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

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Abstract

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. 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 four candidate genes in a GWAS-identified pleiotropic locus on chr 19p13.11 (n=384). 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*), more vascular inflammation (*apobb.1*), and more early-stage atherosclerosis (*ldlra*). Finally, our pipeline helped identify putative causal genes for circulating lipids and early-stage atherosclerosis (*LPAR2*), as well as for diabetes (*GATAD2A*). 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[12,13]. Some of these loci harbor genes with well-known roles in cholesterol metabolism – e.g. *APOE*[14], *APOB*[15] and *LDLR*[16] – and some encode the targets of lipid-lowering drugs, i.e. *HMGCR* (statins)[17], *NPC1L1* (ezetimibe)[18] and *PCSK9* (evolocumab)[19,20]. It thus seems plausible that identifying and characterizing causal genes in the remaining loci could further increase our understanding of cholesterol metabolism, atherosclerosis and CAD pathophysiology, and yield new targets for prevention and treatment of CAD[20,21].

Murine model systems have traditionally been used to characterize genes that play a role in familial hypercholesterolemia and atherosclerosis[22,23]. 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*[24], 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[25]. Importantly, in the context of gene characterization, the zebrafish has a well-characterized genome with orthologues of at least 71.4% of human genes[26]. These genes can now

be efficiently targeted in high-throughput using Clustered, Regulatory Interspaced, Short Palindromic Repeats (CRISPR) and CRISPR-associated systems (Cas)[27]. A range of fluorescent dyes[28–30] and transgenes[31–34] 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[35], disorganized vascular endothelial cells[35], and vascular accumulation of oxidized low-density lipoprotein (oxLDL)[31]. In addition, adult zebrafish fed on a cholesterol supplemented diet showed higher plasma levels of cholesterol, triglycerides and lipoproteins, and formed vascular lesions[36,37].

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[37,38]. 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[39,40], 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 four candidate genes in a GWAS-identified pleiotropic locus on chr 19p13.11 that showed evidence of association with LDLc, triglyceride and total cholesterol levels[12] 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 (**Table 1, Fig. 1, Supplementary Table 1**) 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 2**). 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 3**). Overfeeding resulted in more lipid deposition (**Fig. 2a-ii, Supplementary Fig. 3, Supplementary Table 4**). 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 deposits were at least partly located inside the endothelial cell layer. 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 4**).

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 2), 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 3**). 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 4)**.

As described in earlier studies[35,36,38], we supplemented regular dry food with extra cholesterol using diethyl ether, which may itself affect endogenous cholesterol levels[41]. Our results show that diethyl ether per se indeed resulted in: 1) higher triglyceride (trend) and total cholesterol levels (**Supplementary Table 3**); 2) less vascular co-localization of lipids with neutrophils; 3) a lower endothelial thickness (**Supplementary Table 4**); 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 5)**.

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 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 6**), 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 7**). 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 8**).

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 9**).

Mutations in zebrafish orthologues of APOE, APOB and LDLR 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 10 and 11**). 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 12**). 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 13**). The mutant allele frequency was typically high across the seven targeted sites (i.e. median 0.883, **Supplementary Table 14**).

Most larvae carried two mutated alleles in *apoba* and *apobb.2*, as well as bi-allelic mutations immediately upstream of *ldlrb* that were predicted to modify *ldlrb* gene expression (**Supplementary Tables 13 and 14**). To minimize the risk of a variable capacity for genetic compensation across larvae from affecting the results[42], larvae with at least one unaffected allele or a missed sequencing call in *apoba*, *apobb.2* and *ldlrb* were excluded from the analysis. In the remaining 286 larvae, a genetic burden score comprising the sum of the number of mutated alleles weighted by their predicted effect on protein function across *apoea, apoeb*, *apobb.1* and *ldlra* was normally distributed. This score was associated with higher LDLc levels, more vascular lipid deposition, and more vascular co-localization of lipids with macrophages and neutrophils (**Supplementary Fig. 5, Supplementary Tables 15-17**).

When examining the influence of mutations in each gene separately, we observed that larvae carrying two functionally knocked alleles in *apoea* – i.e. larvae carrying frame shift mutations and/or variants that introduce a premature stop codon in both alleles - tended to be shorter and wider when compared with larvae free from CRISPR-induced mutations in *apoea* (**Fig. 2d-i, Supplementary Table 18**). On average, larvae with two functionally knocked *apoea* alleles also had higher whole-body LDLc (trend) and total cholesterol levels (**Fig. 2d-iii, Supplementary Table 19**), without a concomitant difference in vascular atherogenic and inflammatory profile (**Fig. 2d-ii, Supplementary Table 20**). Larvae with two functionally knocked *apoeb* alleles were comparable on all examined traits to larvae free from CRISPR-induced mutations in *apoeb*, with

