.88E-01	-0.917	1.060	-0.058	0.414	8.88E-01	-0.870	0.754
	dorsal body surface area (in SD)	-	-	-	-	-	-0.177	0.246	4.71E-01	-0.659	0.305	-0.160	0.245	5.14E-01	-0.640	0.320
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.261	0.286	3.61E-01	-0.299	0.821
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.751	0.406	6.40E-02	-0.044	1.546
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.409	0.367	1.24E-04	0.689	2.129
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.008	0.215	9.71E-01	-0.428	0.413
	time of day (in hours since 9AM)	0.062	0.169	7.16E-01	-0.270	0.393	0.188	0.195	3.36E-01	-0.195	0.570	0.500	0.228	2.84E-02	0.053	0.947
	batch 2	-1.617	0.813	4.68E-02	-3.211	-0.023	-1.605	1.080	1.37E-01	-3.722	0.511	-1.421	0.967	1.42E-01	-3.316	0.474
	batch 3	-0.752	0.834	3.67E-01	-2.387	0.882	-0.720	0.791	3.63E-01	-2.269	0.830	-1.398	0.714	5.01E-02	-2.797	0.000
	batch 4	-0.887	0.621	1.53E-01	-2.104	0.330	-0.638	0.817	4.35E-01	-2.240	0.964	-1.172	0.794	1.40E-01	-2.728	0.384
	batch 5	-0.277	0.510	5.87E-01	-1.277	0.722	-0.327	0.550	5.52E-01	-1.405	0.751	-2.983	0.935	1.42E-03	-4.816	-1.150
	batch 6	-2.640	0.635	3.23E-05	-3.885	-1.395	-2.827	0.837	7.28E-04	-4.467	-1.187	-4.597	1.110	3.43E-05	-6.771	-2.422
	intercept	-101.955	224.820	6.50E-01	-542.594	338.684	7.020	339.258	9.83E-01	-657.913	671.953	444.862	301.233	1.40E-01	-145.544	1035.268
	apoba	0.531	1.282	6.79E-01	-1.982	3.045	1.061	1.155	3.58E-01	-1.203	3.324	2.821	1.272	2.66E-02	0.327	5.315
	apobb.2	0.600	0.670	3.71E-01	-0.714	1.913	-0.122	0.678	8.57E-01	-1.451	1.206	1.634	0.789	3.84E-02	0.087	3.180
	ldlrb	251.587	564.907	6.56E-01	-855.610	1358.785	-23.731	850.679	9.78E-01	-1700.000	1643.569	-1100.000	755.388	1.35E-01	-2600.000	350.537

		Vascular co-localization of macrophages with neutrophils														
		236 vs. 37 larvae with 2 vs. 0 mutated alleles (n=273)					205 vs. 34 larvae with 2 vs. 0 mutated alleles (n=239)					205 vs. 34 larvae with 2 vs. 0 mutated alleles (n=239)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.504	0.278	7.02E-02	-0.042	1.050	0.498	0.280	7.53E-02	-0.051	1.047	0.444	0.280	1.13E-01	-0.105	0.993
	apoea	-0.111	0.148	4.54E-01	-0.400	0.179	-0.100	0.157	5.26E-01	-0.407	0.208	-0.073	0.160	6.50E-01	-0.386	0.241
	apobb.1	0.111	0.164	5.00E-01	-0.211	0.432	0.142	0.163	3.84E-01	-0.178	0.462	0.223	0.162	1.69E-01	-0.095	0.542
	ldlra	-0.181	0.126	1.50E-01	-0.428	0.066	-0.178	0.121	1.41E-01	-0.415	0.059	-0.201	0.119	9.11E-02	-0.434	0.032
	body length (in SD)	-	-	-	-	-	0.471	0.145	1.16E-03	0.187	0.755	0.445	0.145	2.21E-03	0.160	0.729
	dorsal body surface area (in SD)	-	-	-	-	-	0.289	0.133	3.01E-02	0.028	0.550	0.250	0.130	5.49E-02	-0.005	0.506
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.073	0.102	4.76E-01	-0.127	0.273
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.082	0.119	4.89E-01	-0.151	0.315
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.078	0.149	6.01E-01	-0.370	0.215
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.256	0.089	3.79E-03	0.083	0.430
	time of day (in hours since 9AM)	0.112	0.077	1.43E-01	-0.038	0.263	0.117	0.090	1.93E-01	-0.059	0.293	0.120	0.092	1.94E-01	-0.061	0.301
	batch 1	0.658	0.409	1.07E-01	-0.143	1.459	0.246	0.463	5.95E-01	-0.661	1.154	0.254	0.535	6.35E-01	-0.794	1.302
	batch 2	0.750	0.544	1.68E-01	-0.316	1.817	0.756	0.498	1.29E-01	-0.221	1.732	0.924	0.538	8.61E-02	-0.131	1.979
	batch 3	-0.204	0.517	6.93E-01	-1.216	0.809	-0.543	0.525	3.01E-01	-1.573	0.486	-0.473	0.551	3.91E-01	-1.552	0.606
	batch 4	1.501	0.490	2.20E-03	0.540	2.462	1.571	0.519	2.46E-03	0.554	2.587	1.458	0.561	9.42E-03	0.357	2.558
	batch 5	0.456	0.449	3.10E-01	-0.424	1.335	-0.114	0.493	8.17E-01	-1.080	0.852	0.084	0.546	8.77E-01	-0.985	1.154
	batch 6	-1.210	0.466	9.40E-03	-2.123	-0.297	-2.083	0.588	3.99E-04	-3.236	-0.930	-1.925	0.620	1.90E-03	-3.139	-0.710
	batch 7	-0.190	0.604	7.53E-01	-1.374	0.994	-1.063	0.767	1.66E-01	-2.567	0.441	-1.109	0.819	1.75E-01	-2.714	0.495
	intercept	69.161	106.517	5.16E-01	-139.609	277.931	-25.456	109.673	8.16E-01	-240.411	189.499	-63.428	102.485	5.36E-01	-264.296	137.440
	apoba	-0.102	0.538	8.50E-01	-1.157	0.953	-0.007	0.546	9.90E-01	-1.076	1.063	0.098	0.569	8.63E-01	-1.017	1.214
	apobb.2	0.017	0.337	9.61E-01	-0.644	0.678	-0.223	0.379	5.57E-01	-0.965	0.520	-0.055	0.374	8.83E-01	-0.788	0.677
	ldlrb	-164.973	266.850	5.36E-01	-687.989	358.042	73.008	274.916	7.91E-01	-465.817	611.833	166.585	256.848	5.17E-01	-336.827	669.997

continued **Supplementary Table 21**

		apobb.1														
		Vascular lipid deposition														
		Model 1					**Model 2**					**Model 3**				
		20 vs. 113 larvae with 2 vs. 0 mutated alleles (n=133)					**20 vs. 95 larvae with 2 vs. 0 mutated alleles (n=115)**					**20 vs. 95 larvae with 2 vs. 0 mutated alleles (n=115)**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	1.765	0.360	9.32E-07	1.060	2.470	2.914	0.809	3.17E-04	1.328	4.499	2.482	0.850	3.50E-03	0.816	4.147
	apoea	-0.406	0.264	1.24E-01	-0.923	0.111	-0.282	0.331	3.95E-01	-0.930	0.367	-0.299	0.339	3.78E-01	-0.964	0.366
	apoeb	0.191	0.190	3.14E-01	-0.181	0.563	0.271	0.230	2.40E-01	-0.181	0.722	0.311	0.247	2.07E-01	-0.173	0.795
	ldlra	0.200	0.174	2.51E-01	-0.142	0.542	0.105	0.193	5.88E-01	-0.274	0.483	0.088	0.199	6.59E-01	-0.303	0.479
	body length (in SD)	-	-	-	-	-	0.704	0.296	1.74E-02	0.124	1.284	0.549	0.337	1.03E-01	-0.111	1.210
	dorsal body surface area (in SD)	-	-	-	-	-	0.510	0.185	5.93E-03	0.147	0.874	0.425	0.201	3.44E-02	0.031	0.819
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.051	0.135	7.09E-01	-0.316	0.215
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.147	0.227	5.16E-01	-0.593	0.298
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.317	0.203	1.19E-01	-0.081	0.715
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.060	0.140	6.69E-01	-0.333	0.214
	time of day (in hours since 9AM)	-0.075	0.114	5.09E-01	-0.299	0.148	-0.155	0.148	2.96E-01	-0.445	0.136	-0.066	0.171	6.98E-01	-0.402	0.270
	batch 2	-1.216	0.674	7.13E-02	-2.538	0.106	-0.149	0.900	8.68E-01	-1.913	1.615	-0.215	0.960	8.23E-01	-2.096	1.666
	batch 3	-1.276	0.499	1.06E-02	-2.255	-0.297	-0.998	0.595	9.38E-02	-2.164	0.169	-1.209	0.651	6.32E-02	-2.484	0.066
	batch 4	-0.845	0.467	7.07E-02	-1.761	0.071	-0.047	0.624	9.40E-01	-1.269	1.175	-0.399	0.722	5.80E-01	-1.815	1.016
	batch 5	-0.211	0.387	5.85E-01	-0.970	0.547	-0.011	0.561	9.85E-01	-1.111	1.090	-0.654	0.712	3.59E-01	-2.050	0.743
	batch 6	-0.162	0.381	6.70E-01	-0.910	0.585	-0.524	0.419	2.11E-01	-1.345	0.297	-1.131	0.595	5.72E-02	-2.297	0.034
	batch 7	-1.058	0.462	2.19E-02	-1.963	-0.153	-1.057	0.544	5.19E-02	-2.122	0.009	-1.729	0.830	3.72E-02	-3.355	-0.103
	intercept	183.351	148.640	2.17E-01	-107.977	474.679	174.210	171.135	3.09E-01	-161.209	509.629	131.729	171.727	4.43E-01	-204.849	468.307
	apoba	0.954	0.808	2.37E-01	-0.629	2.537	0.769	0.923	4.05E-01	-1.040	2.577	0.695	0.964	4.71E-01	-1.195	2.584
	apobb.2	-0.031	0.473	9.48E-01	-0.958	0.895	-0.008	0.509	9.88E-01	-1.006	0.990	0.307	0.554	5.80E-01	-0.779	1.394
	ldlrb	-450.568	372.285	2.26E-01	-1200.000	279.096	-427.256	428.905	3.19E-01	-1300.000	413.383	-321.569	430.563	4.55E-01	-1200.000	522.320

							Vascular infiltration by macrophages									
		26 vs. 143 larvae with 2 vs. 0 mutated alleles (n=169)					**26 vs. 126 larvae with 2 vs. 0 mutated alleles (n=152)**					**26 vs. 126 larvae with 2 vs. 0 mutated alleles (n=152)**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.270	0.214	2.08E-01	-0.690	0.150	-0.300	0.255	2.39E-01	-0.799	0.199	-0.092	0.264	7.28E-01	-0.609	0.426
	apoea	-0.110	0.122	3.66E-01	-0.350	0.129	-0.178	0.135	1.89E-01	-0.443	0.087	-0.229	0.134	8.83E-02	-0.492	0.034
	apoeb	-0.089	0.113	4.30E-01	-0.311	0.132	-0.098	0.125	4.35E-01	-0.343	0.148	-0.143	0.125	2.54E-01	-0.387	0.102
	ldlra	0.067	0.112	5.47E-01	-0.152	0.286	0.086	0.122	4.79E-01	-0.153	0.326	0.104	0.120	3.87E-01	-0.132	0.340
	body length (in SD)	-	-	-	-	-	-0.046	0.121	7.06E-01	-0.284	0.192	0.010	0.123	9.36E-01	-0.231	0.251
	dorsal body surface area (in SD)	-	-	-	-	-	-0.194	0.098	4.73E-02	-0.386	-0.002	-0.157	0.100	1.16E-01	-0.352	0.039
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.120	0.085	1.57E-01	-0.046	0.286
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.055	0.101	5.87E-01	-0.144	0.254
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.258	0.117	2.79E-02	-0.488	-0.028
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.063	0.088	4.76E-01	-0.110	0.236
	time of day (in hours since 9AM)	0.103	0.063	1.01E-01	-0.020	0.225	0.117	0.069	9.19E-02	-0.019	0.253	0.068	0.069	3.23E-01	-0.067	0.203
	intercept_random	11.258	88.626	8.99E-01	-162.446	184.962	-2.079	99.580	9.83E-01	-197.253	193.094	1.267	98.915	9.90E-01	-192.603	195.136
	apoba	-0.485	0.450	2.81E-01	-1.367	0.397	-0.542	0.478	2.58E-01	-1.479	0.396	-0.539	0.470	2.51E-01	-1.460	0.382
	apobb.2	-0.189	0.269	4.82E-01	-0.715	0.337	-0.389	0.303	1.99E-01	-0.983	0.204	-0.606	0.314	5.36E-02	-1.221	0.010
	ldlrb	-24.951	221.876	9.10E-01	-459.821	409.919	9.325	249.131	9.70E-01	-478.963	497.613	2.196	247.481	9.93E-01	-482.857	487.250
random factors	***variance by batch***	*0.574*	*0.172*	-	*0.319*	*1.031*	*0.490*	*0.173*	-	*0.245*	*0.980*	*0.366*	*0.143*	-	*0.170*	*0.787*
	residual	*0.899*	*0.050*	-	*0.805*	*1.003*	*0.931*	*0.055*	-	*0.828*	*1.046*	*0.918*	*0.055*	-	*0.817*	*1.031*

continued **Supplementary Table 21**

		Vascular co-localization of lipids with macrophages														
		20 vs. 108 larvae with 2 vs. 0 mutated alleles (n=128)					**20 vs. 92 larvae with 2 vs. 0 mutated alleles (n=112)**					**20 vs. 92 larvae with 2 vs. 0 mutated alleles (n=112)**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	2.295	0.547	2.72E-05	1.223	3.367	4.048	1.068	1.50E-04	1.956	6.141	3.351	1.013	9.44E-04	1.365	5.337
	apoea	-0.269	0.419	5.21E-01	-1.089	0.552	-0.374	0.514	4.66E-01	-1.381	0.632	-0.199	0.538	7.12E-01	-1.253	0.856
	apoeb	-0.236	0.256	3.57E-01	-0.738	0.266	-0.311	0.283	2.72E-01	-0.867	0.244	-0.408	0.276	1.40E-01	-0.950	0.133
	ldlra	0.360	0.208	8.28E-02	-0.047	0.767	0.256	0.220	2.45E-01	-0.175	0.686	0.408	0.233	7.91E-02	-0.047	0.864
	body length (in SD)	-	-	-	-	-	1.231	0.470	8.75E-03	0.311	2.151	1.121	0.485	2.08E-02	0.170	2.071
	dorsal body surface area (in SD)	-	-	-	-	-	0.847	0.259	1.07E-03	0.339	1.354	0.792	0.300	8.21E-03	0.205	1.380
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.363	0.280	1.95E-01	-0.911	0.186
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.033	0.288	9.10E-01	-0.597	0.532
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.096	0.427	8.22E-01	-0.741	0.932
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.232	0.248	3.50E-01	-0.718	0.254
	time of day (in hours since 9AM)	0.215	0.148	1.48E-01	-0.076	0.505	0.313	0.164	5.67E-02	-0.009	0.634	0.437	0.176	1.29E-02	0.092	0.782
	batch 2	0.570	1.135	6.16E-01	-1.655	2.795	1.855	1.345	1.68E-01	-0.782	4.491	1.208	1.298	3.52E-01	-1.337	3.753
	batch 3	-1.739	0.589	3.14E-03	-2.893	-0.585	-1.631	0.721	2.37E-02	-3.045	-0.218	-1.931	0.799	1.57E-02	-3.498	-0.364
	batch 4	-0.373	0.601	5.35E-01	-1.550	0.805	0.295	0.854	7.30E-01	-1.379	1.968	0.269	0.934	7.73E-01	-1.561	2.099
	batch 5	-0.139	0.595	8.16E-01	-1.306	1.028	-0.859	0.762	2.60E-01	-2.353	0.635	-0.795	0.879	3.66E-01	-2.518	0.928
	batch 6	-0.716	0.577	2.14E-01	-1.846	0.414	-2.288	0.702	1.12E-03	-3.664	-0.912	-2.405	1.136	3.43E-02	-4.631	-0.178
	batch 7	-0.845	0.788	2.84E-01	-2.390	0.701	-2.164	0.826	8.77E-03	-3.782	-0.546	-2.372	1.171	4.27E-02	-4.667	-0.078
	intercept	108.949	133.134	4.13E-01	-151.988	369.886	105.728	213.116	6.20E-01	-311.971	523.427	251.845	259.958	3.33E-01	-257.664	761.353
	apoba	-0.919	1.185	4.38E-01	-3.242	1.405	-0.768	1.116	4.92E-01	-2.956	1.420	-0.610	1.095	5.77E-01	-2.757	1.536
	apobb.2	0.031	0.591	9.59E-01	-1.127	1.188	0.132	0.639	8.36E-01	-1.121	1.385	0.210	0.725	7.73E-01	-1.212	1.631
	ldlrb	-263.818	334.248	4.30E-01	-918.933	391.296	-256.522	532.363	6.30E-01	-1300.000	786.891	-623.857	649.781	3.37E-01	-1900.000	649.691

		Vascular infiltration by neutrophils														
		26 vs. 147 larvae with 2 vs. 0 mutated alleles (n=173)					**26 vs. 129 larvae with 2 vs. 0 mutated alleles (n=155)**					**26 vs. 129 larvae with 2 vs. 0 mutated alleles (n=155)**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.428	0.206	3.77E-02	0.024	0.832	0.281	0.235	2.31E-01	-0.179	0.742	0.466	0.245	5.72E-02	-0.014	0.947
	apoea	-0.152	0.116	1.92E-01	-0.380	0.076	-0.217	0.124	8.05E-02	-0.460	0.026	-0.236	0.124	5.78E-02	-0.479	0.008
	apoeb	0.008	0.108	9.40E-01	-0.204	0.220	0.021	0.115	8.58E-01	-0.205	0.247	-0.014	0.116	9.05E-01	-0.241	0.213
	ldlra	-0.088	0.107	4.10E-01	-0.297	0.121	-0.042	0.112	7.08E-01	-0.261	0.177	-0.019	0.111	8.62E-01	-0.237	0.198
	body length (in SD)	-	-	-	-	-	-0.112	0.110	3.08E-01	-0.328	0.103	-0.061	0.112	5.89E-01	-0.280	0.159
	dorsal body surface area (in SD)	-	-	-	-	-	0.040	0.089	6.53E-01	-0.135	0.215	0.074	0.092	4.19E-01	-0.105	0.253
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.054	0.076	4.76E-01	-0.095	0.204
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.049	0.094	6.02E-01	-0.135	0.232
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.186	0.107	8.18E-02	-0.395	0.023
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.122	0.082	1.34E-01	-0.038	0.282
	time of day (in hours since 9AM)	0.029	0.059	6.29E-01	-0.088	0.145	0.017	0.064	7.95E-01	-0.108	0.141	-0.015	0.064	8.14E-01	-0.140	0.110
	intercept_random	-182.126	85.408	3.30E-02	-349.522	-14.729	-203.375	92.181	2.74E-02	-384.047	-22.702	-198.131	92.230	3.17E-02	-378.899	-17.363
	apoba	0.233	0.431	5.89E-01	-0.612	1.078	0.169	0.441	7.02E-01	-0.695	1.033	0.163	0.436	7.09E-01	-0.693	1.018
	apobb.2	0.004	0.259	9.87E-01	-0.503	0.511	0.142	0.280	6.12E-01	-0.407	0.692	0.045	0.292	8.77E-01	-0.527	0.617
	ldlrb	454.749	213.818	3.34E-02	35.674	873.823	507.788	230.619	2.77E-02	55.782	959.793	495.311	230.758	3.18E-02	43.035	947.588
random factors	***variance by batch***	*0.468*	*0.142*	-	*0.258*	*0.850*	*0.407*	*0.140*	-	*0.207*	*0.798*	*0.308*	*0.126*	-	*0.138*	*0.686*
	residual	*0.867*	*0.048*	-	*0.778*	*0.966*	*0.862*	*0.051*	-	*0.769*	*0.967*	*0.856*	*0.050*	-	*0.763*	*0.961*

continued **Supplementary Table 21**

		Vascular co-localization of lipids with neutrophils														
		19 vs. 106 larvae with 2 vs. 0 mutated alleles (n=125)					19 vs. 89 larvae with 2 vs. 0 mutated alleles (n=108)					19 vs. 89 larvae with 2 vs. 0 mutated alleles (n=108)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	4.082	0.541	4.44E-14	3.022	5.142	6.315	1.281	8.31E-07	3.803	8.826	7.962	1.975	5.54E-05	4.091	11.833
	apoea	-1.717	0.466	2.28E-04	-2.630	-0.804	-1.992	0.694	4.13E-03	-3.353	-0.631	-1.881	0.797	1.82E-02	-3.443	-0.320
	apoeb	-0.611	0.382	1.09E-01	-1.359	0.137	-0.545	0.503	2.79E-01	-1.531	0.441	0.150	0.569	7.92E-01	-0.964	1.264
	ldlra	0.031	0.290	9.15E-01	-0.538	0.599	0.112	0.288	6.98E-01	-0.453	0.677	-0.199	0.375	5.96E-01	-0.933	0.536
	body length (in SD)	-	-	-	-	-	1.422	0.684	3.75E-02	0.082	2.763	1.521	0.820	6.37E-02	-0.087	3.128
	dorsal body surface area (in SD)	-	-	-	-	-	-0.259	0.340	4.46E-01	-0.925	0.407	-0.435	0.374	2.45E-01	-1.169	0.298
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.411	0.337	2.22E-01	-0.249	1.071
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.177	0.558	7.51E-01	-1.272	0.917
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.144	0.616	8.15E-01	-1.352	1.063
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.340	0.467	4.13E-03	0.424	2.256
	time of day (in hours since 9AM)	-0.506	0.180	5.00E-03	-0.860	-0.153	-0.598	0.315	5.76E-02	-1.215	0.019	-0.547	0.350	1.19E-01	-1.233	0.140
	batch 2	-3.868	1.152	7.90E-04	-6.126	-1.609	-3.200	1.213	8.33E-03	-5.577	-0.823	-0.841	1.754	6.32E-01	-4.278	2.596
	batch 3	-1.358	0.854	1.12E-01	-3.033	0.316	-1.330	0.923	1.49E-01	-3.138	0.478	-1.396	1.122	2.14E-01	-3.596	0.804
	batch 4	-1.785	0.808	2.72E-02	-3.369	-0.201	-1.256	0.998	2.08E-01	-3.212	0.700	-1.802	1.075	9.37E-02	-3.909	0.305
	batch 5	-1.321	0.655	4.36E-02	-2.604	-0.038	-1.559	0.883	7.76E-02	-3.290	0.173	-1.916	1.500	2.02E-01	-4.855	1.024
	batch 6	-3.031	0.662	4.74E-06	-4.329	-1.733	-2.775	0.935	2.99E-03	-4.607	-0.943	-2.871	1.403	4.08E-02	-5.621	-0.121
	intercept	-214.663	420.786	6.10E-01	-1000.000	610.062	-472.077	522.037	3.66E-01	-1500.000	551.098	-942.198	584.076	1.07E-01	-2100.000	202.571
	apoba	3.615	1.392	9.41E-03	0.886	6.343	3.721	1.556	1.68E-02	0.671	6.771	4.649	2.299	4.31E-02	0.144	9.154
	apobb.2	0.569	0.805	4.79E-01	-1.008	2.146	0.248	0.958	7.96E-01	-1.629	2.125	1.111	1.180	3.46E-01	-1.202	3.425
	ldlrb	530.344	1051.605	6.14E-01	-1500.000	2591.452	1174.217	1307.275	3.69E-01	-1400.000	3736.429	2338.624	1464.591	1.10E-01	-531.921	5209.169

		Vascular co-localization of macrophages with neutrophils														
		26 vs. 143 larvae with 2 vs. 0 mutated alleles (n=169)					26 vs. 126 larvae with 2 vs. 0 mutated alleles (n=152)					26 vs. 126 larvae with 2 vs. 0 mutated alleles (n=152)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.080	0.279	7.73E-01	-0.467	0.628	0.002	0.312	9.96E-01	-0.609	0.613	0.101	0.328	7.58E-01	-0.542	0.743
	apoea	-0.230	0.158	1.45E-01	-0.540	0.080	-0.287	0.172	9.53E-02	-0.624	0.050	-0.435	0.181	1.63E-02	-0.790	-0.080
	apoeb	-0.011	0.149	9.41E-01	-0.302	0.280	-0.040	0.162	8.03E-01	-0.359	0.278	-0.066	0.156	6.72E-01	-0.371	0.239
	ldlra	-0.041	0.137	7.66E-01	-0.310	0.228	-0.042	0.132	7.52E-01	-0.301	0.218	0.047	0.132	7.21E-01	-0.212	0.307
	body length (in SD)	-	-	-	-	-	-0.026	0.165	8.73E-01	-0.350	0.297	-0.019	0.201	9.23E-01	-0.414	0.375
	dorsal body surface area (in SD)	-	-	-	-	-	0.123	0.142	3.86E-01	-0.155	0.401	0.103	0.150	4.92E-01	-0.191	0.397
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.012	0.143	9.35E-01	-0.268	0.292
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.166	0.147	2.60E-01	-0.454	0.122
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.284	0.219	1.95E-01	-0.714	0.145
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.304	0.112	6.68E-03	0.084	0.524
	time of day (in hours since 9AM)	0.253	0.079	1.25E-03	0.099	0.407	0.235	0.086	6.31E-03	0.066	0.404	0.185	0.093	4.62E-02	0.003	0.367
	batch 1	-0.542	0.505	2.83E-01	-1.533	0.448	-0.413	0.576	4.74E-01	-1.542	0.717	-0.276	0.782	7.24E-01	-1.809	1.257
	batch 2	-0.959	0.494	5.22E-02	-1.927	0.009	-1.027	0.525	5.05E-02	-2.057	0.002	-0.697	0.619	2.60E-01	-1.910	0.515
	batch 3	-1.403	0.500	4.99E-03	-2.383	-0.424	-1.360	0.508	7.39E-03	-2.354	-0.365	-1.238	0.639	5.27E-02	-2.489	0.014
	batch 4	0.258	0.523	6.23E-01	-0.768	1.284	0.275	0.520	5.96E-01	-0.743	1.294	0.232	0.632	7.13E-01	-1.007	1.471
	batch 5	-0.934	0.444	3.53E-02	-1.804	-0.064	-1.058	0.501	3.46E-02	-2.040	-0.076	-0.619	0.603	3.04E-01	-1.800	0.562
	batch 6	-2.488	0.504	7.97E-07	-3.476	-1.500	-2.571	0.611	2.54E-05	-3.767	-1.374	-2.227	0.664	8.01E-04	-3.529	-0.925
	batch 7	-2.134	0.793	7.15E-03	-3.689	-0.579	-2.135	0.849	1.19E-02	-3.799	-0.471	-2.588	1.027	1.17E-02	-4.600	-0.575
	intercept	-185.934	104.046	7.39E-02	-389.861	17.993	-142.067	123.760	2.51E-01	-384.633	100.498	-147.810	126.894	2.44E-01	-396.517	100.898
	apoba	-0.090	0.607	8.82E-01	-1.281	1.100	0.110	0.598	8.54E-01	-1.063	1.282	0.303	0.577	5.99E-01	-0.827	1.434
	apobb.2	-0.339	0.366	3.55E-01	-1.056	0.379	-0.520	0.407	2.02E-01	-1.318	0.279	-0.419	0.388	2.79E-01	-1.179	0.340
	ldlrb	477.129	261.076	6.76E-02	-34.570	988.829	367.600	310.089	2.36E-01	-240.163	975.364	380.686	317.971	2.31E-01	-242.525	1003.897

continued **Supplementary Table 21**

		ldlra														
		Vascular lipid deposition														
		Model 1					Model 2					Model 3				
		130 vs. 90 larvae with 2 vs. 0 mutated alleles (n=220)					117 vs. 80 larvae with 2 vs. 0 mutated alleles (n=197)					117 vs. 80 larvae with 2 vs. 0 mutated alleles (n=197)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.111	0.251	6.58E-01	-0.381	0.603	0.104	0.266	6.97E-01	-0.418	0.626	0.073	0.275	7.91E-01	-0.466	0.612
	apoea	-0.189	0.195	3.32E-01	-0.571	0.193	-0.183	0.212	3.89E-01	-0.598	0.233	-0.172	0.209	4.10E-01	-0.582	0.238
	apoeb	0.308	0.164	6.09E-02	-0.014	0.629	0.394	0.186	3.46E-02	0.029	0.759	0.392	0.191	4.03E-02	0.017	0.768
	apobb.1	0.996	0.161	5.70E-10	0.681	1.310	0.937	0.198	2.13E-06	0.549	1.324	0.898	0.210	1.91E-05	0.486	1.310
	body length (in SD)	-	-	-	-	-	-0.071	0.167	6.70E-01	-0.398	0.256	-0.041	0.175	8.16E-01	-0.384	0.302
	dorsal body surface area (in SD)	-	-	-	-	-	0.197	0.141	1.63E-01	-0.080	0.474	0.213	0.145	1.43E-01	-0.072	0.498
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.015	0.107	8.85E-01	-0.225	0.194
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.045	0.144	7.53E-01	-0.327	0.237
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.140	0.178	4.33E-01	-0.209	0.489
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.042	0.121	7.30E-01	-0.279	0.195
	time of day (in hours since 9AM)	-0.062	0.094	5.07E-01	-0.246	0.122	-0.107	0.117	3.60E-01	-0.335	0.122	-0.086	0.118	4.66E-01	-0.318	0.146
	batch 2	-1.659	0.483	5.94E-04	-2.606	-0.712	-1.871	0.575	1.13E-03	-2.998	-0.745	-1.705	0.605	4.79E-03	-2.890	-0.520
	batch 3	-0.467	0.382	2.21E-01	-1.216	0.282	-0.569	0.399	1.54E-01	-1.351	0.213	-0.644	0.442	1.45E-01	-1.509	0.222
	batch 4	-0.714	0.416	8.63E-02	-1.529	0.102	-0.820	0.449	6.77E-02	-1.699	0.060	-0.818	0.467	8.02E-02	-1.734	0.098
	batch 5	0.372	0.321	2.46E-01	-0.257	1.001	0.208	0.367	5.72E-01	-0.512	0.928	-0.019	0.503	9.70E-01	-1.005	0.967
	batch 6	0.156	0.281	5.80E-01	-0.395	0.707	0.092	0.318	7.72E-01	-0.531	0.716	-0.232	0.535	6.64E-01	-1.281	0.816
	batch 7	-0.554	0.363	1.27E-01	-1.266	0.157	-0.730	0.377	5.27E-02	-1.468	0.008	-0.959	0.554	8.37E-02	-2.046	0.128
	intercept	280.829	147.422	5.68E-02	-8.113	569.772	320.998	153.007	3.59E-02	21.110	620.886	319.158	154.393	3.87E-02	16.554	621.762
	apoba	-0.166	0.630	7.92E-01	-1.401	1.069	-0.357	0.644	5.79E-01	-1.619	0.905	-0.211	0.668	7.52E-01	-1.520	1.098
	apobb.2	-0.046	0.404	9.10E-01	-0.837	0.746	-0.138	0.409	7.36E-01	-0.940	0.665	-0.060	0.419	8.86E-01	-0.881	0.761
	ldlrb	-690.958	368.791	6.10E-02	-1400.000	31.859	-789.795	382.814	3.91E-02	-1500.000	-39.493	-785.887	386.208	4.19E-02	-1500.000	-28.933

							Vascular infiltration by macrophages									
		174 vs. 117 larvae with 2 vs. 0 mutated alleles (n=291)					158 vs. 102 larvae with 2 vs. 0 mutated alleles (n=260)					158 vs. 102 larvae with 2 vs. 0 mutated alleles (n=260)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.077	0.136	5.70E-01	-0.189	0.343	0.029	0.152	8.50E-01	-0.269	0.327	0.000	0.152	1.00E+00	-0.297	0.297
	apoea	-0.126	0.087	1.48E-01	-0.297	0.045	-0.184	0.094	5.13E-02	-0.369	0.001	-0.197	0.094	3.66E-02	-0.382	-0.012
	apoeb	-0.181	0.090	4.53E-02	-0.357	-0.004	-0.170	0.099	8.64E-02	-0.365	0.024	-0.167	0.099	9.21E-02	-0.362	0.027
	apobb.1	-0.190	0.096	4.64E-02	-0.378	-0.003	-0.186	0.106	7.95E-02	-0.393	0.022	-0.207	0.107	5.29E-02	-0.417	0.003
	body length (in SD)	-	-	-	-	-	-0.004	0.083	9.63E-01	-0.167	0.159	-0.009	0.084	9.12E-01	-0.175	0.156
	dorsal body surface area (in SD)	-	-	-	-	-	-0.069	0.068	3.11E-01	-0.202	0.064	-0.071	0.069	3.00E-01	-0.206	0.063
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.086	0.061	1.57E-01	-0.033	0.204
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.073	0.068	2.86E-01	-0.061	0.207
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.060	0.085	4.82E-01	-0.106	0.226
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.074	0.064	2.47E-01	-0.199	0.051
	time of day (in hours since 9AM)	0.008	0.047	8.71E-01	-0.084	0.099	0.012	0.052	8.18E-01	-0.091	0.115	0.017	0.053	7.53E-01	-0.087	0.120
	intercept_random	0.946	1.148	4.10E-01	-1.304	3.196	1.163	1.212	3.37E-01	-1.212	3.538	1.342	1.209	2.67E-01	-1.027	3.711
	apoba	-0.123	0.336	7.14E-01	-0.782	0.535	-0.127	0.365	7.28E-01	-0.841	0.588	-0.186	0.363	6.08E-01	-0.897	0.525
	apobb.2	-0.173	0.218	4.27E-01	-0.601	0.254	-0.228	0.238	3.38E-01	-0.695	0.239	-0.278	0.239	2.45E-01	-0.747	0.191
	ldlrb	-0.088	2.256	9.69E-01	-4.511	4.334	-0.312	2.335	8.94E-01	-4.889	4.266	-0.245	2.333	9.16E-01	-4.817	4.327
random factors	***variance by batch***	*0.442*	*0.129*	-	*0.249*	*0.784*	*0.421*	*0.130*	-	*0.230*	*0.773*	*0.396*	*0.128*	-	*0.211*	*0.744*
	residual	*0.878*	*0.037*	-	*0.808*	*0.954*	*0.903*	*0.040*	-	*0.828*	*0.986*	*0.896*	*0.040*	-	*0.821*	*0.979*

continued **Supplementary Table 21**

		Vascular co-localization of lipids with macrophages														
		128 vs. 89 larvae with 2 vs. 0 mutated alleles (n=217)					115 vs. 79 larvae with 2 vs. 0 mutated alleles (n=194)					115 vs. 79 larvae with 2 vs. 0 mutated alleles (n=194)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.184	0.338	5.87E-01	-0.479	0.846	0.244	0.377	5.19E-01	-0.496	0.983	0.208	0.380	5.84E-01	-0.536	0.952
	apoea	-0.008	0.252	9.76E-01	-0.502	0.487	-0.147	0.270	5.87E-01	-0.676	0.382	-0.168	0.269	5.31E-01	-0.696	0.359
	apoeb	0.023	0.231	9.22E-01	-0.431	0.476	0.141	0.254	5.80E-01	-0.358	0.639	0.136	0.260	6.01E-01	-0.373	0.645
	apobb.1	1.145	0.230	6.01E-07	0.696	1.595	0.895	0.296	2.49E-03	0.315	1.474	0.799	0.363	2.75E-02	0.088	1.510
	body length (in SD)	-	-	-	-	-	-0.164	0.238	4.90E-01	-0.631	0.302	-0.215	0.281	4.45E-01	-0.766	0.336
	dorsal body surface area (in SD)	-	-	-	-	-	0.319	0.150	3.34E-02	0.025	0.613	0.308	0.149	3.88E-02	0.016	0.601
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.094	0.171	5.83E-01	-0.241	0.429
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.118	0.224	5.98E-01	-0.321	0.558
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.178	0.275	5.18E-01	-0.362	0.717
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.088	0.162	5.86E-01	-0.406	0.229
	time of day (in hours since 9AM)	0.091	0.112	4.16E-01	-0.128	0.310	0.088	0.132	5.04E-01	-0.170	0.347	0.117	0.141	4.07E-01	-0.160	0.394
	batch 2	-2.643	0.693	1.38E-04	-4.002	-1.284	-3.005	0.793	1.50E-04	-4.559	-1.452	-3.007	0.802	1.77E-04	-4.579	-1.435
	batch 3	-1.141	0.418	6.35E-03	-1.961	-0.322	-1.133	0.497	2.27E-02	-2.107	-0.158	-1.092	0.549	4.67E-02	-2.169	-0.016
	batch 4	-0.119	0.500	8.12E-01	-1.099	0.861	-0.367	0.567	5.18E-01	-1.477	0.744	-0.283	0.635	6.56E-01	-1.528	0.961
	batch 5	0.440	0.405	2.76E-01	-0.353	1.233	0.151	0.506	7.65E-01	-0.840	1.143	0.003	0.757	9.97E-01	-1.482	1.487
	batch 6	-0.124	0.392	7.52E-01	-0.891	0.644	-0.142	0.452	7.53E-01	-1.028	0.744	-0.318	0.969	7.42E-01	-2.217	1.580
	batch 7	-0.761	0.790	3.35E-01	-2.309	0.787	-1.260	0.764	9.92E-02	-2.758	0.238	-1.208	0.973	2.14E-01	-3.115	0.699
	intercept	563.870	199.665	4.74E-03	172.534	955.207	660.449	204.076	1.21E-03	260.468	1060.430	696.194	205.187	6.91E-04	294.035	1098.352
	apoba	-0.860	1.155	4.57E-01	-3.122	1.403	-1.185	1.185	3.18E-01	-3.508	1.138	-0.979	1.236	4.28E-01	-3.401	1.443
	apobb.2	-0.139	0.519	7.89E-01	-1.156	0.878	-0.355	0.519	4.94E-01	-1.372	0.663	-0.287	0.561	6.09E-01	-1.386	0.813
	ldlrb	-1400.000	498.871	4.96E-03	-2400.000	-423.915	-1600.000	509.990	1.30E-03	-2600.000	-640.783	-1700.000	512.929	7.40E-04	-2700.000	-725.512

		Vascular infiltration by neutrophils														
		175 vs. 118 larvae with 2 vs. 0 mutated alleles (n=293)					159 vs. 103 larvae with 2 vs. 0 mutated alleles (n=262)					159 vs. 103 larvae with 2 vs. 0 mutated alleles (n=262)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.224	0.131	8.60E-02	-0.480	0.032	-0.222	0.141	1.14E-01	-0.498	0.053	-0.218	0.140	1.21E-01	-0.493	0.057
	apoea	-0.033	0.083	6.88E-01	-0.197	0.130	-0.071	0.087	4.18E-01	-0.242	0.100	-0.067	0.087	4.42E-01	-0.238	0.104
	apoeb	-0.053	0.087	5.38E-01	-0.223	0.116	-0.014	0.092	8.81E-01	-0.194	0.166	-0.030	0.092	7.45E-01	-0.210	0.150
	apobb.1	0.126	0.092	1.71E-01	-0.054	0.306	0.034	0.098	7.28E-01	-0.158	0.225	0.057	0.099	5.62E-01	-0.137	0.251
	body length (in SD)	-	-	-	-	-	-0.161	0.076	3.44E-02	-0.310	-0.012	-0.138	0.078	7.50E-02	-0.290	0.014
	dorsal body surface area (in SD)	-	-	-	-	-	0.007	0.062	9.06E-01	-0.114	0.129	0.030	0.063	6.39E-01	-0.094	0.153
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.033	0.055	5.50E-01	-0.141	0.075
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.053	0.063	4.00E-01	-0.070	0.177
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.096	0.077	2.10E-01	-0.247	0.054
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.065	0.059	2.67E-01	-0.050	0.181
	time of day (in hours since 9AM)	-0.014	0.044	7.59E-01	-0.100	0.073	-0.036	0.048	4.48E-01	-0.129	0.057	-0.043	0.048	3.69E-01	-0.137	0.051
	intercept_random	0.244	1.101	8.25E-01	-1.914	2.402	-0.103	1.119	9.27E-01	-2.297	2.091	-0.103	1.119	9.26E-01	-2.296	2.089
	apoba	0.488	0.323	1.30E-01	-0.144	1.120	0.557	0.337	9.81E-02	-0.103	1.218	0.584	0.336	8.20E-02	-0.074	1.243
	apobb.2	-0.169	0.210	4.21E-01	-0.581	0.243	-0.093	0.221	6.73E-01	-0.526	0.340	-0.094	0.222	6.72E-01	-0.529	0.341
	ldlrb	-1.665	2.175	4.44E-01	-5.927	2.598	-1.151	2.169	5.96E-01	-5.403	3.100	-1.232	2.173	5.71E-01	-5.492	3.027
random factors	***variance by batch***	*0.343*	*0.102*	-	*0.192*	*0.615*	*0.314*	*0.098*	-	*0.171*	*0.578*	*0.303*	*0.096*	-	*0.163*	*0.563*
	residual	*0.847*	*0.036*	-	*0.780*	*0.919*	*0.839*	*0.037*	-	*0.769*	*0.915*	*0.834*	*0.037*	-	*0.765*	*0.910*

continued **Supplementary Table 21**

		Vascular co-localization of lipids with neutrophils														
		123 vs. 85 larvae with 2 vs. 0 mutated alleles (n=208)					110 vs. 75 larvae with 2 vs. 0 mutated alleles (n=185)					110 vs. 75 larvae with 2 vs. 0 mutated alleles (n=185)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.043	0.496	9.31E-01	-0.929	1.015	0.299	0.483	5.36E-01	-0.647	1.245	-0.089	0.481	8.53E-01	-1.031	0.853
	apoea	-0.944	0.371	1.09E-02	-1.672	-0.217	-1.037	0.412	1.18E-02	-1.844	-0.229	-1.329	0.471	4.77E-03	-2.252	-0.406
	apoeb	-0.379	0.342	2.69E-01	-1.050	0.292	-0.270	0.324	4.05E-01	-0.905	0.365	-0.234	0.315	4.58E-01	-0.851	0.384
	apobb.1	2.008	0.316	2.06E-10	1.389	2.626	1.756	0.391	6.97E-06	0.990	2.521	2.266	0.444	3.34E-07	1.396	3.136
	body length (in SD)	-	-	-	-	-	-0.593	0.294	4.38E-02	-1.169	-0.016	-0.817	0.276	3.06E-03	-1.358	-0.276
	dorsal body surface area (in SD)	-	-	-	-	-	-0.419	0.210	4.56E-02	-0.830	-0.008	-0.645	0.235	5.97E-03	-1.105	-0.185
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.859	0.339	1.14E-02	0.194	1.524
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.974	0.369	8.26E-03	0.251	1.696
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.482	0.387	2.12E-01	-0.276	1.240
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.588	0.284	3.80E-02	0.032	1.144
	time of day (in hours since 9AM)	-0.130	0.173	4.50E-01	-0.469	0.208	0.204	0.227	3.68E-01	-0.240	0.648	0.345	0.236	1.45E-01	-0.119	0.808
	batch 2	-3.290	0.866	1.44E-04	-4.987	-1.594	-3.777	0.835	6.12E-06	-5.414	-2.140	-3.831	0.924	3.38E-05	-5.642	-2.020
	batch 3	0.046	0.833	9.56E-01	-1.587	1.680	-0.065	0.817	9.36E-01	-1.667	1.536	-0.456	0.766	5.51E-01	-1.958	1.045
	batch 4	-0.858	0.698	2.19E-01	-2.225	0.509	-1.467	0.741	4.77E-02	-2.919	-0.015	-2.263	0.873	9.53E-03	-3.974	-0.552
	batch 5	0.197	0.640	7.59E-01	-1.058	1.451	-0.536	0.667	4.22E-01	-1.842	0.771	-1.466	0.902	1.04E-01	-3.235	0.302
	batch 6	-1.714	0.692	1.32E-02	-3.070	-0.358	-1.552	0.687	2.39E-02	-2.899	-0.205	-1.854	1.026	7.07E-02	-3.865	0.156
	intercept	469.980	217.000	3.03E-02	44.667	895.292	696.320	210.590	9.45E-04	283.570	1109.069	820.268	241.156	6.70E-04	347.611	1292.926
	apoba	2.535	1.153	2.79E-02	0.275	4.795	2.308	1.180	5.05E-02	-0.005	4.620	4.189	1.468	4.33E-03	1.311	7.067
	apobb.2	1.439	0.734	5.01E-02	0.000	2.878	1.334	0.721	6.42E-02	-0.078	2.747	2.106	0.792	7.84E-03	0.554	3.658
	ldlrb	-1200.000	543.813	2.89E-02	-2300.000	-122.607	-1800.000	528.345	8.90E-04	-2800.000	-720.288	-2100.000	605.508	5.99E-04	-3300.000	-891.491