the exception of a trend for larvae without functional *apoeb* to have more vascular co-localization of macrophages and neutrophils that was not driven by whole-body lipoprotein or glucose levels (**Supplementary Fig. 6b-ii, Supplementary Tables 18-20**). On average, larvae with two functionally knocked *apobb.1* alleles were shorter than larvae with two unmodified alleles (**Supplementary Fig. 6c-i, Supplementary Table 18**), and showed a trend for having lower glucose levels (**Supplementary Fig. 6c-iii , Supplementary Table 19**). They were also characterized by more vascular accumulation of neutrophils, and by more vascular co-localization of neutrophils with lipids and macrophages when compared with larvae free from CRISPR-induced mutations in *apobb.1* (**Supplementary Fig. 6c-ii, Supplementary Table 20**). Finally, larvae with two functionally knocked *ldlra* alleles tended to be leaner when compared with larvae with two unmodified *ldlra* alleles (**Fig. 2e-i, Supplementary Table 18**), and showed more - triglyceride-mediated - accumulation of lipids and co-localization of lipids with neutrophils in their vasculature. Larvae with two functionally knocked *ldlra* alleles also showed some evidence of having more vascular co-localization of lipids with macrophages, and less co-localization of macrophages with neutrophils when compared with larvae free from CRISPR-induced mutations in *ldlra* (**Fig. 2e-ii, Supplementary Table 20**).

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 21-23**). In the presence of a genetic effect, the effect size of two vs. zero functionally knocked alleles was approximately twice the additive per allele effect for most trait-gene combinations (**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 24**).

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 when comparing larvae with two vs. zero functionally knocked alleles as well as under an additive model shows cautious evidence of a positive interaction between mutations in *apoea* and *ldlra* for whole-body total cholesterol levels and for vascular accumulation of lipids (**Supplementary Tables 25-27**).

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)[43] 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 interventions 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[44–47]. 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 28**).

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

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[48], we used DEPICT[49] to prioritize candidate genes in 23 triglyceride-associated loci[12]. 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 29**), which we targeted simultaneously (**Supplementary Table 30**).

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 31**). Compared with the reference genome, the 384 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 32**). In spite of having pre-tested the CRISPR gRNAs for efficiency, all 384 screened 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* (0.024), *lpar2a* (0.015), and *lpar2b* (0.008) (**Supplementary Table 33**).

In spite of the low statistical power to find associations, we observed some 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 lipid deposition, more vascular accumulation of neutrophils, and more vascular co-localization of lipids with neutrophils. Larvae with a mutated *lpar2a* allele also had substantially more vascular co-localization of lipids with macrophages (**Fig. 3a**, **Supplementary Tables 34-36**). In addition to the effects observed for *lpar2a*, the six larvae with a mutated *lpar2b* allele tended to be longer and leaner, and had lower HDLc levels compared with larvae free from CRISPR-induced *lpar2b* mutations (**Fig. 3b**, **Supplementary Tables 34-36**). Finally, the 18 larvae with a mutated *gatad2ab* allele tended to have lower glucose levels when compared with larvae with two unmodified alleles (**Fig. 3c**, **Supplementary Tables 34-36**). Our experimental results suggest that *LPAR2* influences cholesterol metabolism and early-stage vascular atherosclerosis and inflammation, while *GATAD2A* influences glucose metabolism. Lower glucose levels in *gatad2ab* mutant zebrafish larvae are directionally consistent with the minor T allele in rs3794991 being associated with a higher expression of *GATAD2A* in whole blood, as well as with a higher risk of type-2 diabetes in humans[50]. Exclusion of larvae with suboptimal image quality or quantification is unlikely to have influenced the results (**Supplementary Table 37**).

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* 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*, *APOB* and *LDLR* trigger a 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 in glucose metabolism to *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 macrophages and 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. Also, mutations in *apoea* resulted in higher whole-body LDLc levels at 10dpf, without affecting vascular lipid deposition. This suggests that while loss of Apoea may direct abundant triglyceride-rich chylomicrons in the circulation to mature into LDLc stoichiometrically[54,55], it does not immediately affect vascular accumulation of lipids.

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. Directionally consistent (i.e. opposite) effects on these outcomes were observed for dietary cholesterol supplementation. Moreover, cholesterol supplementation or drug treatment did not affect accumulation of oxLDL 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[56,57] and genetic association studies[58,59] 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.

Like in humans and mouse models, zebrafish larvae with two functionally knocked *ldlra* alleles on average had a more pro-inflammatory and pro-atherogenic vascular profile. The lack of

a main effect of *ldlra* on LDLc and total cholesterol levels in zebrafish larvae as opposed to mouse models and humans may reflect the ability of zebrafish to perform a *cetp*-facilitated exchange of a triglyceride for a cholesteryl ester or vice versa between LDL or VLDL and HDL; in addition to the presence of a second – albeit downregulated - *LDLR* orthologue (*ldlrb*). The presence of a main effect of manipulation of *ldlra* on early-stage vascular inflammation and atherosclerosis in absence of an effect on LDLc levels is noteworthy, and hints towards a direct vascular role of *LDLR*.