		Vascular co-localization of macrophages with neutrophils														
		173 vs. 117 larvae with 2 vs. 0 mutated alleles (n=290)					157 vs. 102 larvae with 2 vs. 0 mutated alleles (n=259)					157 vs. 102 larvae with 2 vs. 0 mutated alleles (n=259)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.299	0.223	1.80E-01	-0.736	0.138	-0.455	0.232	4.99E-02	-0.910	0.000	-0.465	0.233	4.57E-02	-0.922	-0.009
	apoea	-0.150	0.128	2.39E-01	-0.401	0.100	-0.158	0.134	2.38E-01	-0.420	0.104	-0.156	0.136	2.50E-01	-0.422	0.110
	apoeb	0.072	0.131	5.83E-01	-0.185	0.329	0.118	0.140	4.01E-01	-0.157	0.393	0.095	0.138	4.92E-01	-0.176	0.365
	apobb.1	-0.072	0.153	6.36E-01	-0.372	0.227	-0.085	0.147	5.64E-01	-0.373	0.203	-0.039	0.147	7.91E-01	-0.328	0.250
	body length (in SD)	-	-	-	-	-	0.236	0.122	5.37E-02	-0.004	0.475	0.228	0.131	8.27E-02	-0.030	0.486
	dorsal body surface area (in SD)	-	-	-	-	-	0.350	0.116	2.46E-03	0.123	0.576	0.357	0.121	3.14E-03	0.120	0.595
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.031	0.106	7.70E-01	-0.177	0.238
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.024	0.112	8.31E-01	-0.196	0.244
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.104	0.150	4.86E-01	-0.398	0.189
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.125	0.095	1.88E-01	-0.061	0.310
	time of day (in hours since 9AM)	0.025	0.080	7.50E-01	-0.131	0.181	0.011	0.083	8.94E-01	-0.151	0.173	-0.006	0.086	9.45E-01	-0.174	0.162
	batch 1	0.300	0.321	3.51E-01	-0.330	0.930	0.107	0.354	7.63E-01	-0.588	0.802	0.093	0.430	8.29E-01	-0.750	0.935
	batch 2	0.189	0.490	7.00E-01	-0.771	1.149	0.246	0.462	5.94E-01	-0.659	1.152	0.208	0.501	6.78E-01	-0.773	1.189
	batch 3	-0.660	0.441	1.34E-01	-1.525	0.204	-0.643	0.433	1.38E-01	-1.492	0.206	-0.589	0.479	2.19E-01	-1.528	0.349
	batch 4	0.442	0.381	2.46E-01	-0.304	1.187	0.573	0.399	1.51E-01	-0.209	1.355	0.502	0.447	2.61E-01	-0.374	1.378
	batch 5	0.067	0.387	8.63E-01	-0.692	0.826	-0.183	0.405	6.51E-01	-0.976	0.610	-0.028	0.457	9.52E-01	-0.923	0.868
	batch 6	-1.557	0.403	1.11E-04	-2.346	-0.768	-2.058	0.465	9.81E-06	-2.970	-1.145	-1.927	0.489	8.25E-05	-2.886	-0.968
	batch 7	-0.537	0.550	3.28E-01	-1.614	0.540	-1.034	0.592	8.08E-02	-2.195	0.127	-1.022	0.734	1.64E-01	-2.461	0.416
	intercept	3.443	0.942	2.58E-04	1.596	5.291	3.341	0.936	3.57E-04	1.507	5.176	2.978	0.976	2.29E-03	1.064	4.892
	apoba	0.309	0.508	5.43E-01	-0.686	1.304	0.480	0.492	3.30E-01	-0.485	1.444	0.565	0.483	2.42E-01	-0.382	1.513
	apobb.2	-0.009	0.273	9.73E-01	-0.544	0.526	-0.039	0.276	8.89E-01	-0.579	0.502	0.004	0.276	9.88E-01	-0.538	0.546
	ldlrb	0.307	0.742	6.79E-01	-1.146	1.760	0.522	0.879	5.52E-01	-1.200	2.244	0.893	0.997	3.71E-01	-1.062	2.848

Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis and examined using hierarchical linear models. Effects shown are for larvae with two mutated alleles that are highly likely to affect protein function as predicted by Ensembl's Varient Effect Predictor (VEP) compared with larvae with zero CRISPR-mutated alleles. Associations were adjusted for the number of mutated alleles in the other six orthologues, weighted by their predicted effect on protein function, as well as for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 22 - The additive effect of mutated alleles in *apoea* , *apoeb* , *apobb.1* and *ldlra* on body size

		Body length (n=339)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.008	0.063	8.96E-01	-0.115	0.131
	apoeb	-0.010	0.070	8.89E-01	-0.146	0.127
	apoba	-0.039	0.233	8.67E-01	-0.495	0.417
	apobb.1	-0.336	0.065	2.57E-07	-0.464	-0.208
	apobb.2	0.393	0.162	1.52E-02	0.076	0.711
	ldlra	0.058	0.054	2.85E-01	-0.048	0.164
	time of day (in hours since 9AM)	-0.039	0.036	2.76E-01	-0.110	0.032
	intercept	-1.203	0.891	1.77E-01	-2.950	0.544
	ldlrb	2.088	1.789	2.43E-01	-1.418	5.595
random factors	***variance by batch***	*0.497*	*0.135*	-	*0.292*	*0.846*
	residual	*0.698*	*0.027*	-	*0.647*	*0.753*

		Dorsal body surface area (n=339)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.120	0.074	1.08E-01	-0.266	0.026
	apoeb	0.122	0.083	1.39E-01	-0.040	0.284
	apoba	0.072	0.276	7.94E-01	-0.469	0.613
	apobb.1	0.114	0.077	1.39E-01	-0.037	0.266
	apobb.2	-0.426	0.192	2.67E-02	-0.802	-0.049
	ldlra	-0.069	0.064	2.80E-01	-0.195	0.056
	time of day (in hours since 9AM)	0.029	0.043	4.99E-01	-0.055	0.112
	intercept	1.396	1.050	1.83E-01	-0.661	3.454
	ldlrb	-2.842	2.122	1.80E-01	-7.001	1.316
random factors	***variance by batch***	*0.475*	*0.134*	-	*0.273*	*0.827*
	residual	*0.828*	*0.032*	-	*0.768*	*0.894*

		Lateral body surface area (n=335)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.131	0.076	8.49E-02	-0.281	0.018
	apoeb	0.169	0.086	4.83E-02	0.001	0.337
	apoba	-0.013	0.286	9.63E-01	-0.573	0.547
	apobb.1	0.020	0.079	8.04E-01	-0.136	0.175
	apobb.2	-0.207	0.196	2.92E-01	-0.592	0.178
	ldlra	-0.026	0.066	6.99E-01	-0.155	0.104
	time of day (in hours since 9AM)	0.014	0.044	7.51E-01	-0.072	0.099
	intercept	1.049	1.076	3.30E-01	-1.061	3.158
	ldlrb	-2.429	2.170	2.63E-01	-6.682	1.823
random factors	***variance by batch***	*0.469*	*0.132*	-	*0.270*	*0.814*
	residual	*0.845*	*0.033*	-	*0.783*	*0.913*

		Body volume (n=328)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.111	0.076	1.43E-01	-0.259	0.037
	apoeb	0.170	0.085	4.48E-02	0.004	0.336
	apoba	0.015	0.281	9.57E-01	-0.535	0.566
	apobb.1	0.047	0.079	5.52E-01	-0.107	0.201
	apobb.2	-0.294	0.195	1.32E-01	-0.676	0.089
	ldlra	-0.043	0.065	5.11E-01	-0.171	0.085
	time of day (in hours since 9AM)	0.036	0.044	4.09E-01	-0.050	0.122
	intercept	1.177	1.058	2.66E-01	-0.897	3.250
	ldlrb	-2.747	2.123	1.96E-01	-6.909	1.415
random factors	***variance by batch***	*0.478*	*0.134*	-	*0.276*	*0.827*
	residual	*0.826*	*0.033*	-	*0.765*	*0.893*

All outcomes were normalized for length using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models. Effects shown are for each additional mutated allele in *apoea* , *apoeb* , *apoba* , *apobb.1*, *apobb.2* , *ldlra* and *ldlrb*, weighted by the allele's predicted effect on protein function (i.e. additive model, mutually adjusted). Associations were adjusted for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 23 - The additive effect of mutated alleles in *apoea* , *apoeb* , *apobb.1* and *ldlra* on

		LDL cholesterol levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.183	0.080	2.31E-02	0.025	0.341
	apoeb	0.068	0.089	4.43E-01	-0.106	0.243
	apoba	0.164	0.300	5.86E-01	-0.425	0.753
	apobb.1	0.043	0.085	6.17E-01	-0.124	0.209
	apobb.2	0.293	0.211	1.65E-01	-0.120	0.706
	ldlra	-0.027	0.068	6.94E-01	-0.160	0.107
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	0.055	0.043	2.00E-01	-0.029	0.138
	intercept	0.392	1.169	7.38E-01	-1.900	2.684
	ldlrb	-3.665	2.418	1.30E-01	-8.405	1.074
random factors	***variance by batch***	*0.331*	*0.119*	-	*0.164*	*0.668*
	residual	*0.948*	*0.035*	-	*0.882*	*1.018*

		HDL cholesterol levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.031	0.073	6.76E-01	-0.113	0.174
	apoeb	0.092	0.081	2.54E-01	-0.066	0.250
	apoba	0.013	0.273	9.63E-01	-0.522	0.547
	apobb.1	0.079	0.077	3.06E-01	-0.072	0.230
	apobb.2	0.318	0.191	9.60E-02	-0.056	0.693
	ldlra	0.066	0.062	2.83E-01	-0.055	0.187
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	-0.028	0.040	4.83E-01	-0.107	0.050
	intercept	-1.030	1.076	3.39E-01	-3.138	1.079
	ldlrb	0.847	2.194	6.99E-01	-3.453	5.147
random factors	***variance by batch***	*0.592*	*0.160*	-	*0.348*	*1.006*
	residual	*0.857*	*0.031*	-	*0.797*	*0.921*

		Triglyceride levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.083	0.058	1.53E-01	-0.198	0.031
	apoeb	0.008	0.064	9.06E-01	-0.118	0.133
	apoba	-0.178	0.217	4.11E-01	-0.604	0.247
	apobb.1	0.108	0.061	7.86E-02	-0.012	0.228
	apobb.2	-0.298	0.152	4.99E-02	-0.596	0.000
	ldlra	0.025	0.049	6.05E-01	-0.071	0.122
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	-0.143	0.032	9.33E-06	-0.206	-0.080
	intercept	1.064	0.883	2.28E-01	-0.667	2.795
	ldlrb	-0.236	1.746	8.93E-01	-3.658	3.187
random factors	***variance by batch***	*0.771*	*0.198*	-	*0.467*	*1.275*
	residual	*0.681*	*0.025*	-	*0.634*	*0.732*

continued **Supplementary Table 23**

		Total cholesterol levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.046	0.070	5.08E-01	-0.090	0.182
	apoeb	0.049	0.076	5.20E-01	-0.101	0.199
	apoba	0.192	0.259	4.57E-01	-0.315	0.700
	apobb.1	-0.219	0.073	2.69E-03	-0.363	-0.076
	apobb.2	-0.109	0.181	5.47E-01	-0.465	0.246
	ldlra	-0.027	0.059	6.46E-01	-0.142	0.088
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	0.075	0.038	5.04E-02	0.000	0.150
	intercept	0.130	1.036	9.00E-01	-1.899	2.160
	ldlrb	-1.012	2.082	6.27E-01	-5.092	3.068
random factors	***variance by batch***	*0.748*	*0.198*	-	*0.445*	*1.255*
	residual	*0.812*	*0.030*	-	*0.756*	*0.873*

		Glucose levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.062	0.080	4.36E-01	-0.220	0.095
	apoeb	0.121	0.089	1.71E-01	-0.053	0.295
	apoba	-0.141	0.300	6.38E-01	-0.728	0.446
	apobb.1	-0.172	0.085	4.27E-02	-0.338	-0.006
	apobb.2	-0.385	0.210	6.69E-02	-0.797	0.027
	ldlra	-0.076	0.068	2.63E-01	-0.209	0.057
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	0.038	0.043	3.72E-01	-0.046	0.122
	intercept	1.544	1.167	1.86E-01	-0.744	3.832
	ldlrb	-1.971	2.410	4.13E-01	-6.694	2.752
random factors	***variance by batch***	*0.384*	*0.121*	-	*0.207*	*0.710*
	residual	*0.943*	*0.035*	-	*0.878*	*1.014*

All outcomes were normalized for length using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models. Effects shown are for each additional mutated allele in *apoea* , *apoeb* , *apoba* , *apobb.1*, *apobb.2* , *ldlra* and *ldlrb*, weighted by the allele's predicted effect on protein function (i.e. additive model, mutually adjusted). Associations were adjusted for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 24 - The additive effect of mutated alleles in *apoea* , *apoeb* , *apobb.1* and *ldlra* on image-based vascular atherogenic traits

		Vascular lipid deposition														
		Model 1 (n=306)					Model 2 (n=272)					Model 3 (n=272)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	-0.120	0.158	4.47E-01	-0.431	0.190	-0.169	0.173	3.28E-01	-0.509	0.170	-0.124	0.172	4.71E-01	-0.462	0.214
	apoeb	0.189	0.146	1.96E-01	-0.098	0.476	0.231	0.160	1.49E-01	-0.083	0.546	0.227	0.162	1.61E-01	-0.090	0.545
	apoba	0.003	0.508	9.95E-01	-0.993	0.999	-0.093	0.521	8.58E-01	-1.114	0.928	0.113	0.515	8.26E-01	-0.896	1.122
	apobb.1	0.972	0.144	1.52E-11	0.690	1.255	0.972	0.183	1.02E-07	0.614	1.329	0.947	0.196	1.30E-06	0.564	1.331
	apobb.2	-0.330	0.410	4.20E-01	-1.133	0.473	-0.341	0.412	4.09E-01	-1.148	0.467	-0.152	0.405	7.07E-01	-0.946	0.641
	ldlra	0.007	0.137	9.62E-01	-0.261	0.274	0.018	0.142	8.98E-01	-0.260	0.296	0.001	0.144	9.95E-01	-0.280	0.282
	body length (in SD)	-	-	-	-	-	-0.030	0.158	8.47E-01	-0.340	0.279	0.017	0.161	9.16E-01	-0.299	0.333
	dorsal body surface area (in SD)	-	-	-	-	-	0.176	0.126	1.61E-01	-0.070	0.423	0.196	0.128	1.25E-01	-0.055	0.447
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.060	0.092	5.18E-01	-0.241	0.121
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.118	0.126	3.49E-01	-0.364	0.128
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.193	0.170	2.56E-01	-0.140	0.527
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.049	0.104	6.40E-01	-0.254	0.156
	time of day (in hours since 9AM)	-0.107	0.080	1.81E-01	-0.263	0.050	-0.177	0.099	7.39E-02	-0.372	0.017	-0.148	0.104	1.56E-01	-0.352	0.056
	batch 1	2.477	0.423	4.67E-09	1.648	3.305	2.692	0.492	4.40E-08	1.728	3.656	2.861	0.549	1.90E-07	1.784	3.937
	batch 2	1.303	0.517	1.17E-02	0.290	2.315	1.415	0.531	7.69E-03	0.374	2.455	1.764	0.613	3.99E-03	0.563	2.965
	batch 3	1.771	0.500	3.96E-04	0.791	2.752	1.970	0.524	1.69E-04	0.943	2.996	1.986	0.545	2.69E-04	0.918	3.055
	batch 4	1.559	0.513	2.38E-03	0.553	2.565	1.753	0.528	8.92E-04	0.719	2.788	1.914	0.541	4.06E-04	0.853	2.975
	batch 5	2.972	0.518	9.40E-09	1.957	3.986	3.193	0.592	6.96E-08	2.032	4.353	2.949	0.656	6.99E-06	1.663	4.235
	batch 6	2.623	0.443	3.33E-09	1.754	3.492	2.794	0.553	4.44E-07	1.709	3.878	2.462	0.596	3.55E-05	1.295	3.629
	batch 7	1.974	0.515	1.25E-04	0.965	2.982	2.088	0.611	6.26E-04	0.892	3.285	1.827	0.631	3.76E-03	0.591	3.063
	intercept	-4.563	1.643	5.47E-03	-7.783	-1.344	-4.567	1.623	4.90E-03	-7.748	-1.385	-5.112	1.615	1.55E-03	-8.276	-1.947
	ldlrb	17.601	3.301	9.70E-08	11.131	24.070	18.155	3.236	2.01E-08	11.813	24.496	17.829	3.207	2.72E-08	11.543	24.115

		Vascular infiltration by macrophages														
		Model 1 (n=368)					Model 2 (n=328)					Model 3 (n=328)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	-0.067	0.075	3.70E-01	-0.213	0.079	-0.111	0.081	1.67E-01	-0.269	0.047	-0.126	0.081	1.20E-01	-0.285	0.033
	apoeb	-0.145	0.082	7.49E-02	-0.305	0.015	-0.125	0.089	1.59E-01	-0.299	0.049	-0.129	0.089	1.49E-01	-0.303	0.046
	apoba	-0.144	0.275	6.02E-01	-0.683	0.396	-0.165	0.295	5.76E-01	-0.743	0.413	-0.178	0.294	5.44E-01	-0.754	0.398
	apobb.1	-0.222	0.080	5.54E-03	-0.379	-0.065	-0.208	0.087	1.72E-02	-0.379	-0.037	-0.222	0.089	1.23E-02	-0.396	-0.048
	apobb.2	-0.300	0.193	1.21E-01	-0.678	0.079	-0.373	0.209	7.41E-02	-0.782	0.036	-0.425	0.211	4.37E-02	-0.838	-0.012
	ldlra	0.034	0.063	5.91E-01	-0.090	0.158	0.013	0.070	8.50E-01	-0.124	0.150	-0.002	0.070	9.74E-01	-0.139	0.135
	body length (in SD)	-	-	-	-	-	0.045	0.072	5.36E-01	-0.097	0.186	0.046	0.073	5.25E-01	-0.097	0.190
	dorsal body surface area (in SD)	-	-	-	-	-	-0.044	0.061	4.67E-01	-0.163	0.075	-0.045	0.061	4.67E-01	-0.165	0.076
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.058	0.055	2.87E-01	-0.049	0.165
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.079	0.061	1.91E-01	-0.040	0.199
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.034	0.074	6.50E-01	-0.112	0.179
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.043	0.054	4.32E-01	-0.149	0.064
	time of day (in hours since 9AM)	0.031	0.041	4.41E-01	-0.048	0.111	0.030	0.046	5.16E-01	-0.060	0.120	0.032	0.046	4.87E-01	-0.058	0.122
	intercept	1.063	1.075	3.23E-01	-1.044	3.170	1.346	1.122	2.30E-01	-0.853	3.544	1.478	1.121	1.87E-01	-0.719	3.675
	ldlrb	-0.104	2.197	9.62E-01	-4.411	4.202	-0.347	2.258	8.78E-01	-4.773	4.079	-0.329	2.258	8.84E-01	-4.755	4.097
random factors	***variation by batch***	*0.514*	*0.140*	-	*0.301*	*0.877*	*0.509*	*0.143*	-	*0.293*	*0.884*	*0.479*	*0.138*	-	*0.272*	*0.844*
	residual	*0.858*	*0.032*	-	*0.798*	*0.923*	*0.878*	*0.035*	-	*0.812*	*0.949*	*0.874*	*0.035*	-	*0.809*	*0.944*

continued **Supplementary Table 24**

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=301)					Model 2 (n=269)					Model 3 (n=269)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	-0.299	0.234	2.02E-01	-0.758	0.160	-0.410	0.246	9.58E-02	-0.893	0.073	-0.351	0.244	1.51E-01	-0.830	0.128
	apoeb	-0.142	0.180	4.31E-01	-0.496	0.212	-0.123	0.198	5.34E-01	-0.512	0.265	-0.113	0.198	5.67E-01	-0.501	0.275
	apoba	0.123	0.760	8.71E-01	-1.367	1.613	0.108	0.745	8.85E-01	-1.353	1.569	0.456	0.805	5.71E-01	-1.122	2.035
	apobb.1	1.049	0.204	2.71E-07	0.649	1.449	0.963	0.248	1.05E-04	0.476	1.449	0.881	0.273	1.27E-03	0.345	1.416
	apobb.2	-0.154	0.475	7.46E-01	-1.086	0.778	-0.233	0.499	6.41E-01	-1.211	0.746	0.002	0.496	9.96E-01	-0.970	0.975
	ldlra	-0.096	0.193	6.22E-01	-0.475	0.284	-0.079	0.191	6.79E-01	-0.454	0.296	-0.102	0.191	5.95E-01	-0.476	0.273
	body length (in SD)	-	-	-	-	-	-0.093	0.245	7.05E-01	-0.574	0.388	-0.060	0.256	8.14E-01	-0.563	0.442
	dorsal body surface area (in SD)	-	-	-	-	-	0.096	0.152	5.30E-01	-0.203	0.394	0.068	0.154	6.58E-01	-0.233	0.369
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.086	0.151	5.69E-01	-0.382	0.210
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.009	0.170	9.58E-01	-0.325	0.343
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.316	0.235	1.78E-01	-0.144	0.776
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.116	0.137	3.95E-01	-0.384	0.151
	time of day (in hours since 9AM)	0.031	0.090	7.32E-01	-0.146	0.208	0.026	0.115	8.23E-01	-0.199	0.250	0.092	0.122	4.48E-01	-0.146	0.331
	batch 1	1.673	0.598	5.14E-03	0.501	2.845	1.703	0.705	1.57E-02	0.321	3.086	1.674	0.786	3.32E-02	0.134	3.214
	batch 2	1.054	0.863	2.22E-01	-0.637	2.745	0.884	0.862	3.05E-01	-0.805	2.574	0.758	0.928	4.14E-01	-1.060	2.577
	batch 3	0.934	0.618	1.30E-01	-0.277	2.145	0.910	0.646	1.59E-01	-0.356	2.176	0.785	0.664	2.37E-01	-0.517	2.086
	batch 4	1.449	0.652	2.62E-02	0.171	2.727	1.271	0.677	6.02E-02	-0.055	2.598	1.260	0.720	7.98E-02	-0.150	2.671
	batch 5	2.334	0.705	9.37E-04	0.951	3.717	2.246	0.827	6.64E-03	0.624	3.867	1.773	0.883	4.46E-02	0.043	3.504
	batch 6	1.190	0.648	6.62E-02	-0.080	2.460	1.252	0.865	1.48E-01	-0.443	2.947	0.663	0.932	4.77E-01	-1.164	2.489
	batch 7	0.737	0.971	4.48E-01	-1.166	2.640	0.545	1.090	6.17E-01	-1.592	2.682	0.141	1.122	9.00E-01	-2.057	2.340
	intercept	-5.120	1.899	7.02E-03	-8.842	-1.398	-4.899	1.863	8.54E-03	-8.550	-1.248	-5.421	1.971	5.95E-03	-9.284	-1.558
	ldlrb	14.867	3.709	6.11E-05	7.598	22.136	15.184	3.380	7.03E-06	8.560	21.808	14.218	3.406	2.98E-05	7.543	20.893

		Vascular infiltration by neutrophils														
		Model 1 (n=371)					Model 2 (n=330)					Model 3 (n=330)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	-0.047	0.076	5.36E-01	-0.196	0.102	-0.076	0.081	3.52E-01	-0.234	0.083	-0.083	0.082	3.11E-01	-0.244	0.078
	apoeb	0.001	0.084	9.87E-01	-0.162	0.165	0.028	0.090	7.54E-01	-0.147	0.204	0.010	0.090	9.09E-01	-0.166	0.186
	apoba	0.099	0.281	7.25E-01	-0.452	0.650	0.111	0.296	7.07E-01	-0.469	0.692	0.110	0.295	7.10E-01	-0.469	0.689
	apobb.1	0.103	0.082	2.07E-01	-0.057	0.264	0.042	0.088	6.32E-01	-0.130	0.214	0.061	0.089	4.96E-01	-0.114	0.235
	apobb.2	-0.056	0.198	7.79E-01	-0.443	0.332	0.021	0.210	9.19E-01	-0.391	0.434	0.006	0.212	9.76E-01	-0.410	0.423
	ldlra	-0.074	0.064	2.51E-01	-0.200	0.052	-0.066	0.070	3.47E-01	-0.204	0.072	-0.069	0.070	3.29E-01	-0.207	0.069
	body length (in SD)	-	-	-	-	-	-0.111	0.071	1.19E-01	-0.250	0.028	-0.098	0.072	1.71E-01	-0.239	0.043
	dorsal body surface area (in SD)	-	-	-	-	-	0.050	0.060	4.00E-01	-0.067	0.168	0.067	0.060	2.67E-01	-0.051	0.186
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.006	0.054	9.15E-01	-0.099	0.111
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.083	0.060	1.72E-01	-0.036	0.201
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.054	0.072	4.50E-01	-0.195	0.086
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.062	0.054	2.55E-01	-0.045	0.169
	time of day (in hours since 9AM)	0.016	0.041	6.95E-01	-0.064	0.095	-0.020	0.045	6.63E-01	-0.107	0.068	-0.022	0.045	6.28E-01	-0.109	0.066
	intercept	0.777	1.093	4.77E-01	-1.364	2.919	0.584	1.122	6.03E-01	-1.615	2.782	0.617	1.122	5.82E-01	-1.582	2.815
	ldlrb	-2.049	2.254	3.63E-01	-6.467	2.369	-1.571	2.281	4.91E-01	-6.041	2.900	-1.525	2.285	5.05E-01	-6.005	2.954
random factors	***variation by batch***	*0.352*	*0.100*	-	*0.201*	*0.615*	*0.323*	*0.097*	-	*0.179*	*0.583*	*0.296*	*0.092*	-	*0.161*	*0.543*
	residual	*0.882*	*0.033*	-	*0.820*	*0.948*	*0.888*	*0.035*	-	*0.822*	*0.959*	*0.885*	*0.035*	-	*0.819*	*0.956*

continued **Supplementary Table 24**

		Vascular co-localization of lipids with neutrophils														
		Model 1 (n=282)					Model 2 (n=250)					Model 3 (n=250)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	-0.154	0.268	5.65E-01	-0.679	0.371	-0.015	0.284	9.58E-01	-0.572	0.542	-0.361	0.318	2.57E-01	-0.985	0.263
	apoeb	0.079	0.270	7.71E-01	-0.451	0.608	0.177	0.278	5.24E-01	-0.369	0.723	0.181	0.277	5.14E-01	-0.361	0.723
	apoba	0.520	0.995	6.01E-01	-1.431	2.471	0.985	0.931	2.90E-01	-0.840	2.811	1.882	1.019	6.48E-02	-0.116	3.880
	apobb.1	1.722	0.263	5.80E-11	1.206	2.237	1.619	0.309	1.54E-07	1.015	2.224	1.547	0.357	1.43E-05	0.848	2.246
	apobb.2	0.441	0.640	4.91E-01	-0.814	1.696	0.187	0.654	7.75E-01	-1.095	1.468	1.103	0.719	1.25E-01	-0.308	2.513
	ldlra	0.033	0.247	8.93E-01	-0.451	0.517	0.040	0.254	8.76E-01	-0.458	0.537	-0.071	0.245	7.71E-01	-0.551	0.408
	body length (in SD)	-	-	-	-	-	-0.035	0.259	8.94E-01	-0.542	0.473	-0.272	0.275	3.22E-01	-0.811	0.267
	dorsal body surface area (in SD)	-	-	-	-	-	0.122	0.231	5.96E-01	-0.330	0.575	-0.014	0.233	9.52E-01	-0.471	0.443
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.620	0.267	2.04E-02	0.096	1.143
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.513	0.331	1.22E-01	-0.137	1.162
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.085	0.342	1.49E-03	0.415	1.754
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.339	0.202	9.27E-02	-0.056	0.735
	time of day (in hours since 9AM)	-0.184	0.167	2.69E-01	-0.511	0.142	-0.151	0.207	4.66E-01	-0.557	0.255	-0.085	0.207	6.82E-01	-0.491	0.321
	batch 2	-1.524	0.842	7.03E-02	-3.174	0.126	-1.617	0.913	7.67E-02	-3.407	0.173	-0.683	1.032	5.08E-01	-2.706	1.340
	batch 3	-0.627	0.721	3.84E-01	-2.039	0.785	-0.692	0.679	3.08E-01	-2.023	0.638	-1.417	0.659	3.15E-02	-2.709	-0.125
	batch 4	-0.239	0.580	6.80E-01	-1.376	0.897	-0.154	0.654	8.14E-01	-1.437	1.128	-0.859	0.667	1.98E-01	-2.167	0.449
	batch 5	0.980	0.549	7.45E-02	-0.097	2.056	0.862	0.629	1.71E-01	-0.371	2.094	-1.191	0.923	1.97E-01	-3.001	0.619
	batch 6	-1.064	0.550	5.31E-02	-2.143	0.014	-0.926	0.600	1.23E-01	-2.102	0.250	-2.069	0.970	3.30E-02	-3.971	-0.168
	batch 7	-1.512	0.951	1.12E-01	-3.377	0.353	-1.677	1.009	9.65E-02	-3.654	0.300	-3.366	1.259	7.52E-03	-5.834	-0.898
	intercept	-28.073	216.656	8.97E-01	-452.711	396.565	61.871	235.125	7.92E-01	-398.965	522.707	201.886	254.650	4.28E-01	-297.219	700.991
	ldlrb	66.921	543.258	9.02E-01	-997.846	1131.688	-160.054	589.423	7.86E-01	-1300.000	995.195	-515.165	638.098	4.19E-01	-1800.000	735.485

		Vascular co-localization of macrophages with neutrophils														
		Model 1 (n=367)					Model 2 (n=327)					Model 3 (n=327)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	-0.102	0.116	3.77E-01	-0.329	0.125	-0.094	0.123	4.45E-01	-0.334	0.147	-0.092	0.124	4.58E-01	-0.335	0.151
	apoeb	0.133	0.118	2.60E-01	-0.099	0.366	0.136	0.126	2.81E-01	-0.111	0.383	0.121	0.124	3.30E-01	-0.122	0.363
	apoba	0.055	0.417	8.96E-01	-0.762	0.871	0.302	0.411	4.63E-01	-0.504	1.108	0.350	0.410	3.93E-01	-0.453	1.153
	apobb.1	0.036	0.140	7.96E-01	-0.237	0.310	0.079	0.141	5.77E-01	-0.198	0.356	0.109	0.143	4.45E-01	-0.172	0.391
	apobb.2	-0.252	0.300	4.01E-01	-0.840	0.336	-0.387	0.335	2.48E-01	-1.044	0.269	-0.297	0.320	3.53E-01	-0.924	0.330
	ldlra	-0.141	0.108	1.90E-01	-0.352	0.070	-0.189	0.108	7.87E-02	-0.401	0.022	-0.178	0.109	1.02E-01	-0.392	0.035
	body length (in SD)	-	-	-	-	-	0.308	0.112	5.73E-03	0.090	0.527	0.269	0.120	2.51E-02	0.034	0.505
	dorsal body surface area (in SD)	-	-	-	-	-	0.271	0.110	1.35E-02	0.056	0.487	0.267	0.116	2.16E-02	0.039	0.495
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.066	0.092	4.72E-01	-0.114	0.247
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.016	0.100	8.73E-01	-0.213	0.181
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.049	0.123	6.93E-01	-0.290	0.193
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.119	0.081	1.44E-01	-0.041	0.278
	time of day (in hours since 9AM)	0.074	0.068	2.75E-01	-0.059	0.206	0.086	0.073	2.38E-01	-0.057	0.228	0.073	0.075	3.33E-01	-0.075	0.220
	batch 1	0.378	0.325	2.45E-01	-0.259	1.014	0.123	0.361	7.34E-01	-0.585	0.831	0.236	0.418	5.72E-01	-0.583	1.056
	batch 2	0.213	0.485	6.61E-01	-0.738	1.165	0.222	0.454	6.26E-01	-0.669	1.112	0.353	0.477	4.60E-01	-0.583	1.289
	batch 3	-0.552	0.397	1.64E-01	-1.331	0.226	-0.656	0.403	1.04E-01	-1.445	0.134	-0.534	0.429	2.13E-01	-1.376	0.307
	batch 4	0.911	0.392	2.01E-02	0.143	1.679	0.999	0.417	1.65E-02	0.182	1.816	0.992	0.445	2.57E-02	0.120	1.863
	batch 5	0.171	0.373	6.46E-01	-0.560	0.903	-0.182	0.394	6.44E-01	-0.955	0.590	-0.012	0.441	9.78E-01	-0.877	0.852
	batch 6	-1.591	0.383	3.32E-05	-2.342	-0.840	-2.219	0.456	1.13E-06	-3.113	-1.326	-2.105	0.475	9.32E-06	-3.036	-1.174
	batch 7	-0.432	0.491	3.79E-01	-1.395	0.531	-1.048	0.569	6.57E-02	-2.163	0.068	-1.007	0.646	1.19E-01	-2.273	0.258
	intercept	3.948	0.846	3.06E-06	2.290	5.605	3.908	0.912	1.82E-05	2.121	5.695	3.376	0.937	3.16E-04	1.539	5.213
	ldlrb	0.044	0.776	9.54E-01	-1.477	1.566	0.090	0.894	9.20E-01	-1.662	1.843	0.663	1.014	5.14E-01	-1.326	2.651

All outcomes were normalized for length using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models. Effects shown are for each additional mutated allele in *apoea* , *apoeb* , *apoba* , *apobb.1*, *apobb.2* , *ldlra* and *ldlrb*, weighted by the allele's predicted effect on protein function (i.e. additive model, mutually adjusted). Associations were adjusted for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 25 - The additive effect of mutated alleles in *apoea* , *apoeb* , *apoba* , *apobb.1*, *apobb.2*, *ldlra* and *ldlrb* on image and image quantification quality

	Debris included in the segmentation for body size (n=374)				
	OR	**SE**	***P***	**lci**	**uci**
apoea	0.580	0.179	7.70E-02	0.317	1.061
apoeb	1.511	0.525	2.34E-01	0.765	2.986
apoba	2.543	3.029	4.33E-01	0.246	26.260
apobb.1	0.569	0.189	8.91E-02	0.297	1.090
apobb.2	2.123	1.781	3.69E-01	0.410	10.993
ldlra	0.791	0.187	3.22E-01	0.497	1.258
ldlrb	355	13000	8.74E-01	0.000	-
time of day (in hours since 9AM)	1.088	0.148	5.33E-01	0.834	1.420
intercept	0.001	0.009	6.20E-01	0.000	-

	Many false positive lipid deposits																			
	Model 1 (n=373)					**Model 2 (n=245)**					**Model 3 (n=245)**					**Model 4 (n=245)**				
	OR	**SE**	***P***	**lci**	**uci**	**OR**	**SE**	***P***	**lci**	**uci**	**OR**	**SE**	***P***	**lci**	**uci**	**OR**	**SE**	***P***	**lci**	**uci**
apoea	0.837	0.187	4.26E-01	0.539	1.298	0.979	0.295	9.44E-01	0.542	1.767	1.081	0.343	8.07E-01	0.580	2.014	1.284	0.429	4.54E-01	0.667	2.472
apoeb	0.918	0.234	7.38E-01	0.557	1.514	0.899	0.311	7.57E-01	0.456	1.771	0.919	0.322	8.09E-01	0.462	1.827	0.907	0.324	7.85E-01	0.450	1.828
apoba	0.845	0.698	8.38E-01	0.167	4.264	0.189	0.230	1.72E-01	0.017	2.065	0.189	0.240	1.89E-01	0.016	2.265	0.213	0.279	2.37E-01	0.017	2.755
apobb.1	0.842	0.201	4.70E-01	0.527	1.344	0.658	0.212	1.94E-01	0.349	1.238	0.640	0.206	1.66E-01	0.340	1.203	0.660	0.217	2.06E-01	0.347	1.256
apobb.2	0.514	0.300	2.54E-01	0.164	1.611	0.202	0.244	1.85E-01	0.019	2.145	0.296	0.371	3.31E-01	0.025	3.455	0.343	0.453	4.18E-01	0.026	4.571
ldlra	1.175	0.222	3.93E-01	0.812	1.701	1.507	0.385	1.09E-01	0.913	2.487	1.544	0.402	9.54E-02	0.927	2.573	1.623	0.442	7.50E-02	0.952	2.766
ldlrb	1927	58000	8.03E-01	0.000	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
time of day (in hours since 9AM)	1.243	0.129	3.62E-02	1.014	1.524	0.998	0.143	9.90E-01	0.754	1.321	0.989	0.142	9.37E-01	0.747	1.309	0.977	0.143	8.77E-01	0.733	1.303
body length (in SD)	-	-	-	-	-	1.838	0.423	8.20E-03	1.170	2.885	1.613	0.385	4.52E-02	1.010	2.576	1.667	0.427	4.58E-02	1.010	2.754
dorsal body surface area (in SD)	-	-	-	-	-	2.156	0.448	2.17E-04	1.435	3.240	1.959	0.427	2.02E-03	1.278	3.002	1.901	0.418	3.44E-03	1.236	2.924
LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.580	0.113	5.30E-03	0.395	0.851
HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.915	0.194	6.75E-01	0.605	1.385
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.678	0.345	1.18E-02	1.122	2.509	1.718	0.364	1.06E-02	1.134	2.602
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.035	0.176	8.40E-01	0.742	1.444	1.077	0.189	6.74E-01	0.763	1.519
intercept	0.022	0.270	7.56E-01	0.000		38.951	132.322	2.81E-01	0.050	30000	19.083	67.600	4.05E-01	0.018	20000	9.277	34.040	5.44E-01	0.007	12000

Associations are shown for criteria that resulted in the exclusion of at least 10 larvae. Many false positives: >20% of true negative objects were falsely detected by the quantification pipeline. Associations were examined using logistic regression models. Model 1: adjusted for time of day; Model 2: additionally adjusted for body length and dorsal surface area; Model 3: additionally adjusted for whole-body triglyceride and glucose levels; Model 4: additionally adjusted for whole-body LDL and HDL cholesterol levels. Dorsal body surface area was normalized for body length using residuals; whole-body LDL cholesterol, HDL cholesterol, triglyceride and glucose levels were normalized for protein level using residuals. Effects shown for *apoea* , *apoeb* , *apoba* , *apobb.1* , *apobb.2* and *ldlra* are for each additional mutated allele. Adjusting for batch would have resulted in the exclusion of larvae. Lci and uci are lower and upper boundaries of the 95% confidence

Supplementary Table 26 - The effect of gene x gene interactions on body size

		Body length (n=339)					Dorsal body surface area (n=339)					Lateral body surface area (n=335)					Body volume (n=328)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.223	0.170	1.90E-01	-0.557	0.110	-0.155	0.204	4.49E-01	-0.555	0.246	-0.078	0.207	7.08E-01	-0.484	0.328	-0.055	0.206	7.88E-01	-0.460	0.349
	apoeb	-0.090	0.121	4.56E-01	-0.327	0.147	0.069	0.145	6.36E-01	-0.216	0.353	0.205	0.148	1.66E-01	-0.085	0.495	0.167	0.149	2.61E-01	-0.124	0.458
	apobb.1	-0.119	0.215	5.78E-01	-0.540	0.301	-0.018	0.257	9.43E-01	-0.523	0.486	-0.180	0.266	4.99E-01	-0.702	0.342	-0.118	0.262	6.52E-01	-0.633	0.396
	ldlra	0.179	0.208	3.89E-01	-0.228	0.586	-0.165	0.249	5.08E-01	-0.653	0.324	-0.223	0.254	3.80E-01	-0.721	0.275	-0.217	0.250	3.87E-01	-0.707	0.274
	apoea* x *apoeb	0.087	0.107	4.19E-01	-0.124	0.297	0.040	0.129	7.56E-01	-0.212	0.293	-0.071	0.131	5.88E-01	-0.328	0.186	-0.025	0.131	8.46E-01	-0.281	0.231
	apoea* x *apobb.1	0.081	0.101	4.22E-01	-0.117	0.278	-0.059	0.121	6.26E-01	-0.296	0.178	0.010	0.124	9.33E-01	-0.232	0.253	-0.024	0.124	8.46E-01	-0.267	0.219
	apoea* x *ldlra	0.034	0.077	6.60E-01	-0.116	0.184	0.002	0.092	9.85E-01	-0.178	0.182	0.040	0.094	6.73E-01	-0.144	0.223	-0.007	0.093	9.36E-01	-0.190	0.175
	apoeb* x *apobb.1	-0.075	0.122	5.39E-01	-0.315	0.165	0.083	0.147	5.71E-01	-0.204	0.371	0.052	0.151	7.33E-01	-0.245	0.348	0.057	0.149	7.02E-01	-0.235	0.349
	apoeb* x *ldlra	-0.036	0.103	7.30E-01	-0.237	0.166	0.046	0.123	7.11E-01	-0.196	0.288	0.060	0.126	6.34E-01	-0.187	0.308	0.074	0.124	5.50E-01	-0.170	0.318
	apobb.1* x *ldlra	-0.156	0.081	5.56E-02	-0.316	0.004	0.058	0.098	5.53E-01	-0.133	0.250	0.106	0.099	2.88E-01	-0.089	0.301	0.098	0.099	3.23E-01	-0.096	0.291
	time of day (in hours since 9AM)	-0.054	0.036	1.36E-01	-0.125	0.017	0.039	0.043	3.60E-01	-0.045	0.124	0.023	0.044	5.99E-01	-0.063	0.109	0.047	0.044	2.82E-01	-0.039	0.133
	intercept	0.284	0.288	3.25E-01	-0.281	0.849	-0.173	0.316	5.84E-01	-0.793	0.447	-0.231	0.319	4.68E-01	-0.856	0.394	-0.311	0.319	3.29E-01	-0.936	0.314
random factors	***variance by batch***	*0.510*	*0.138*	-	*0.300*	*0.866*	*0.469*	*0.133*	-	*0.269*	*0.818*	*0.467*	*0.131*	-	*0.269*	*0.809*	*0.469*	*0.131*	-	*0.271*	*0.813*
	residual	*0.696*	*0.027*	-	*0.645*	*0.751*	*0.835*	*0.033*	-	*0.774*	*0.902*	*0.845*	*0.033*	-	*0.783*	*0.912*	*0.829*	*0.033*	-	*0.767*	*0.895*

Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis. Associations and interactions were examined using hierarchical linear models in larvae carrying two mutated alleles in apoba, apobb.2 and ldlrb. Associations and interactions were examined for each additional mutated allele, weighted by its predicted effect on protein function, i.e. using an additive model. Associations were adjusted for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 27 - The effect of gene x gene interactions on whole-body lipid and glucose levels

		LDL cholesterol levels (n=381)					HDL cholesterol levels (n=381)					Triglyceride levels (n=381)					Total cholesterol levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.183	0.216	3.97E-01	-0.606	0.240	0.001	0.196	9.94E-01	-0.383	0.386	-0.164	0.156	2.93E-01	-0.469	0.141	-0.041	0.185	8.26E-01	-0.404	0.322
	apoeb	-0.014	0.147	9.22E-01	-0.303	0.274	0.036	0.134	7.89E-01	-0.226	0.298	-0.123	0.106	2.47E-01	-0.331	0.085	0.001	0.126	9.94E-01	-0.246	0.248
	apobb.1	0.103	0.284	7.16E-01	-0.453	0.660	0.188	0.258	4.66E-01	-0.317	0.693	-0.163	0.205	4.26E-01	-0.563	0.238	-0.127	0.243	6.02E-01	-0.604	0.350
	ldlra	0.026	0.273	9.25E-01	-0.510	0.561	0.102	0.249	6.83E-01	-0.386	0.589	-0.102	0.197	6.05E-01	-0.489	0.285	-0.088	0.235	7.07E-01	-0.548	0.372
	apoea x apoeb	0.103	0.136	4.48E-01	-0.163	0.369	0.113	0.123	3.62E-01	-0.129	0.355	0.054	0.098	5.84E-01	-0.138	0.246	0.013	0.116	9.08E-01	-0.215	0.242
	apoea x apobb.1	0.070	0.132	5.97E-01	-0.188	0.328	-0.077	0.120	5.21E-01	-0.312	0.158	0.063	0.095	5.09E-01	-0.123	0.249	0.140	0.113	2.16E-01	-0.082	0.361
	apoea x ldlra	0.122	0.098	2.12E-01	-0.070	0.314	-0.082	0.089	3.54E-01	-0.257	0.092	-0.047	0.071	5.06E-01	-0.185	0.091	-0.030	0.084	7.16E-01	-0.195	0.134
	apoeb x apobb.1	-0.023	0.161	8.86E-01	-0.339	0.293	-0.074	0.147	6.14E-01	-0.361	0.213	0.138	0.116	2.34E-01	-0.089	0.366	-0.026	0.138	8.49E-01	-0.297	0.245
	apoeb x ldlra	-0.049	0.135	7.17E-01	-0.313	0.215	-0.004	0.123	9.72E-01	-0.244	0.236	0.088	0.097	3.68E-01	-0.103	0.278	0.100	0.116	3.85E-01	-0.126	0.327
	apobb.1 x ldlra	-0.078	0.105	4.57E-01	-0.285	0.128	0.033	0.096	7.31E-01	-0.155	0.220	0.009	0.076	9.03E-01	-0.139	0.158	-0.104	0.090	2.50E-01	-0.281	0.073
	time of day (in hours since 9AM)	0.044	0.043	3.01E-01	-0.039	0.128	-0.035	0.040	3.82E-01	-0.114	0.044	-0.131	0.032	4.36E-05	-0.194	-0.068	0.079	0.038	3.92E-02	0.004	0.153
	intercept	-0.091	0.299	7.60E-01	-0.678	0.495	-0.158	0.325	6.28E-01	-0.795	0.480	0.379	0.335	2.58E-01	-0.277	1.035	-0.074	0.353	8.35E-01	-0.766	0.619
random factors	***variance by batch***	*0.350*	*0.120*	-	*0.179*	*0.685*	*0.592*	*0.160*	-	*0.348*	*1.006*	*0.763*	*0.196*	-	*0.462*	*1.261*	*0.746*	*0.197*	-	*0.445*	*1.250*
	residual	*0.945*	*0.035*	-	*0.880*	*1.016*	*0.858*	*0.031*	-	*0.799*	*0.922*	*0.680*	*0.025*	-	*0.633*	*0.731*	*0.810*	*0.030*	-	*0.753*	*0.870*

		Glucose levels (n=381)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.068	0.216	7.51E-01	-0.491	0.354
	apoeb	-0.004	0.147	9.77E-01	-0.292	0.284
	apobb.1	-0.477	0.283	9.22E-02	-1.032	0.078
	ldlra	-0.101	0.273	7.12E-01	-0.635	0.434
	apoea x apoeb	0.101	0.136	4.55E-01	-0.165	0.367
	apoea x apobb.1	-0.090	0.131	4.95E-01	-0.347	0.168
	apoea x ldlra	-0.087	0.098	3.75E-01	-0.278	0.105
	apoeb x apobb.1	0.171	0.161	2.89E-01	-0.145	0.486
	apoeb x ldlra	0.021	0.134	8.74E-01	-0.242	0.285
	apobb.1 x ldlra	0.087	0.105	4.08E-01	-0.119	0.293
	time of day (in hours since 9AM)	0.052	0.043	2.20E-01	-0.031	0.136
	intercept	0.046	0.303	8.78E-01	-0.547	0.640
random factors	***variance by batch***	*0.375*	*0.119*	-	*0.201*	*0.699*
	residual	*0.943*	*0.035*	-	*0.878*	*1.013*

Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis. Associations and interactions were examined using hierarchical linear models in larvae carrying two mutated alleles in apoba, apobb.2 and ldlrb. Associations and interactions were examined for each additional mutated allele, weighted by its predicted effect on protein function, i.e. using an additive model. Associations were adjusted for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 28 - The effect of gene x gene interactions on image-based vascular atherogenic traits

		Vascular lipid deposition									
		2 vs. 0 mutated alleles (n=62)					Additive model (n=272)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	-3.380	0.895	1.59E-04	-5.134	-1.626	-1.173	0.618	5.77E-02	-2.385	0.038
	apoeb	0.078	0.312	8.01E-01	-0.533	0.690	0.148	0.374	6.92E-01	-0.586	0.882
	apobb.1	1.104	0.294	1.75E-04	0.527	1.680	0.675	0.563	2.30E-01	-0.428	1.778
	ldlra	-0.726	0.367	4.75E-02	-1.445	-0.008	-0.481	0.520	3.55E-01	-1.500	0.538
	apoea* x *apoeb	-	-	-	-	-	0.129	0.354	7.16E-01	-0.564	0.821
	apoea* x *apobb.1	-	-	-	-	-	0.134	0.278	6.30E-01	-0.411	0.678
	apoea* x *ldlra	4.368	1.256	5.07E-04	1.906	6.830	0.518	0.200	9.51E-03	0.127	0.910
	apoeb* x *apobb.1	-	-	-	-	-	0.008	0.328	9.80E-01	-0.634	0.650
	apoeb* x *ldlra	-	-	-	-	-	-0.024	0.260	9.28E-01	-0.533	0.486
	apobb.1* x *ldlra	-	-	-	-	-	0.188	0.192	3.28E-01	-0.189	0.565
	time of day (in hours since 9AM)	0.144	0.177	4.16E-01	-0.204	0.492	-0.168	0.108	1.19E-01	-0.379	0.043
	body length (in SD)	-0.129	0.270	6.32E-01	-0.659	0.401	-0.044	0.170	7.97E-01	-0.377	0.289
	dorsal body surface area (in SD)	-0.190	0.319	5.50E-01	-0.815	0.434	0.156	0.125	2.13E-01	-0.090	0.401
	batch 1	-	-	-	-	-	3.176	0.477	2.89E-11	2.241	4.112
	batch 2	-0.500	1.066	6.39E-01	-2.589	1.589	1.667	0.523	1.42E-03	0.643	2.691
	batch 3	-0.479	0.871	5.82E-01	-2.186	1.228	2.417	0.505	1.73E-06	1.426	3.407
	batch 4	-1.364	0.832	1.01E-01	-2.996	0.267	2.344	0.516	5.59E-06	1.333	3.356
	batch 5	-0.177	0.716	8.05E-01	-1.580	1.226	3.737	0.618	1.49E-09	2.526	4.949
	batch 6	1.265	0.763	9.76E-02	-0.231	2.761	3.373	0.582	6.84E-09	2.232	4.514
	batch 7	0.398	0.843	6.37E-01	-1.255	2.051	2.776	0.669	3.32E-05	1.465	4.088
	intercept	3.518	0.862	4.53E-05	1.827	5.208	2.330	0.646	3.09E-04	1.064	3.596

		Vascular co-localization of lipids with macrophages									
		2 vs. 0 mutated alleles (n=63)					Additive model (n=269)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	-17.245	1.068	1.15E-58	-19.338	-15.152	-0.324	0.757	6.68E-01	-1.808	1.159
	apoeb	-0.189	0.297	5.25E-01	-0.771	0.393	0.264	0.477	5.80E-01	-0.670	1.199
	apobb.1	1.360	0.463	3.32E-03	0.452	2.268	1.309	0.889	1.41E-01	-0.433	3.050
	ldlra	-1.833	0.671	6.34E-03	-3.149	-0.517	-0.974	0.628	1.21E-01	-2.205	0.257
	apoea* x *apoeb	-	-	-	-	-	-0.419	0.419	3.18E-01	-1.241	0.404
	apoea* x *apobb.1	-	-	-	-	-	-0.491	0.463	2.89E-01	-1.398	0.417
	apoea* x *ldlra	19.351	1.238	4.67E-55	16.924	21.778	0.843	0.327	1.00E-02	0.202	1.485
	apoeb* x *apobb.1	-	-	-	-	-	0.067	0.437	8.78E-01	-0.789	0.923
	apoeb* x *ldlra	-	-	-	-	-	0.040	0.272	8.84E-01	-0.493	0.572
	apobb.1* x *ldlra	-	-	-	-	-	0.066	0.283	8.16E-01	-0.490	0.621
	time of day (in hours since 9AM)	0.429	0.204	3.55E-02	0.029	0.829	-0.022	0.128	8.62E-01	-0.272	0.228
	body length (in SD)	-1.065	0.446	1.71E-02	-1.940	-0.190	-0.123	0.255	6.29E-01	-0.622	0.376
	dorsal body surface area (in SD)	-0.253	0.382	5.08E-01	-1.003	0.496	0.077	0.159	6.28E-01	-0.234	0.388
	batch 1	3.022	1.075	4.93E-03	0.915	5.129	2.389	0.665	3.24E-04	1.087	3.692
	batch 2	0.013	1.734	9.94E-01	-3.385	3.411	1.704	0.900	5.84E-02	-0.061	3.468
	batch 3	0.181	1.070	8.66E-01	-1.916	2.278	1.347	0.621	3.02E-02	0.129	2.564
	batch 4	0.071	1.197	9.53E-01	-2.276	2.417	2.070	0.688	2.61E-03	0.723	3.418
	batch 5	1.672	1.212	1.68E-01	-0.704	4.047	3.066	0.810	1.54E-04	1.478	4.654
	batch 6	2.193	1.367	1.09E-01	-0.486	4.872	2.085	0.839	1.30E-02	0.440	3.729
	batch 7	0.385	1.696	8.20E-01	-2.939	3.709	1.495	1.121	1.82E-01	-0.702	3.692
	intercept	-1.275	1.320	3.34E-01	-3.862	1.312	0.298	0.848	7.25E-01	-1.364	1.960

Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis. Associations and interactions were examined using hierarchical linear models in larvae carrying two mutated alleles in apoba, apobb.2 and ldlrb. Associations and interactions were examined for each additional mutated allele, weighted by its predicted effect on protein function, i.e. using an additive model. Associations were adjusted for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 29 - The association of image-based vascular atherogenic traits with whole-body lipid and glucose levels

		Vascular lipid deposition (n=1,118)				
		Effect	**SE**	***P***	**lci**	**uci**
negative binomial terms	**LDL cholesterol levels (in SD)**	-0.010	0.080	8.92E-01	-0.160	0.140
	HDL cholesterol levels (in SD)	-0.060	0.080	4.65E-01	-0.220	0.100
	triglyceride levels (in SD)	0.600	0.110	2.00E-07	0.370	0.820
	glucose levels (in SD)	-0.370	0.100	3.57E-04	-0.570	-0.170
	body length (in SD)	0.110	0.110	3.07E-01	-0.100	0.310
	dorsal body surface area (in SD)	0.070	0.100	4.95E-01	-0.130	0.260
	Tg(hsp70:IK17:EGFP; mpeg1:mCherry) carriers vs. Tg(mpo:EGFP) & Tg(mpeg1:mCherry) carriers	-3.040	0.640	2.18E-06	-4.290	-1.780
	Tg(flk:EGFP) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-1.710	0.410	3.72E-05	-2.520	-0.900
	batch 15	0.790	0.580	1.71E-01	-0.340	1.920
	batch 16	0.360	0.590	5.42E-01	-0.790	1.510
	batch 17	0.980	0.600	1.03E-01	-0.200	2.160
	batch 18	0.290	0.590	6.26E-01	-0.870	1.450
	batch 19	0.000	0.650	1.00E+00	-1.270	1.270
	batch 33	-0.620	0.410	1.31E-01	-1.430	0.190
	batch 34	-0.280	0.460	5.42E-01	-1.190	0.630
	batch 36	0.380	0.660	5.61E-01	-0.910	1.680
	batch 37	-19.770	0.560	1.35E-269	-20.870	-18.660
	batch 38	1.660	0.550	2.63E-03	0.580	2.740
	batch 39	-1.180	0.570	3.73E-02	-2.300	-0.070
	batch 40	1.320	0.420	1.61E-03	0.500	2.140
	batch 41	0.260	0.620	6.77E-01	-0.960	1.470
	batch 42	0.060	0.410	8.82E-01	-0.750	0.870
	batch 43	0.620	0.500	2.19E-01	-0.370	1.600
	batch 44	0.840	0.500	8.90E-02	-0.130	1.820
	batch 45	0.510	0.340	1.35E-01	-0.160	1.180
	intercept	4.450	0.300	5.28E-51	3.870	5.030

		Vascular infiltration by oxidized LDL (n=677)				
		Effect	**SE**	***P***	**lci**	**uci**
negative binomial terms	**LDL cholesterol levels (in SD)**	-0.040	0.040	2.26E-01	-0.110	0.030
	HDL cholesterol levels (in SD)	0.080	0.040	1.85E-02	0.010	0.160
	triglyceride levels (in SD)	0.090	0.060	1.31E-01	-0.030	0.210
	glucose levels (in SD)	0.080	0.060	2.43E-01	-0.050	0.200
	body length (in SD)	0.130	0.050	1.08E-02	0.030	0.240
	dorsal body surface area (in SD)	0.100	0.050	4.49E-02	0.000	0.190
	batch 15	1.280	0.170	1.21E-14	0.960	1.610
	batch 16	0.530	0.180	2.62E-03	0.190	0.880
	batch 17	0.520	0.160	9.04E-04	0.210	0.830
	batch 18	1.190	0.170	1.86E-12	0.860	1.520
	batch 19	1.240	0.170	1.80E-13	0.910	1.570
	batch 36	1.590	0.160	1.73E-22	1.270	1.910
	batch 37	0.870	0.170	3.02E-07	0.540	1.210
	batch 38	1.420	0.150	4.02E-21	1.130	1.720
	intercept	5.410	0.140	0.00E+00	5.140	5.680

		Vascular co-localization of lipids and macrophages (n=908)				
		Effect	**SE**	***P***	**lci**	**uci**
negative binomial terms	**LDL cholesterol levels (in SD)**	0.140	0.130	2.89E-01	-0.120	0.400
	HDL cholesterol levels (in SD)	0.030	0.130	8.38E-01	-0.240	0.290
	triglyceride levels (in SD)	0.820	0.180	7.91E-06	0.460	1.190
	glucose levels (in SD)	-0.340	0.160	3.14E-02	-0.650	-0.030
	body length (in SD)	-0.280	0.190	1.33E-01	-0.650	0.090
	dorsal body surface area (in SD)	0.200	0.170	2.32E-01	-0.130	0.520
	batch 39	0.380	0.920	6.82E-01	-1.430	2.180
	batch 40	2.480	0.680	2.75E-04	1.150	3.820
	batch 41	1.380	0.900	1.23E-01	-0.370	3.140
	batch 42	0.910	0.620	1.44E-01	-0.310	2.130
	batch 43	2.030	0.710	4.22E-03	0.640	3.420
	batch 44	1.970	0.700	5.04E-03	0.590	3.350
	batch 45	0.780	0.590	1.83E-01	-0.370	1.930
	intercept	1.180	0.530	2.46E-02	0.150	2.220

continued **Supplementary Table 29**

		Vascular co-localization of macrophages and oxidized LDL (n=619)				
		Effect	**SE**	***P***	**lci**	**uci**
negative binomial terms	**LDL cholesterol levels (in SD)**	-0.080	0.050	1.43E-01	-0.190	0.030
	HDL cholesterol levels (in SD)	0.020	0.050	7.23E-01	-0.070	0.100
	triglyceride levels (in SD)	0.320	0.100	1.67E-03	0.120	0.530
	glucose levels (in SD)	-0.190	0.090	2.77E-02	-0.360	-0.020
	body length (in SD)	-0.050	0.080	5.52E-01	-0.200	0.110
	dorsal body surface area (in SD)	0.010	0.070	9.07E-01	-0.130	0.150
	batch 15	0.560	0.270	3.84E-02	0.030	1.080
	batch 16	0.230	0.290	4.35E-01	-0.340	0.800
	batch 17	-0.650	0.300	2.77E-02	-1.240	-0.070
	batch 18	0.430	0.270	1.18E-01	-0.110	0.960
	batch 19	0.730	0.250	3.48E-03	0.240	1.210
	batch 36	0.320	0.250	2.11E-01	-0.180	0.810
	batch 37	0.320	0.290	2.58E-01	-0.240	0.880
	batch 38	1.250	0.240	1.80E-07	0.780	1.710
	intercept	2.540	0.230	3.49E-29	2.090	2.980

		Vascular co-localization of lipids and neutrophils (n=271)				
		Effect	**SE**	***P***	**lci**	**uci**
negative binomial terms	**LDL cholesterol levels (in SD)**	0.540	0.230	1.83E-02	0.090	1.000
	HDL cholesterol levels (in SD)	0.730	0.310	1.81E-02	0.120	1.330
	triglyceride levels (in SD)	1.100	0.260	3.53E-05	0.580	1.610
	glucose levels (in SD)	0.060	0.190	7.65E-01	-0.320	0.440
	body length (in SD)	-0.830	0.220	2.05E-04	-1.270	-0.390
	dorsal body surface area (in SD)	-0.200	0.200	3.13E-01	-0.600	0.190
	batch 40	4.600	1.190	1.03E-04	2.280	6.930
	batch 41	3.710	1.520	1.44E-02	0.740	6.680
	batch 42	2.740	1.130	1.50E-02	0.530	4.950
	batch 43	3.020	1.030	3.24E-03	1.010	5.030
	batch 44	3.770	1.010	1.97E-04	1.790	5.760
	batch 45	3.770	1.110	6.87E-04	1.590	5.940
	batch 46	3.040	1.410	3.14E-02	0.270	5.800
	intercept	-2.790	0.980	4.32E-03	-4.710	-0.870

		Vascular co-localization of macrophages and neutrophils (n=327)				
		Effect	**SE**	***P***	**lci**	**uci**
negative binomial terms	**LDL cholesterol levels (in SD)**	0.110	0.090	2.36E-01	-0.070	0.280
	HDL cholesterol levels (in SD)	-0.060	0.100	5.65E-01	-0.260	0.140
	triglyceride levels (in SD)	-0.040	0.130	7.29E-01	-0.290	0.210
	glucose levels (in SD)	0.110	0.080	1.69E-01	-0.050	0.270
	body length (in SD)	0.200	0.130	1.21E-01	-0.050	0.450
	dorsal body surface area (in SD)	0.230	0.120	4.87E-02	0.000	0.450
	batch 40	0.550	0.380	1.51E-01	-0.200	1.300
	batch 41	0.660	0.500	1.89E-01	-0.330	1.650
	batch 42	-0.330	0.360	3.48E-01	-1.030	0.360
	batch 43	1.400	0.500	4.56E-03	0.430	2.370
	batch 44	0.480	0.350	1.63E-01	-0.200	1.160
	batch 45	-1.630	0.390	2.39E-05	-2.390	-0.870
	batch 46	-0.620	0.510	2.23E-01	-1.620	0.380
	intercept	3.740	0.290	6.31E-38	3.170	4.310

Associations were examined using negative binomial regresion using data from the dietary, drug treatment and genetic proof-of-concept interventions combined. Dorsal body surface area was normalized for body length using residuals; whole-body LDL cholesterol, HDL cholesterol, triglyceride and glucose levels were normalized for protein level using residuals. Lci and uci are lower and upper boundaries of the 95% confidence interval and have been calculated using robust standard errors.

Supplementary Table 30 - Orthologues of candidate genes in the triglyceride, LDLc and total cholesterol-associated locus on chr 19p13.11

Human gene	ENSG	Zebrafish orthologue	ENSDARG	Chr	Target %identity	Query %identity	Main human protein	Top hit BLAST	%identity (protein)	Conserved genes in locus
LPAR2	ENSG00000064547	*lpar2a*	ENSDARG00000042338	3	49.16	49.86	ENSP0000384665	ENSDARP00000154087	54.95	*PBX4, ATP13A1, GMIP*
		lpar2b	ENSDARG00000042561	1	51.76	54.42		ENSDARP00000062425	60.00	none
GMIP	ENSG00000089639	*gmip*	ENSDARG00000077249	3	36.91	34.02	ENSP00000203556	ENSDARP00000131373	43.92	*ATP13A1, PBX4, LPAR2*
GATAD2A	ENSG00000167491	*gatad2ab*	ENSDARG00000006192	22	53.16	53.00	ENSP00000351552	ENSDARP00000115930	53.8	*GMIP, CILP2, YJEFN3, TSSK6, TM6SF2, HAPLN4, NCAN, NR2C2AP, RFXANK, BORCS8, MEF2B, TMEM161A, SLC25A42, ARMC6, HOMER3*
TM6SF2	ENSG00000213996	*tm6sf2*	ENSDARG00000029057	22	43.32	42.97	ENSP00000374014	ENSDARP00000118571	45.86	*GMIP, HAPLN4, NCAN, NR2C2AP, RFXANK, BORCS8, MEF2B, TMEM161A, GATAD2A, TSSK6, YJEFN3, HOMER3, GMIP, SCL25A42, ARMC6*
		zgc:85843	ENSDARG00000105208	2	43.86	39.79		ENSDARP00000130339	45.67	

Target %identity: percentage of the orthologous sequence matching the human sequence; Query %identity: percentage of the human sequence matching the sequence of the orthologue; Main human protein: Ensembl protein ID for the main transcript; %identity protein: percentage of the aligned query (input sequence, i.e. main human protein) which is identical to the subject (hit) sequence; conserved genes in locus: neighbouring genes conserved across danio rerio and homo sapiens locus according to Genomicus.

Supplementary Table 31 - Identification of moderate-to-highly active CRISPR-Cas9 guide RNAs for 19p13.11 candidate genes

Human gene	Zebrafish orthologue	CRISPR gRNA target sequen	Genomic location (dabRer11/GRCz11) Chr	Pos	Exon	Strand	GC (%)	Self-complementarity	Off-targets 0	1	2	3	Predicted efficiency	CRISPRscan score	Target activity (NA[a], no[b], low[c], moderate[d], high[e] or very high[f])	Forward primer	Reverse primer	product size
LPAR2	*lpar2a*	GATGCCAGCGAAGAGGTCA	3	53,091,511	2 of 3	+	60	0	0	0	0	6	0.65	-	NA	ATTGTCAACCGAAAGTTCCACT	TGAGGCTCATGTTAATCAATGC	175
		GgGCACTCATGACTTTGT	**3**	**53,091,654**	**2 of 3**	**-**	**55**	**1**	**0**	**0**	**0**	**1**	**0.63**	**53**	**high**	**TTAACAGCTGTGAGGCTTTTGA**	**AGTGGAACTTTCGGTTGACAAT**	**186**
	lpar2b	**GGGGACTAAAGCGAAGG**	**1**	**59,206,929**	**2 of 7**	**-**	**65**	**1**	**0**	**0**	**0**	**0**	**0.76**	**76**	**very high**	**TTTTCTTCTACAGCATCAGCCA**	**CCAGCAGGTAATAAATGGGGTA**	**174**
		GGTCAAACACAAGGAGACC	1	59,204,504	3 of 7	-	55	0	0	0	1	1	0.70	49	high, but only inframe variants	CTACACGCGCATCTTCATTTAC	CGCTAAAATGGAAGCTGAATCT	187
GMIP	*gmip*	**GgTCCACGCCATCCTCGC**	**3**	**52,763,869**	**5 of 20**	**-**	**70**	**1**	**0**	**0**	**0**	**0**	**0.68**	**-**	**moderate**	**GTTGATGCTGATGTGTTCGTTT**	**TCCAGCCTAATACAATGTGTCG**	**243**
		gGTGAAGATCTGCCGTGAA	3	52,753,647	4 of 20	+	50	0	0	0	0	1	0.62	-	moderate	TGCCACTGGGAATATTAAAAGC	ACGAGTTCTCATCCCAAATCTC	205
GATAD2A	*gatad2ab*	GAGAAGATGTCAGAAGACC	22	18,353,216	2 of 11	+	50	0	0	0	0	3	0.70	51	NA	GGTCAGACCACTTGTATGTCCA	TCTACAGCTCCAGGTTCTCCTC	207
		GGTGAAGGCCACCATCAA	**22**	**18,353,404**	**2 of 11**	**+**	**60**	**1**	**0**	**0**	**1**	**1**	**0.63**	**51**	**moderate/high**	**GAGGAGAACCTGGAGCTGTAGA**	**ATGATCGACCCTAGTTAGCAGC**	**194**
TM6SF2	*tm6sf2*	GGTTATTCTTGAAATTGGCC	22	17,790,559	3 of 11	+	40	0	0	0	0	7	0.60	10	no	ACAACCTCAGCATCCTATTTCC	GGATCCTTAGGAGGATTGAAGC	239
		GAGGTCAATGACACACGTG	22	17,792,919	4 of 11	-	50	1	0	0	0	0	0.63	62	NA	ACACCACAACACTGAAAGCAAT	ACGCTAACCGTTTTCTGGTAGA	186
		GgGTAGCGAGGTAGACCA	**22**	**17,790,601**	**3 of 11**	**-**	**65**	**1**	**0**	**0**	**0**	**0**	**0.67**	**69**	**very high**	**ttctatcccacagcaagctaaa**	**aggatgaaatgcagaatgtgg**	**229**
		GAGGATTGAAGCGCGTAGC	22	17,790,613	3 of 11	-	60	1	0	0	0	0	0.63	58	very high	ttctatcccacagcaagctaaa	aggatgaaatgcagaatgtgg	229
	zgc:85843	GATGCTGACAACAGACGTG	2	56,897,287	3 of 10	-	50	0	0	0	4	2	0.63	54	moderate	GATGGGGAGGAGAGAGGGAG*	AAAGTCCATGAAGCCTTTGATG*	231
		gGGTCTTACCGTAGAACAG	2	56,896,546	2 of 10	-	45	1	0	0	0	1	0.57	46	NA	TGGATGTGTTGTGTGAAATGAT	GCCTAATTATCCTAACCTGCCCA	241
		GgGATGATGAGCTACTGGG	2	56,904,057	4 of 10	+	50	0	0	0	0	6	0.68	70	very high	CTTGTGCTGTTGTTGTAGGCAG	cacaggagggcgaatagtttag	244
		gGACACTGAGGTTTGCCA	**2**	**56,896,504**	**2 of 10**	**-**	**55**	**0**	**0**	**0**	**0**	**4**	**0.66**	**40**	**very high**	**TGAATGGATGTGTTGTGTGAAA**	**ttgtctccagaacaaacacctg**	**280**

CRISPR gRNA target sequences were preferably selected based on location (i.e. in an early exon that affects all transcripts), complementarity (i.e. no complementarity), and free from predicted off targets. Target activity was examined by micro-injections in eight fertilized eggs in multiplex, followed by fragment length PCR analysis at 3 days post-fertilization. Results from target efficiency testing are shown, where NA: Not available due to failed capilary electrophoresis while estimating the length of the targeted region of an exon; No: 8 of 8 larvae test-injected with the gRNA only showed wildtype sequences; Low: 8 of 8 larvae showed wildtype sequence and fewer than 4 of 8 also contained indel sequence; Moderate: 8 of 8 larvae showed wildtype sequence and >4 of 8 also contained indel sequence; High: 8 of 8 larvae showed wildtype as well as indel sequence; Very high: Fewer than 4 of 8 larvae showed wildtype sequence and all larvae showed indel sequence. Target sequences highlighted in bold were selected and used to generate multiplexed mutant zebrafish.

Supplementary Table 32 - Unique CRISPR-Cas9-induced mutations for 19p13.11 candidate genes

Zebrafish orthologue	Sequence	Annotation	Number of alleles	mean ± SD number of reads
lpar2a	**TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACCACAAAGTCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG**	**142M (wildtype reference)**	**1083**	**742 ± 537**
	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACCAAAGTCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	69M2D71M	8	512 ± 569
	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	69M8D65M	2	327 ± 65
	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCAAAGTCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	66M5D71M	1	673
lpar2b	**GTGAAAGCGGCGGTTCATGAAGATGGCCGCCATCACCAGGATGTTGGTGAAGATGACAAAAACACTGACCAGCAGCCCCATACCCACCACCGCCTTCGCTTTAGTCCCCCACGTATCGCTGATGTTCTTA**	**130M (wildtype reference)**	**1086**	**310 ± 174**
	GTGAAAGCGGCGGTTCATGAAGATGGCCGCCATCACCAGGATGTTGGTGAAGATGACAAAAACACTGACCAGCAGCCCCATACCCACCACCTTCGCTTTAGTCCCCCACGTATCGCTGATGTTCTTA	89M3D38M	6	278 ± 91
gatad2ab	**TGGACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCACCATCAAGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA**	**150M (wildtype reference)**	**1062**	**1091 ± 567**
	TGGACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	64M12D74M	27	584 ± 349
	TGGACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCACCATCAGGTGGTGCAGACCAGCGGTGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTC(	77M1S1M12I1M1S2M1S66M	2	424 ± 98
	TGAACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCAAGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	2M1S66M6D75M	2	323 ± 48
	TGGACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	70M8D72M	1	436

Annotation shows the sequential number of base pairs that - when compared with the reference genome from Ensembl - represent a match (M), deletion (D), insertion (I), or substitution (S). For each unique sequence, the number of alleles in which it was observed is shown, as well as the mean and standrard deviation for the number of reads that were observed for the sequence.

Supplementary Table 33 - Unique CRISPR-Cas9-induced mutations in 19p13.11 candidate genes and their predicted functional consequences

Zebrafish orthologue	Chr	Start	End	Mutation	Nett base pair change	Annotation VEP	VEP impact	$n_{affected\ alleles}$
		53,091,655	53,091,659	CACCA/-	-5	frameshift variant	high	1
lpar2a	3	53,091,658	53,091,659	CA/-	-2	frameshift variant	high	8
		53,091,658	53,091,665	CACAAAGT/-	-8	frameshift variant	high	2
lpar2b	1	59,206,932	59,206,934	CCG/-	-3	inframe deletion	moderate	6
		18,353,408	18,353,419	AAGGCCACCATC/-	-12	inframe deletion	moderate	27
		18,353,413	18,353,418	CACCAT/-	-6	inframe deletion	moderate	2
		18,353,414	18,353,421	ACCATCAA/-	-8	frameshift variant	high	1
gatad2ab	22	18,353,421	18,353,421	A/G	0	missense variant	moderate	2
		18,353,423	18,353,422	-/TGGTGCAGACCA	12	inframe insertion	moderate	2
		18,353,424	18,353,424	T/C	0	missense variant	moderate	2
		18,353,427	18,353,427	A/T	0	missense variant	moderate	2

VEP: Ensembl's variant effect predictor; $n_{affected\ alleles}$: the number of alleles across the sequenced larvae in which the variant was observed.

Supplementary Table 34 - Sequencing results expressed in number of mutated alleles for 19p13.11 candidate genes

Zebrafish orthologue	Number of mutated alleles			Missing genotypes	Total	Non-missing	Mutant allele freq	P_{HWE_LR}
	0	1	2					
lpar2a	536	11	0	5	552	547	0.010	0.99
lpar2b	540	6	0	6	552	546	0.005	0.02
gatad2ab	515	32	0	5	552	547	0.029	0.47

The number of mutated alleles does not take into account the mutation's probability of affecting protein function. Dosage scores summed across both alleles were used in the association analyses. Four larvae were wildtype controls used to exclude variants that are inherently present from influencing the results, and five more larvae were excluded for having more than two missing calls across the seven successfully sequenced orthologues. Only genes for which some larvae were successfully mutated are shown. P_{HWE_LR}: *P*- value for a Hardy-Weinberg equilibrium likelihood-ratio chi-squared statistic, considering a ±30 base pair window around the CRISPR cut site as one locus.

Supplementary Table 35 - The effect of a mutated allele in *lpar2a* , *lpar2b* and *gatad2ab* on body size

		Body length (n=505)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.016	0.243	9.47E-01	-0.493	0.460
	lpar2b	1.075	0.490	2.80E-02	0.116	2.035
	gatad2ab	-0.161	0.224	4.71E-01	-0.600	0.277
	age (11dpf vs. 10dpf)	0.301	0.101	2.94E-03	0.103	0.500
	time of day (in hours since 9AM)	0.000	0.019	9.79E-01	-0.036	0.037
	intercept	0.114	0.290	6.95E-01	-0.454	0.682
random factors	***variance by batch***	*0.779*	*0.025*	-	*0.732*	*0.829*
	residual	*0.673*	*0.200*	-	*0.376*	*1.204*

		Dorsal body surface area (n=505)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	0.016	0.263	9.53E-01	-0.500	0.531
	lpar2b	-0.831	0.530	1.17E-01	-1.869	0.207
	gatad2ab	0.825	0.242	6.52E-04	0.351	1.299
	age (11dpf vs. 10dpf)	0.214	0.109	4.99E-02	0.000	0.429
	time of day (in hours since 9AM)	0.007	0.020	7.45E-01	-0.033	0.046
	intercept	0.012	0.237	9.58E-01	-0.452	0.477
random factors	***variance by batch***	*0.843*	*0.027*	-	*0.792*	*0.897*
	residual	*0.527*	*0.158*	-	*0.292*	*0.949*

		Lateral body surface area (n=502)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	0.281	0.279	3.14E-01	-0.265	0.827
	lpar2b	0.070	0.561	9.01E-01	-1.030	1.169
	gatad2ab	0.710	0.256	5.59E-03	0.208	1.212
	age (11dpf vs. 10dpf)	0.263	0.115	2.27E-02	0.037	0.489
	time of day (in hours since 9AM)	-0.040	0.021	6.13E-02	-0.082	0.002
	intercept	0.170	0.213	4.26E-01	-0.248	0.588
random factors	***variance by batch***	*0.892*	*0.028*	-	*0.839*	*0.950*
	residual	*0.454*	*0.140*	-	*0.248*	*0.831*

		Body volume (n=495)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	0.200	0.276	4.69E-01	-0.341	0.740
	lpar2b	0.152	0.606	8.03E-01	-1.037	1.340
	gatad2ab	0.924	0.254	2.72E-04	0.426	1.421
	age (11dpf vs. 10dpf)	0.286	0.115	1.31E-02	0.060	0.512
	time of day (in hours since 9AM)	-0.005	0.021	8.04E-01	-0.047	0.037
	intercept	0.023	0.220	9.16E-01	-0.408	0.454
random factors	***variance by batch***	*0.883*	*0.028*	-	*0.830*	*0.940*
	residual	*0.474*	*0.146*	-	*0.259*	*0.866*

All outcomes were normalized for length using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models. Effects shown are for the effect of carrying a mutated allele in *lpar2a, lpar2b and gatad2ab* , weighted by the allele's predicted effect on protein function (i.e. additive model, mutually adjusted). All associations were adjusted for age (i.e. 11 vs. 10 days post fertilization (dpf), time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 36 - The effect of a mutated allele in *lpar2a, lpar2b* and *gatad2ab* on whole-body lipid

		LDL cholesterol levels (n=513)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.607	0.310	5.00E-02	-1.215	0.000
	lpar2b	-0.539	0.724	4.57E-01	-1.959	0.881
	gatad2ab	-0.159	0.262	5.45E-01	-0.673	0.356
	age (11dpf vs. 10dpf)	-0.263	0.121	2.98E-02	-0.500	-0.026
	time of day (in hours since 9AM)	0.010	0.024	6.86E-01	-0.037	0.056
	intercept	0.108	0.160	5.01E-01	-0.206	0.422
random factors	***variance by batch***	*0.946*	*0.030*	-	*0.889*	*1.006*
	residual	*0.284*	*0.101*	-	*0.141*	*0.572*

		HDL cholesterol levels (n=513)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.346	0.318	2.77E-01	-0.970	0.278
	lpar2b	-1.264	0.744	8.96E-02	-2.723	0.195
	gatad2ab	-0.486	0.269	7.11E-02	-1.014	0.042
	age (11dpf vs. 10dpf)	-0.122	0.122	3.17E-01	-0.362	0.117
	time of day (in hours since 9AM)	0.020	0.024	4.03E-01	-0.027	0.067
	intercept	-0.059	0.144	6.81E-01	-0.341	0.223
random factors	***variance by batch***	0.972	0.031	-	0.914	1.034
	residual	0.218	0.084	-	0.103	0.462

		Triglyceride levels (n=513)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.652	0.278	1.92E-02	-1.197	-0.106
	lpar2b	-0.001	0.650	9.99E-01	-1.276	1.274
	gatad2ab	0.394	0.236	9.45E-02	-0.068	0.857
	age (11dpf vs. 10dpf)	0.007	0.111	9.52E-01	-0.210	0.224
	time of day (in hours since 9AM)	0.085	0.022	7.12E-05	0.043	0.128
	intercept	-0.328	0.232	1.57E-01	-0.783	0.126
random factors	***variance by batch***	*0.849*	*0.027*	-	*0.798*	*0.903*
	residual	*0.512*	*0.156*	-	*0.282*	*0.929*

		Total cholesterol levels (n=513)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.739	0.306	1.58E-02	-1.340	-0.139
	lpar2b	0.369	0.716	6.07E-01	-1.035	1.773
	gatad2ab	0.118	0.260	6.48E-01	-0.390	0.627
	age (11dpf vs. 10dpf)	-0.487	0.120	4.89E-05	-0.722	-0.252
	time of day (in hours since 9AM)	0.018	0.023	4.39E-01	-0.028	0.064
	intercept	0.034	0.166	8.37E-01	-0.291	0.360
random factors	***variance by batch***	*0.935*	*0.029*	-	*0.879*	*0.994*
	residual	*0.306*	*0.105*	-	*0.156*	*0.598*

continued **Supplementary Table 36**

		Glucose levels (n=513)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.146	0.308	6.36E-01	-0.748	0.457
	lpar2b	-0.001	0.719	9.99E-01	-1.410	1.408
	gatad2ab	-0.371	0.260	1.55E-01	-0.881	0.140
	age (11dpf vs. 10dpf)	0.147	0.120	2.23E-01	-0.089	0.383
	time of day (in hours since 9AM)	-0.080	0.024	6.71E-04	-0.126	-0.034
	intercept	0.240	0.168	1.53E-01	-0.089	0.569
random factors	***variance by batch***	*0.938*	*0.029*	-	*0.882*	*0.998*
	residual	*0.311*	*0.103*	-	*0.162*	*0.594*

All outcomes were normalized for protein level using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models. Effects shown are for the effect of carrying a mutated allele in *lpar2a* , *lpar2b* and *gatad2ab* , weighted by the allele's predicted effect on protein function (i.e. additive model, mutually adjusted). Associations were adjusted for age (i.e. 11 vs. 10 days post fertilization (dpf), time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 37 - The effect of a mutated allele in *lpar2a, lpar2b* and *gatad2ab* on vascular atherogenic traits

		Vascular lipid deposition														
		Model 1 (n=280)					Model 2 (n=258)					Model 3 (n=233)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***lpar2a***	1.870	1.003	6.23E-02	-0.096	3.836	1.622	1.001	1.05E-01	-0.340	3.584	1.795	0.995	7.13E-02	-0.156	3.746
	lpar2b	0.994	1.191	4.04E-01	-1.340	3.328	0.861	1.139	4.50E-01	-1.371	3.093	0.912	1.351	5.00E-01	-1.736	3.560
	gatad2ab	-0.006	0.334	9.87E-01	-0.659	0.648	-0.058	0.316	8.55E-01	-0.676	0.561	-0.277	0.313	3.75E-01	-0.890	0.336
	body length (in SD)	-	-	-	-	-	0.152	0.116	1.92E-01	-0.076	0.379	0.194	0.126	1.24E-01	-0.054	0.442
	dorsal body surface area (in SD)	-	-	-	-	-	0.153	0.131	2.44E-01	-0.104	0.410	0.202	0.139	1.46E-01	-0.070	0.474
	age (11dpf vs. 10dpf)	0.263	0.503	6.01E-01	-0.722	1.249	0.328	0.497	5.09E-01	-0.646	1.302	0.229	0.462	6.20E-01	-0.677	1.136
	time of day (in hours since 9AM)	-0.079	0.038	4.00E-02	-0.154	-0.004	-0.075	0.041	7.06E-02	-0.156	0.006	-0.045	0.052	3.93E-01	-0.147	0.058
	batch 1	3.239	0.635	3.42E-07	1.994	4.484	3.299	0.621	1.09E-07	2.082	4.517	3.364	0.580	6.46E-09	2.228	4.500
	batch 2	4.939	0.746	3.50E-11	3.477	6.400	4.771	0.782	1.03E-09	3.239	6.304	4.686	0.744	3.00E-10	3.228	6.144
	batch 3	4.581	0.725	2.66E-10	3.160	6.003	4.361	0.749	5.83E-09	2.893	5.829	4.486	0.683	4.99E-11	3.148	5.824
	batch 4	3.656	0.738	7.39E-07	2.209	5.103	3.855	0.726	1.11E-07	2.431	5.279	3.953	0.653	1.46E-09	2.672	5.234
	batch 5	3.903	0.732	9.59E-08	2.469	5.337	3.705	0.751	8.02E-07	2.233	5.176	3.635	0.689	1.31E-07	2.285	4.985
	intercept	0.802	0.720	2.65E-01	-0.609	2.212	0.766	0.702	2.75E-01	-0.610	2.143	0.597	0.639	3.50E-01	-0.656	1.850
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.189	0.096	4.94E-02	-0.377	0.000
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.084	0.075	2.65E-01	-0.063	0.231
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.070	0.105	5.09E-01	-0.137	0.276
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.016	0.108	8.82E-01	-0.227	0.195

		Vascular infiltration by macrophages															
		Model 1 (n=363)						Model 2 (n=331)					Model 3 (n=305)				
		Effect	SE	*P*	lci	uci		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***lpar2a***	0.307	0.374	4.12E-01	-0.426	1.041	363	0.282	0.368	4.44E-01	-0.440	1.003	0.238	0.420	5.70E-01	-0.584	1.061
	lpar2b	0.528	0.520	3.09E-01	-0.490	1.546		0.597	0.512	2.43E-01	-0.406	1.601	0.649	0.636	3.08E-01	-0.598	1.896
	gatad2ab	0.404	0.254	1.11E-01	-0.093	0.902		0.472	0.261	7.08E-02	-0.040	0.984	0.458	0.267	8.68E-02	-0.066	0.982
	body length (in SD)	-	-	-	-	-		0.020	0.059	7.38E-01	-0.096	0.136	0.029	0.062	6.36E-01	-0.092	0.150
	dorsal body surface area (in SD)	-	-	-	-	-		0.077	0.055	1.63E-01	-0.031	0.186	0.056	0.057	3.28E-01	-0.056	0.168
	age (11dpf vs. 10dpf)	-0.149	0.151	3.24E-01	-0.445	0.147		-0.146	0.148	3.25E-01	-0.436	0.144	-0.124	0.147	3.97E-01	-0.411	0.163
	time of day (in hours since 9AM)	0.042	0.023	6.53E-02	-0.003	0.086		0.043	0.023	6.58E-02	-0.003	0.088	0.010	0.027	7.21E-01	-0.043	0.063
	intercept	-0.101	0.172	5.56E-01	-0.438	0.235		-0.139	0.169	4.12E-01	-0.470	0.193	-0.029	0.157	8.55E-01	-0.336	0.278
	HDL cholesterol levels (in SD)	-	-	-	-	-		-	-	-	-	-	-0.001	0.048	9.81E-01	-0.095	0.092
	LDL cholesterol levels (in SD)	-	-	-	-	-		-	-	-	-	-	-0.012	0.046	7.88E-01	-0.103	0.078
	glucose levels (in SD)	-	-	-	-	-		-	-	-	-	-	-0.021	0.052	6.84E-01	-0.123	0.080
	triglyceride levels (in SD)	-	-	-	-	-		-	-	-	-	-	0.094	0.057	9.68E-02	-0.017	0.205
random factors	***intercept***	*0.822*	*0.031*	-	*0.764*	*0.885*		*0.805*	*0.032*		*0.746*	*0.870*	*0.812*	*0.033*		*0.749*	*0.879*
	variation by batch	*0.311*	*0.103*	-	*0.162*	*0.595*		*0.294*	*0.099*		*0.151*	*0.569*	*0.218*	*0.086*		*0.100*	*0.474*

continued **Supplementary Table 37**

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=263)					Model 2 (n=241)					Model 3 (n=217)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***lpar2a***	3.463	1.204	4.02E-03	1.103	5.823	3.511	1.207	3.63E-03	1.145	5.877	3.408	1.167	3.50E-03	1.120	5.696
	lpar2b	0.851	1.083	4.32E-01	-1.270	2.973	0.747	1.018	4.63E-01	-1.248	2.743	0.284	1.368	8.35E-01	-2.396	2.965
	gatad2ab	0.248	0.491	6.13E-01	-0.714	1.210	0.495	0.518	3.39E-01	-0.520	1.509	0.404	0.582	4.87E-01	-0.737	1.545
	body length (in SD)	-	-	-	-	-	0.101	0.190	5.94E-01	-0.271	0.473	0.223	0.197	2.57E-01	-0.162	0.609
	dorsal body surface area (in SD)	-	-	-	-	-	-0.063	0.179	7.25E-01	-0.414	0.288	0.059	0.200	7.70E-01	-0.334	0.452
	age (11dpf vs. 10dpf)	0.248	0.642	6.99E-01	-1.010	1.506	0.261	0.634	6.81E-01	-0.981	1.502	-0.196	0.678	7.73E-01	-1.524	1.133
	time of day (in hours since 9AM)	-0.129	0.054	1.65E-02	-0.235	-0.024	-0.150	0.060	1.17E-02	-0.267	-0.033	-0.124	0.087	1.55E-01	-0.294	0.047
	batch 1	4.433	0.824	7.38E-08	2.819	6.048	4.418	0.831	1.06E-07	2.789	6.048	4.521	0.825	4.31E-08	2.904	6.139
	batch 2	5.985	0.974	7.89E-10	4.076	7.893	5.875	0.994	3.37E-09	3.928	7.823	5.222	1.122	3.25E-06	3.023	7.422
	batch 3	5.635	0.928	1.28E-09	3.815	7.454	5.649	0.948	2.51E-09	3.792	7.507	5.258	1.068	8.46E-07	3.165	7.351
	batch 4	4.252	1.026	3.40E-05	2.241	6.262	4.352	1.082	5.73E-05	2.232	6.472	4.120	1.109	2.02E-04	1.947	6.293
	batch 5	4.694	0.939	5.84E-07	2.853	6.535	4.494	0.969	3.55E-06	2.594	6.394	4.039	1.033	9.29E-05	2.014	6.065
	intercept	-1.384	0.956	1.48E-01	-3.258	0.490	-1.303	0.965	1.77E-01	-3.195	0.589	-1.141	1.126	3.11E-01	-3.348	1.066
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.098	0.139	4.82E-01	-0.371	0.175
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.105	0.107	3.23E-01	-0.104	0.314
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.274	0.167	1.01E-01	-0.601	0.053
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.170	0.139	2.22E-01	-0.442	0.103

		Vascular infiltration by neutrophils														
		Model 1 (n=363)					Model 2 (n=334)					Model 3 (n=307)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***lpar2a***	0.743	0.387	5.46E-02	-0.015	1.501	0.678	0.386	7.89E-02	-0.078	1.435	0.566	0.423	1.80E-01	-0.262	1.395
	lpar2b	0.130	0.537	8.09E-01	-0.922	1.182	0.035	0.538	9.48E-01	-1.019	1.090	0.045	0.642	9.44E-01	-1.213	1.303
	gatad2ab	-0.315	0.267	2.38E-01	-0.837	0.208	-0.452	0.278	1.04E-01	-0.996	0.093	-0.353	0.274	1.97E-01	-0.889	0.183
	body length (in SD)	-	-	-	-	-	0.145	0.061	1.76E-02	0.025	0.264	0.197	0.063	1.72E-03	0.074	0.320
	dorsal body surface area (in SD)	-	-	-	-	-	0.053	0.059	3.68E-01	-0.062	0.168	0.016	0.060	7.88E-01	-0.101	0.134
	age (11dpf vs. 10dpf)	-0.120	0.152	4.30E-01	-0.418	0.178	-0.157	0.150	2.97E-01	-0.451	0.138	-0.159	0.150	2.89E-01	-0.453	0.135
	time of day (in hours since 9AM)	0.025	0.023	2.83E-01	-0.021	0.070	0.025	0.024	2.92E-01	-0.022	0.072	0.019	0.027	4.92E-01	-0.034	0.072
	intercept	0.033	0.195	8.65E-01	-0.348	0.415	0.023	0.179	9.00E-01	-0.329	0.374	0.038	0.186	8.36E-01	-0.325	0.402
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.029	0.048	5.54E-01	-0.066	0.123
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.135	0.046	3.67E-03	-0.226	-0.044
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.033	0.052	5.35E-01	-0.070	0.135
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.049	0.057	3.88E-01	-0.160	0.062
random factors	***intercept***	*0.849*	*0.032*	-	*0.789*	*0.914*	*0.846*	*0.033*		*0.783*	*0.913*	*0.818*	*0.033*		*0.755*	*0.886*
	variation by batch	*0.379*	*0.121*	-	*0.202*	*0.710*	*0.320*	*0.111*		*0.162*	*0.630*	*0.329*	*0.114*		*0.167*	*0.649*

continued **Supplementary Table 37**

		Vascular co-localization of lipids with neutrophils														
		Model 1 (n=260)					Model 2 (n=242)					Model 3 (n=217)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***lpar2a***	2.718	1.321	3.96E-02	0.129	5.307	2.614	1.314	4.67E-02	0.038	5.189	3.548	1.292	6.03E-03	1.016	6.081
	lpar2b	-0.034	1.109	9.75E-01	-2.207	2.139	-0.260	1.167	8.24E-01	-2.547	2.027	-2.627	1.687	1.20E-01	-5.934	0.681
	gatad2ab	-1.383	1.031	1.80E-01	-3.403	0.638	-1.613	1.014	1.12E-01	-3.601	0.375	-2.236	1.025	2.91E-02	-4.245	-0.227
	body length (in SD)	-	-	-	-	-	0.260	0.182	1.53E-01	-0.097	0.617	0.178	0.185	3.37E-01	-0.185	0.542
	dorsal body surface area (in SD)	-	-	-	-	-	0.077	0.182	6.72E-01	-0.280	0.434	0.000	0.187	9.98E-01	-0.367	0.368
	age (11dpf vs. 10dpf)	0.838	0.610	1.69E-01	-0.357	2.033	0.853	0.608	1.60E-01	-0.338	2.044	0.390	0.632	5.38E-01	-0.849	1.628
	time of day (in hours since 9AM)	-0.126	0.069	6.76E-02	-0.262	0.009	-0.134	0.068	4.74E-02	-0.267	-0.002	-0.219	0.078	5.16E-03	-0.372	-0.065
	batch 1	3.057	1.022	2.78E-03	1.054	5.060	3.136	0.981	1.39E-03	1.213	5.059	3.287	0.840	9.06E-05	1.641	4.933
	batch 2	4.126	1.202	5.98E-04	1.770	6.482	3.865	1.213	1.44E-03	1.488	6.243	4.036	1.086	2.01E-04	1.908	6.164
	batch 3	3.450	1.162	2.99E-03	1.173	5.727	3.265	1.137	4.09E-03	1.036	5.494	3.350	1.010	9.10E-04	1.371	5.330
	batch 4	3.911	1.181	9.27E-04	1.596	6.225	4.210	1.145	2.36E-04	1.966	6.453	4.467	0.971	4.21E-06	2.564	6.370
	batch 5	2.912	1.171	1.29E-02	0.617	5.208	3.073	1.122	6.16E-03	0.874	5.272	3.193	0.965	9.33E-04	1.303	5.084
	intercept	-1.356	1.157	2.41E-01	-3.624	0.911	-1.388	1.105	2.09E-01	-3.554	0.778	-1.071	0.999	2.83E-01	-3.029	0.886
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.312	0.165	5.79E-02	-0.635	0.010
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.088	0.132	5.05E-01	-0.171	0.347
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.134	0.145	3.53E-01	-0.149	0.417
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.135	0.171	4.30E-01	-0.200	0.471

		Vascular co-localization of macrophages with neutrophils														
		Model 1 (n=345)					Model 2 (n=317)					Model 3 (n=291)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***lpar2a***	0.219	0.301	4.67E-01	-0.371	0.808	0.185	0.304	5.44E-01	-0.411	0.781	0.023	0.315	9.41E-01	-0.594	0.641
	lpar2b	-0.073	0.473	8.77E-01	-1.000	0.853	0.022	0.452	9.62E-01	-0.864	0.907	0.225	0.513	6.61E-01	-0.780	1.229
	gatad2ab	-0.409	0.357	2.52E-01	-1.108	0.290	-0.514	0.417	2.18E-01	-1.330	0.303	-0.676	0.384	7.84E-02	-1.429	0.077
	body length (in SD)	-	-	-	-	-	-0.084	0.073	2.49E-01	-0.226	0.059	-0.027	0.077	7.29E-01	-0.177	0.124
	dorsal body surface area (in SD)	-	-	-	-	-	0.100	0.066	1.26E-01	-0.028	0.229	0.096	0.068	1.60E-01	-0.038	0.230
	age (11dpf vs. 10dpf)	-0.209	0.165	2.05E-01	-0.532	0.114	-0.186	0.165	2.59E-01	-0.510	0.137	-0.199	0.174	2.51E-01	-0.540	0.141
	time of day (in hours since 9AM)	0.019	0.028	4.97E-01	-0.036	0.075	0.021	0.029	4.65E-01	-0.035	0.077	0.030	0.032	3.60E-01	-0.034	0.093
	batch 1	0.026	0.176	8.83E-01	-0.318	0.370	0.084	0.178	6.39E-01	-0.266	0.433	0.038	0.205	8.54E-01	-0.365	0.440
	batch 2	0.491	0.255	5.39E-02	-0.008	0.991	0.528	0.311	8.94E-02	-0.081	1.137	0.512	0.349	1.43E-01	-0.173	1.196
	batch 3	1.144	0.236	1.26E-06	0.681	1.606	1.137	0.267	2.00E-05	0.615	1.660	1.223	0.314	9.78E-05	0.608	1.838
	batch 4	-0.467	0.259	7.09E-02	-0.975	0.040	-0.514	0.258	4.65E-02	-1.021	-0.008	-0.560	0.255	2.78E-02	-1.059	-0.061
	batch 5	-0.311	0.228	1.73E-01	-0.758	0.136	-0.313	0.238	1.88E-01	-0.779	0.153	-0.299	0.264	2.58E-01	-0.816	0.219
	intercept	4.047	0.208	1.95E-84	3.639	4.454	4.021	0.211	8.39E-81	3.607	4.435	3.978	0.253	7.40E-56	3.483	4.473
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.035	0.054	5.11E-01	-0.141	0.070
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.105	0.060	7.96E-02	-0.222	0.012
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.005	0.062	9.36E-01	-0.126	0.116
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.024	0.072	7.35E-01	-0.166	0.117

Associations were examined using negative binomial regression for outcomes that showed a negative binomial distribution; and using hierarchical linear models on inverse-normally transformed outcomes for outcomes that were (borderline) normally distributed (i.e. vascular accumulation of macrophages and neutrophils). Effects shown are for the effect of carrying a mutated allele in *lpar2a* , *lpar2b* and *gatad2ab* , weighted by the allele's predicted effect on protein function (i.e. additive model, mutually adjusted). Model 1: adjusted for time of day and batch; Model 2: additionally adjusted for body length and dorsal body surface area normalized for length; Model 3: additionally adjusted for whole-body LDL cholesterol, HDL cholesterol, triglyceride and glucose levels normalized for protein level. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 38 - The effect of a mutated allele in *lpar2a*, *lpar2b* and *gatad2ab* on image and image quantification quality

	Region of interest not detected														
	Model 1 (n=297)					Model 2 (n=276)					Model 3 (n=253)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	1.021	1.184	9.85E-01	0.105	9.899	3.326	4.200	3.41E-01	0.280	39.519	2.918	3.880	4.21E-01	0.215	39.528
lpar2b	all 39 larvae with an undetected vessel are wildtype for mutations in *lpar2b* ; 0.74 mutant larvae were expected.														
gatad2ab	all 39 larvae with an undetected vessel are wildtype for mutations in *gatad2ab* ; 1.84 mutant larvae were expected.														
age (11dpf vs. 10dpf)	3.904	1.404	1.52E-04	1.929	7.898	2.172	0.848	4.71E-02	1.010	4.670	2.011	0.802	7.99E-02	0.920	4.395
time of day (in hours since 9AM)	0.923	0.080	3.56E-01	0.780	1.093	0.999	0.099	9.92E-01	0.823	1.212	1.060	0.109	5.68E-01	0.867	1.297
body length (in SD)	-	-	-	-	-	0.334	0.083	9.35E-06	0.206	0.543	0.344	0.091	5.17E-05	0.205	0.576
dorsal body surface area (in SD)	-	-	-	-	-	0.345	0.089	3.82E-05	0.208	0.573	0.356	0.097	1.59E-04	0.208	0.609
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.076	0.262	7.63E-01	0.668	1.734
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.161	0.247	4.81E-01	0.766	1.761
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.634	0.157	6.58E-02	0.390	1.030
glucose levels	-	-	-	-	-	-	-	-	-	-	1.054	0.239	8.16E-01	0.676	1.643
intercept	0.139	0.063	1.19E-05	0.057	0.336	0.096	0.050	6.94E-06	0.035	0.267	0.069	0.038	1.68E-06	0.023	0.205

	Many false positive lipid deposits														
	Model 1 (n=364)					Model 2 (n=331)					Model 3 (n=305)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	all 90 larvae with many false positive lipid deposits were wildtype for mutations in *lpar2a* ; 1.22 mutant larvae were expected.														
lpar2b	all 90 larvae with many false positive lipid deposits were wildtype or had a missed call for mutations in *lpar2b* ; 1.46 mutant larvae were expected.														
gatad2ab	3.137	1.951	6.59E-02	0.927	10.613	4.301	2.900	3.05E-02	1.147	16.125	3.799	2.631	5.40E-02	0.977	14.766
age (11dpf vs. 10dpf)	0.772	0.265	4.50E-01	0.394	1.512	0.639	0.228	2.09E-01	0.317	1.286	0.642	0.232	2.20E-01	0.316	1.304
time of day (in hours since 9AM)	0.968	0.059	5.92E-01	0.859	1.090	0.981	0.066	7.76E-01	0.859	1.120	0.985	0.074	8.41E-01	0.850	1.141
body length (in SD)	-	-	-	-	-	0.753	0.113	5.92E-02	0.561	1.011	0.764	0.126	1.04E-01	0.552	1.057
dorsal body surface area (in SD)	-	-	-	-	-	0.697	0.099	1.13E-02	0.527	0.921	0.708	0.109	2.45E-02	0.523	0.957
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.867	0.116	2.86E-01	0.667	1.127
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.105	0.152	4.69E-01	0.843	1.448
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.113	0.178	5.03E-01	0.813	1.524
glucose levels	-	-	-	-	-	-	-	-	-	-	0.843	0.122	2.39E-01	0.635	1.120
intercept	0.382	0.122	2.67E-03	0.204	0.716	0.386	0.134	5.99E-03	0.196	0.761	0.384	0.140	8.74E-03	0.188	0.785

continued **Supplementary Table 38**

	Many false negative lipid deposits														
	Model 1 (n=287)					Model 2 (n=265)					Model 3 (n=243)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	all 19 larvae with many false negative lipid deposits were wildtype for mutations in *lpar2a* ; 0.32 mutant larvae were expected.														
lpar2b	all 19 larvae with many false negative lipid deposits were wildtype for mutations in *lpar2b* ; 0.38 mutant larvae were expected.														
gatad2ab	0.934	1.481	9.66E-01	0.042	20.905	1.128	1.885	9.42E-01	0.043	29.838	2.649	4.643	5.78E-01	0.085	82.204
age (11dpf vs. 10dpf)	2.011	1.051	1.81E-01	0.722	5.601	1.209	0.651	7.25E-01	0.421	3.476	1.270	0.702	6.66E-01	0.430	3.752
time of day (in hours since 9AM)	0.872	0.103	2.47E-01	0.691	1.100	0.917	0.117	4.97E-01	0.715	1.177	1.000	0.133	1.00E+00	0.770	1.299
body length (in SD)	-	-	-	-	-	0.542	0.158	3.51E-02	0.307	0.958	0.564	0.179	7.11E-02	0.303	1.050
dorsal body surface area (in SD)	-	-	-	-	-	0.449	0.139	9.81E-03	0.244	0.824	0.479	0.157	2.49E-02	0.252	0.911
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.064	0.293	8.22E-01	0.620	1.826
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.437	0.375	1.65E-01	0.861	2.397
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.749	0.231	3.49E-01	0.409	1.371
glucose levels	-	-	-	-	-	-	-	-	-	-	1.389	0.367	2.13E-01	0.828	2.332
intercept	0.110	0.064	1.38E-04	0.035	0.342	0.106	0.065	2.63E-04	0.032	0.355	0.063	0.044	5.84E-05	0.017	0.243

	Transparant larvae														
	Model 1 (n=280)					Model 2 (n=258)					Model 3 (n=236)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	all 12 larvae that appeared particularly transparant were wildtype for mutations in *lpar2a* ; 0.21 mutant larvae were expected.														
lpar2b	all 12 larvae that appeared particularly transparant were wildtype for mutations in *lpar2b* ; 0.25 mutant larvae were expected.														
gatad2ab	1.849	2.961	7.01E-01	0.080	42.635	1.376	2.245	8.45E-01	0.056	33.657	0.753	1.386	8.77E-01	0.020	27.745
age (11dpf vs. 10dpf)	2.166	1.382	2.26E-01	0.620	7.565	3.442	2.524	9.18E-02	0.818	14.488	2.309	1.942	3.20E-01	0.444	12.004
time of day (in hours since 9AM)	0.900	0.135	4.83E-01	0.671	1.207	0.871	0.131	3.60E-01	0.648	1.170	0.902	0.185	6.17E-01	0.603	1.350
body length (in SD)	-	-	-	-	-	1.344	0.452	3.80E-01	0.695	2.598	0.762	0.295	4.83E-01	0.357	1.626
dorsal body surface area (in SD)	-	-	-	-	-	1.923	0.681	6.49E-02	0.960	3.851	1.344	0.553	4.73E-01	0.599	3.012
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.160	0.335	6.07E-01	0.659	2.045
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.915	0.293	7.81E-01	0.489	1.714
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	4.396	1.989	1.06E-03	1.811	10.669
glucose levels	-	-	-	-	-	-	-	-	-	-	0.756	0.268	4.30E-01	0.377	1.516
intercept	0.057	0.043	1.51E-04	0.013	0.251	0.043	0.035	1.12E-04	0.009	0.211	0.019	0.023	8.75E-04	0.002	0.197

continued **Supplementary Table 38**

	Bad quality images of macrophages															
	Model 1 (n=323)					Model 2 (n=291)						Model 3 (n=269)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**		**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	all 12 larvae that had bad quality images for macrophages were wildtype for mutations in *lpar2a* ; 0.27 mutant larvae were expected.															
lpar2b	all 12 larvae that had bad quality images for macrophages were wildtype for mutations in *lpar2b* ; 0.13 mutant larvae were expected.															
gatad2ab	all 12 larvae that had bad quality images for macrophages were wildtype for mutations in *gatad2ab* ; 0.83 mutant larvae were expected.															
time of day (in hours since 9AM)	1.004	0.144	9.79E-01	0.758	1.329	1.097	0.201	6.12E-01	0.767	1.570	291	1.256	0.277	3.01E-01	0.815	1.935
body length (in SD)	-	-	-	-	-	0.301	0.110	1.00E-03	0.147	0.615	291	0.309	0.120	2.39E-03	0.145	0.660
dorsal body surface area (in SD)	-	-	-	-	-	1.353	0.508	4.20E-01	0.649	2.825	291	1.734	0.737	1.95E-01	0.754	3.988
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	291	0.942	0.366	8.77E-01	0.440	2.016
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	291	1.071	0.358	8.38E-01	0.556	2.063
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	291	0.668	0.284	3.42E-01	0.290	1.536
glucose levels	-	-	-	-	-	-	-	-	-	-	291	0.709	0.250	3.30E-01	0.355	1.416
intercept	0.038	0.027	5.64E-06	0.009	0.156	0.015	0.015	1.26E-05	0.002	0.100	291	0.008	0.009	3.87E-05	0.001	0.078

	Many false positve macrophages														
	Model 1 (n=401)					Model 2 (n=371)					Model 3 (n=348)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	all 10 larvae that had many false positive macrophages were wildtype for mutations in *lpar2a* ; 0.22 mutant larvae were expected.														
lpar2b	all 10 larvae that had many false positive macrophages were wildtype for mutations in *lpar2b* ; 0.11 mutant larvae were expected.														
gatad2ab	all 10 larvae that had many false positive macrophages were wildtype for mutations in *gatad2ab* ; 0.69 mutant larvae were expected.														
age (11dpf vs. 10dpf)	1.645	1.155	4.78E-01	0.416	6.513	1.454	1.060	6.07E-01	0.349	6.069	2.040	1.563	3.52E-01	0.455	9.154
time of day (in hours since 9AM)	0.907	0.143	5.35E-01	0.666	1.235	0.909	0.143	5.42E-01	0.668	1.236	0.733	0.149	1.27E-01	0.492	1.092
body length (in SD)	-	-	-	-	-	0.718	0.246	3.34E-01	0.367	1.406	0.646	0.255	2.68E-01	0.298	1.400
dorsal body surface area (in SD)	-	-	-	-	-	1.489	0.513	2.48E-01	0.758	2.924	1.005	0.378	9.90E-01	0.481	2.101
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	2.512	1.011	2.21E-02	1.141	5.528
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.728	0.297	4.35E-01	0.327	1.618
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.196	0.509	6.73E-01	0.520	2.752
glucose levels	-	-	-	-	-	-	-	-	-	-	0.843	0.317	6.51E-01	0.404	1.762
intercept	0.035	0.026	9.99E-06	0.008	0.154	0.036	0.026	7.34E-06	0.008	0.153	0.050	0.042	3.21E-04	0.010	0.257

continued **Supplementary Table 38**

	Clumped macrophages														
	Model 1 (n=408)					Model 2 (n=378)					Model 3 (n=353)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	all 11 larvae with clumped macrophages were wildtype for mutations in *lpar2a* ; 0.25 mutant larvae were expected.														
lpar2b	28.540	53.945	7.62E-02	0.702	1159.755	29.048	56.199	8.16E-02	0.655	1287.961	82.944	202.163	6.99E-02	0.698	9850.414
gatad2ab	all 11 larvae with clumped macrophages were wildtype for mutations in *gatad2ab* ; 0.76 mutant larvae were expected.														
age (11dpf vs. 10dpf)	0.380	0.404	3.63E-01	0.047	3.054	0.368	0.395	3.51E-01	0.045	3.014	0.333	0.368	3.19E-01	0.038	2.904
time of day (in hours since 9AM)	0.615	0.117	1.07E-02	0.424	0.893	0.628	0.120	1.49E-02	0.432	0.913	0.557	0.136	1.67E-02	0.345	0.899
body length (in SD)	-	-	-	-	-	0.871	0.304	6.93E-01	0.439	1.727	0.605	0.251	2.26E-01	0.268	1.364
dorsal body surface area (in SD)	-	-	-	-	-	1.251	0.414	4.99E-01	0.654	2.394	1.297	0.480	4.83E-01	0.628	2.678
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.771	0.732	1.66E-01	0.788	3.981
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.618	0.221	1.79E-01	0.306	1.247
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.681	0.281	3.53E-01	0.303	1.530
glucose levels	-	-	-	-	-	-	-	-	-	-	1.245	0.449	5.44E-01	0.614	2.524
intercept	0.171	0.111	6.52E-03	0.048	0.611	0.171	0.112	7.11E-03	0.047	0.619	0.170	0.134	2.40E-02	0.037	0.792

	Macrophages outside the region of interest														
	Model 1 (n=406)					Model 2 (n=376)					Model 3 (n=354)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	all 15 larvae with many macropahages outside the region of interest were wildtype for mutations in *lpar2a* ; 0.33 mutant larvae were expected.														
lpar2b	all 15 larvae with many macropahages outside the region of interest were wildtype for mutations in *lpar2b* ; 0.17 mutant larvae were expected.														
gatad2ab	all 15 larvae with many macropahages outside the region of interest were wildtype for mutations in *gatad2ab* ; 1.02 mutant larvae were expected.														
age (11dpf vs. 10dpf)	1.361	0.819	6.08E-01	0.418	4.429	1.031	0.636	9.61E-01	0.308	3.453	1.141	0.731	8.37E-01	0.325	4.003
time of day (in hours since 9AM)	0.742	0.107	3.76E-02	0.560	0.983	0.848	0.130	2.82E-01	0.628	1.145	0.818	0.133	2.18E-01	0.594	1.126
body length (in SD)	-	-	-	-	-	0.310	0.121	2.80E-03	0.144	0.668	0.245	0.103	7.82E-04	0.108	0.557
dorsal body surface area (in SD)	-	-	-	-	-	0.573	0.208	1.25E-01	0.282	1.167	0.541	0.198	9.35E-02	0.264	1.109
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	2.382	0.801	9.83E-03	1.233	4.604
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.436	0.512	3.11E-01	0.713	2.890
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.965	0.359	9.23E-01	0.465	1.999
glucose levels	-	-	-	-	-	-	-	-	-	-	1.103	0.355	7.60E-01	0.587	2.071
intercept	0.116	0.068	2.27E-04	0.037	0.364	0.045	0.034	3.76E-05	0.010	0.196	0.037	0.030	6.52E-05	0.007	0.186

continued **Supplementary Table 38**

	Clumped neutrophils														
	Model 1 (n=456)					Model 2 (n=427)					Model 3 (n=402)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	3.869	3.250	1.07E-01	0.746	20.074	3.695	3.109	1.20E-01	0.710	19.221	3.609	3.246	1.54E-01	0.619	21.040
lpar2b	all 34 larvae with clumped neutrophils were wildtype for mutations in *lpar2b* ; 0.44 mutant larvae were expected.														
gatad2ab	0.892	1.010	9.20E-01	0.097	8.215	0.835	0.955	8.75E-01	0.089	7.863	1.235	1.439	8.56E-01	0.126	12.110
age (11dpf vs. 10dpf)	0.891	0.404	8.00E-01	0.367	2.166	0.790	0.367	6.12E-01	0.318	1.965	0.767	0.371	5.83E-01	0.298	1.978
time of day (in hours since 9AM)	0.980	0.086	8.17E-01	0.825	1.164	0.997	0.092	9.75E-01	0.832	1.194	0.961	0.103	7.10E-01	0.779	1.185
body length (in SD)	-	-	-	-	-	0.859	0.166	4.33E-01	0.588	1.255	1.023	0.232	9.20E-01	0.657	1.594
dorsal body surface area (in SD)	-	-	-	-	-	1.073	0.207	7.16E-01	0.735	1.566	0.916	0.197	6.85E-01	0.601	1.397
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.876	0.182	5.25E-01	0.584	1.316
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.959	0.184	8.28E-01	0.659	1.396
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.838	0.186	4.28E-01	0.542	1.296
glucose levels	-	-	-	-	-	-	-	-	-	-	1.151	0.223	4.69E-01	0.787	1.684
intercept	0.087	0.038	2.33E-08	0.037	0.204	0.089	0.040	5.86E-08	0.037	0.213	0.091	0.044	6.33E-07	0.036	0.234

	Partly imaged larvae (n=386)				
	Effect	**SE**	***P***	**lci**	**uci**
lpar2a	all 29 larvae that were only partly imaged were wildtype for mutations in *lpar2a* ; 0.58 mutant larvae were expected.				
lpar2b	all 29 larvae that were only partly imaged were wildtype for mutations in *lpar2b* ; 0.35 mutant larvae were expected.				
gatad2ab	0.889	1.012	9.18E-01	0.096	8.270
time of day (in hours since 9AM)	1.170	0.112	1.02E-01	0.969	1.411
intercept	0.039	0.020	5.32E-10	0.014	0.108

Associations are shown for criteria that resulted in the exclusion of at least 10 larvae. Many false positives: >20% of true negative objects were falsely detected by the quantification pipeline. Many false negatives: >20% of true positives objects were falsely excluded by the quantification pipeline.Associations were examined using logistic regression models. Model 1: adjusted for time of day; Model 2: additionally adjusted for body length and dorsal surface area; Model 3: additionally adjusted for whole-body triglyceride and glucose levels. Dorsal body surface area was normalized for body length using residuals; whole-body LDL cholesterol, HDL cholesterol, triglyceride and glucose levels were normalized for protein level using residuals. Effects shown for *lpar2a*, *lpar2b* and *gatad2ab* are for each additional mutated allele. Adjusting for batch would have resulted in the exclusion of larvae. Lci and uci are lower and upper boundaries of the 95% confidence interval.

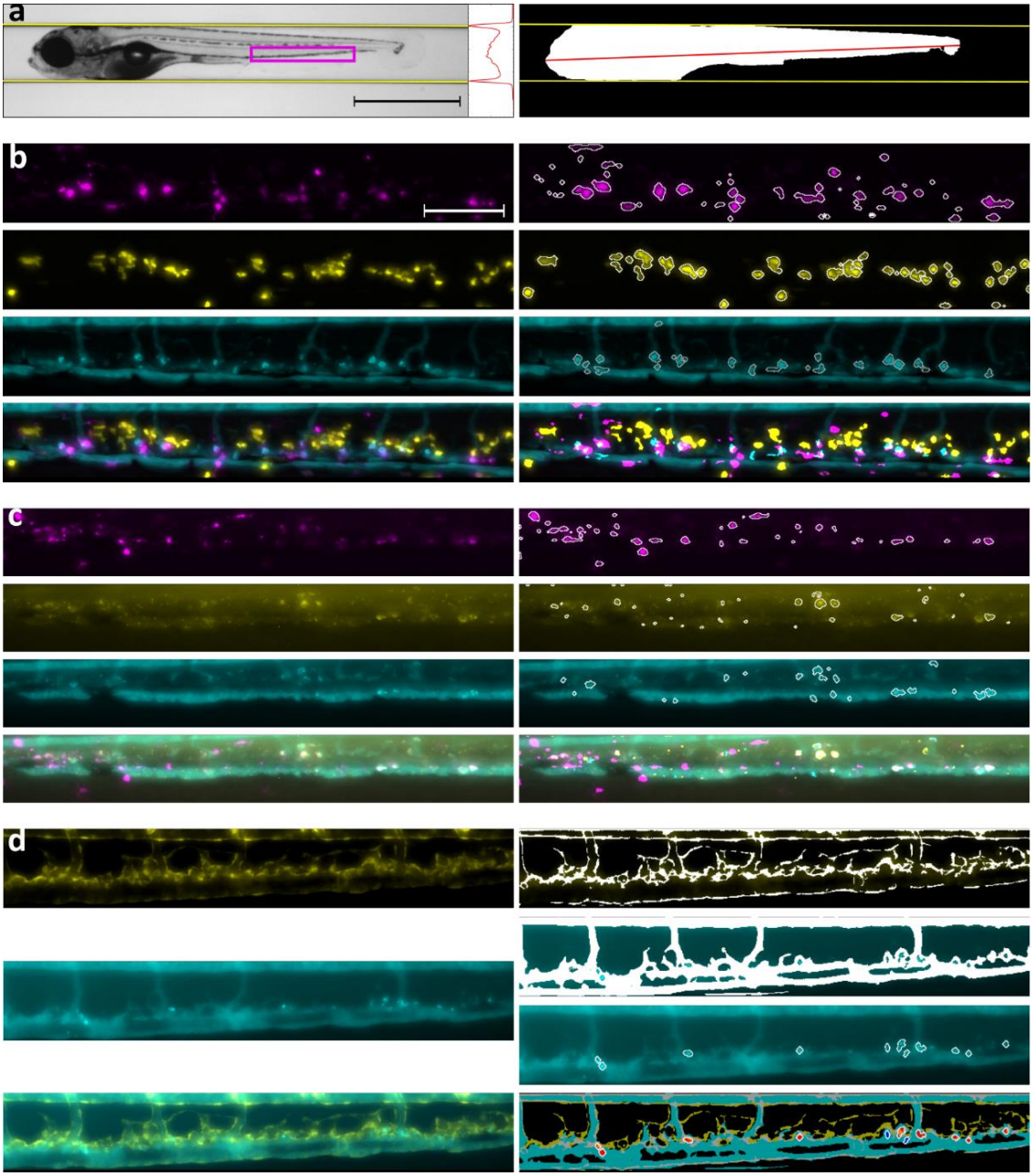

Figure 1. Raw data (left) and objective, semi-automated quantification (right) of body size and early-stage atherosclerosis in 10-day-old zebrafish larvae. a) Left: A bright field image of a zebrafish larva in lateral orientation with projection of all intensity values to the y-axis. The two distinct minima in the projection represent the walls of the capillary, outlined in yellow (scale bar = 1 mm). The region of the tail that was imaged to quantify vascular atherogenic traits is highlighted in magenta. Right: a binary mask of the same larva, with lateral surface area in white, and body length in red. b) A Tg(mpeg1-mCherry; mpo-EGFP) transgenic larva with fluorescently labelled macrophages (top, magenta) and neutrophils (2nd from top, yellow). Circulating lipids and vascular lipid deposits were stained with a dye (3rd from the top, cyan). The overlay (bottom) shows co-localization of all traits (scale bar = 100µm). c) A Tg(mpeg1-mCherry; hsp70:IK17-EGFP) transgenic larva with fluorescently labelled macrophages (top, magenta) and oxidized LDL (2nd from top, yellow) with stained lipids (3rd from top, cyan). The overlay shows co-localization of all traits (bottom). d) A Tg(flk-EGFP) transgenic larva with fluorescently labelled endothelial cells showing endothelial surface area (top, yellow); stained lipids (2nd from top, cyan) from which both circulating lipids (right, 2nd from top) and vascular lipid deposition (right, 3rd from top) were quantified; and an overlay that enabled distinguishing between lipid deposition inside (in red) and outside the endothelium (bottom right, blue).

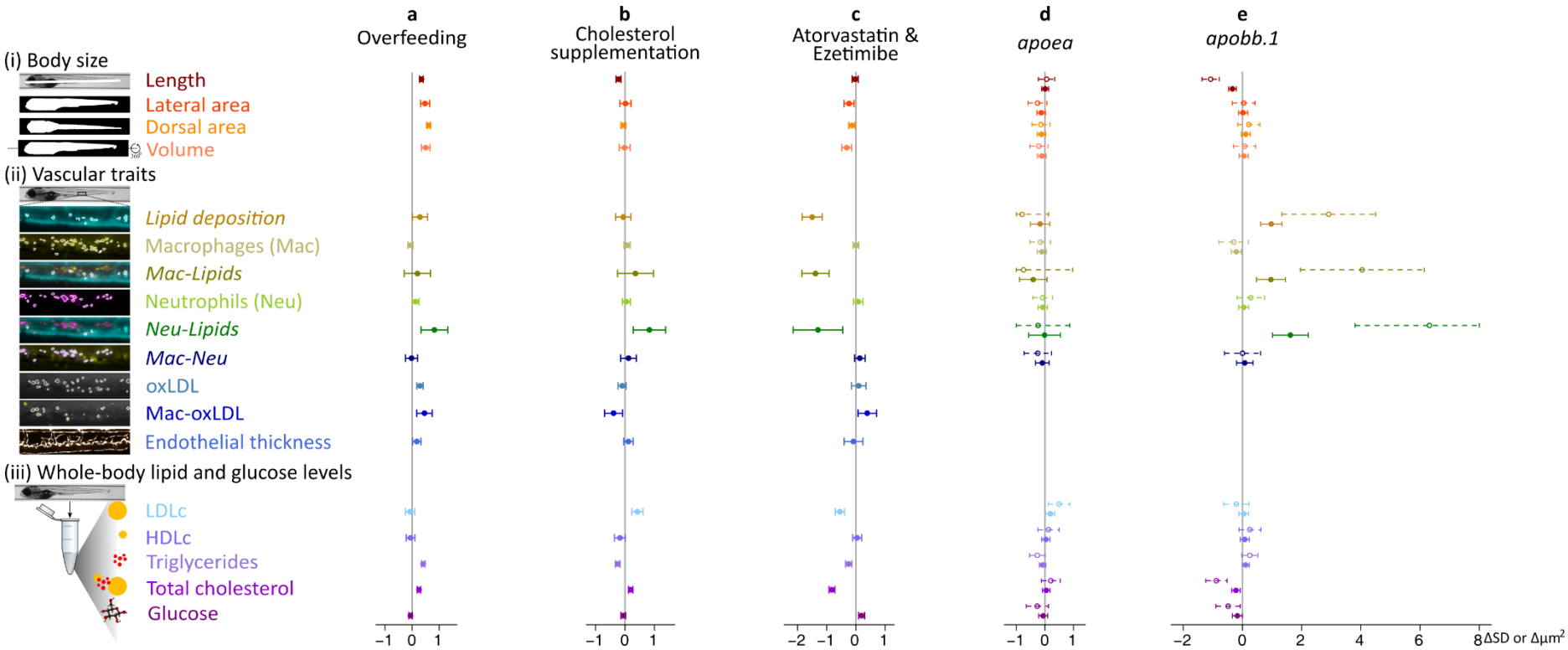

Figure 2. The effect of overfeeding and cholesterol supplementation (n>2000); treatment with atorvastatin and ezetimibe (n>1000); and mutations in apoea and apobb.1 (n=384) on body size (i), vascular atherogenic traits (ii) and whole-body lipid and glucose levels (iii). Across a-e, dorsal and lateral body surface area and body volume were normalized for body length before the analysis; whole-body lipid and glucose levels were normalized for protein levels; and endothelial thickness was normalized for surface area of the circulation. For normally distributed traits, associations were examined using hierarchical linear models on inverse-normally transformed outcomes. For these traits effect sizes and 95% confidence intervals are expressed in standard deviation units (SD). The remaining vascular atherogenic traits (shown in italics) showed a negative binomial distribution and data were analyzed accordingly. For these traits, effect sizes and 95% confidence intervals are expressed in μm^2. In d and e, open circles and the dotted lines represent the effect of two functionally knocked-out alleles vs. two unmodified alleles, and full circles and filled lines represent the additive per mutated allele effect. Associations were adjusted for time of day; use of diethyl ether (for overfeeding and cholesterol supplementation); cholesterol supplementation (for overfeeding); the amount fed (for cholesterol supplementation); body length and dorsal body surface area (for vascular outcomes); batch; and transgenic background.

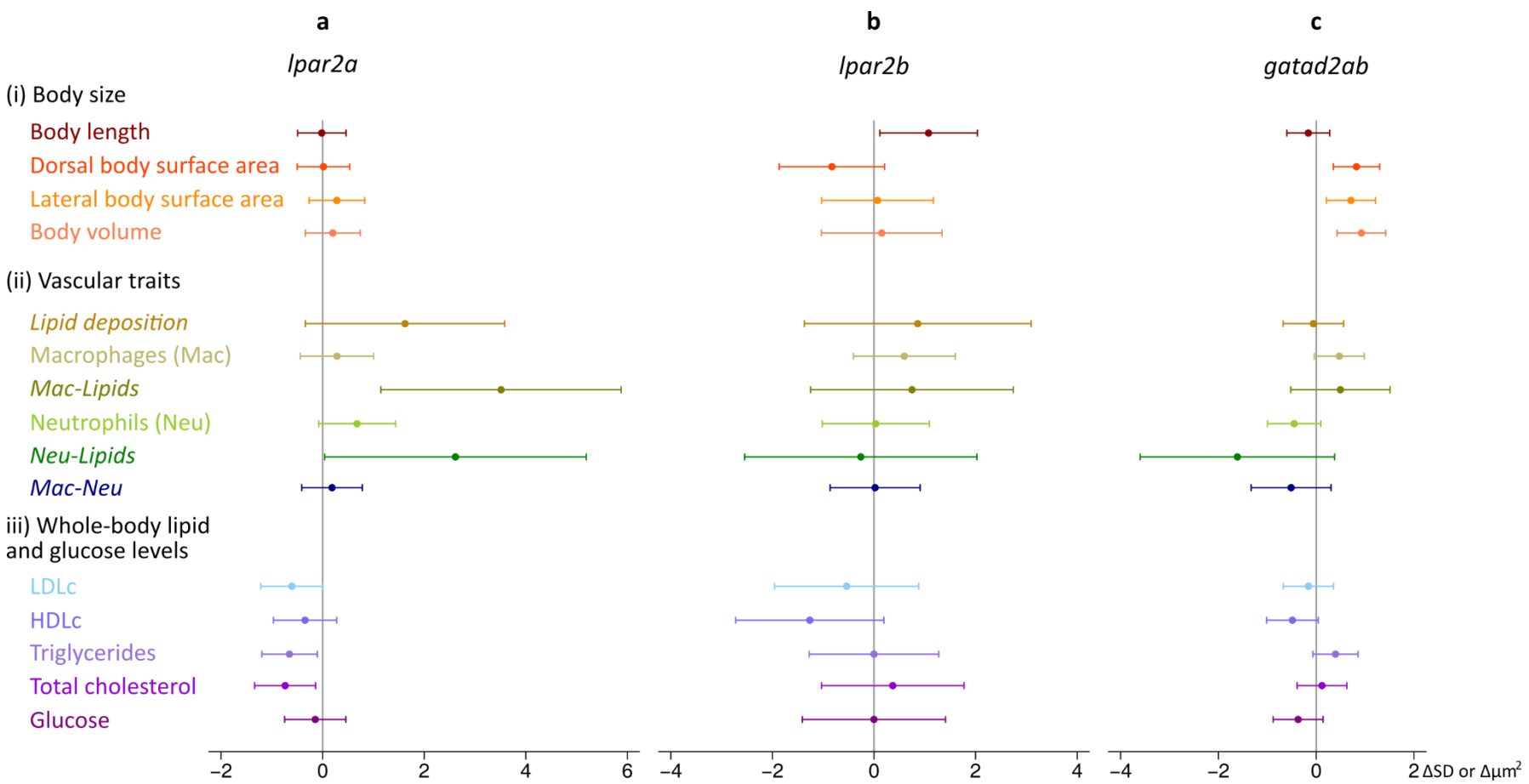

Figure 3. The mutually adjusted effect of mutations in zebrafish orthologues of LPAR2 and GATAD2A (n=547) on body size (i), vascular atherogenic traits (ii) and whole-body lipid and glucose levels (iii) using an additive model. Dorsal and lateral body surface area and body volume were normalized for body length; and whole-body lipid and glucose levels were normalized for protein levels before the analysis. For normally distributed traits, associations were examined using hierarchical linear models on inverse-normally transformed outcomes. For these traits, effect sizes and 95% confidence intervals are expressed in standard deviation units (SD). Some vascular atherogenic traits showed a negative binomial distribution and associations were analyzed accordingly. For these traits (shown in italics), effect sizes and 95% confidence intervals are expressed in μm^2. Associations were adjusted for time of day; body length and dorsal body surface area (for vascular outcomes); and batch.