Our results confirm and expand previously reported main effects of *ldlra* manipulation on vascular lipid deposition in zebrafish lavae, but do not confirm earlier findings for its effects on LDLc, triglyceride, and/or total cholesterol levels[38,60]. While differences in age, food intake, enzymatic assays, normalization for protein[61], genetic manipulation[42] and adjustment for co-variables across studies may have influenced the results, the difference in sample size 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[38], while Liu et al. compared triglyceride and total cholesterol levels in four wildtype larvae and four larvae that were homozygous for mutations in *ldlra*[60]. In contrast, we compared cholesterol levels in 139 and 83 individual larvae with two and zero functionally knocked alleles, respectively, and included data from 284 larvae in our additive analyses. Like humans, zebrafish are genetically heterogeneous, and we observed a normal or negative binomial distribution for the examined outcomes, with a 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 and 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 glucose 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. With *LPAR2* and *TM6SF2*, two genes in this locus have now been implicated in cholesterol metabolism. 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[62–64]. Unfortunately, CRISPR-based mutagenesis of the two zebrafish orthologues of *TM6SF2* was unsuccessful. However, lower triglyceride, LDLc and total cholesterol levels in *lpar2a* mutant zebrafish larvae, alongside a trend for more vascular accumulation of lipids is compatible with more accumulation of neutral lipids in the liver, and spillover of those lipids back into the circulation. Besides both affecting circulating lipid levels, *LPAR2* and *TM6SF2* may thus also both influence hepatic lipid accumulation, which we did not examine.

Our data shows that in spite of having lower triglyceride and LDLc levels, zebrafish larvae with mutations in *lpar2a* are prone to early-stage atherosclerosis. This effect may be driven by higher LPA levels, since LPA increases NFκB, IL-8 and MCP-1 secretion from endothelial cells, which attract neutrophils and macrophages[65,66]; and induces barrier dysfunction and elevated monocyte adhesion of the atherosclerotic plaque in minimally modified LDL and within the intima of atherosclerotic lesions[67]. Based on the association between hepatic fat accumulation and

insulin resistance, one could anticipate an effect of mutations in *Tm6sf2* and/or *lpar2a* on the risk of diabetes. However, *Tm6sf2* knockout mice had normal serum glucose and insulin levels[64], and we observed no effect of mutations in *lpar2a* on glucose levels in zebrafish larvae. Instead, larvae with a mutated *gatad2ab* allele showed a trend for lower glucose levels. This association is directionally consistent with the minor allele in rs3794991 being associated with a higher expression of *gatad2ab* in blood, as well as with a higher risk of type-2 diabetes in humans[50].

Taken together, we hypothesize that reduced expression of *LPAR2*, *TM6SF2* and *GATD2A* in the presence of the minor C allele of the regulatory rs10401969 results in: 1) an *LPAR2*- and *TM6SF2*-mediated lowering of circulating lipids; 2) a *TM6SF2* and possibly *LPAR2*-mediated higher risk of fatty liver disease; 3) a *TM6SF2*-mediated lower risk of atherosclerosis; 4) an *LPAR2*-mediated higher risk of atherosclerosis; and 5) a *GATAD2A*-mediated lower risk of type-2 diabetes. This range of bi-directional, pleiotropic effects explains why the minor 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)[68], which is clearly not representative for the relevance of this locus for cardiometabolic risk.

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 and early-stage atherosclerosis and inflammation (*LPAR2*), as well as glucose metabolism (*GATAD2A*). 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[29] (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*[32]) and neutrophils (*Tg:mpo-EGFP*[34]) were crossed to yield a stable line in which we can visualize and quantify vascular accumulation and co-localization of lipids[29], macrophages[32] and neutrophils[34] (**Fig. 1b**). Secondly, we in-crossed zebrafish that express a fluorescently labelled antibody (IK17) against oxLDL (*Tg:hsp70:IK17-EGFP*)[31] to allow visualization and quantification of vascular accumulation of lipids[29] and oxLDL[31], and we crossed *Tg:hsp70:IK17-EGFP*[31] 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[29], oxLDL[31] and macrophages[32] (**Fig. 1b-c**). Thirdly, carriers of the flk:EGFP transgene (*Tg:flk-EGFP*[33]) 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)[29].

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)[35]; 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[69–71]. 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[37,38]. In addition, evidence suggests that treatment with atorvastatin and ezetimibe may reduce vascular lipid deposition[38,72].

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[72] 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[73]. 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[14–16]. 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.[27].

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[74], and a literature search[75] (**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[49]-identified candidate genes in triglyceride-associated loci[12], 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)[39,40], 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 F1 generation (median 0.88, interquartile range 0.52 to 0.98, **Supplementary Table 14**).

With 100% and 96.9% of successfully sequenced larvae carrying two mutated alleles in *apoba* and *apobb.2* (**Supplementary Table 14**), we could not examine the role of these orthologues.

Furthermore, *apobb.1* was previously shown to account for ~95% of ApoB protein in zebrafish[75]. For *ldlrb*, 99.7% of successfully sequenced larvae carried modifier mutations immediately upstream of *ldlrb* in both alleles (**Supplementary Table 14**). Hence, we excluded larvae with at least one unmodified *apobb.2* or *ldlrb* allele, or a missed call in one of these genes from the analysis, thereby preventing the possibility of a variable capacity of genetic compensation from influencing the results.

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.

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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 and TK 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.

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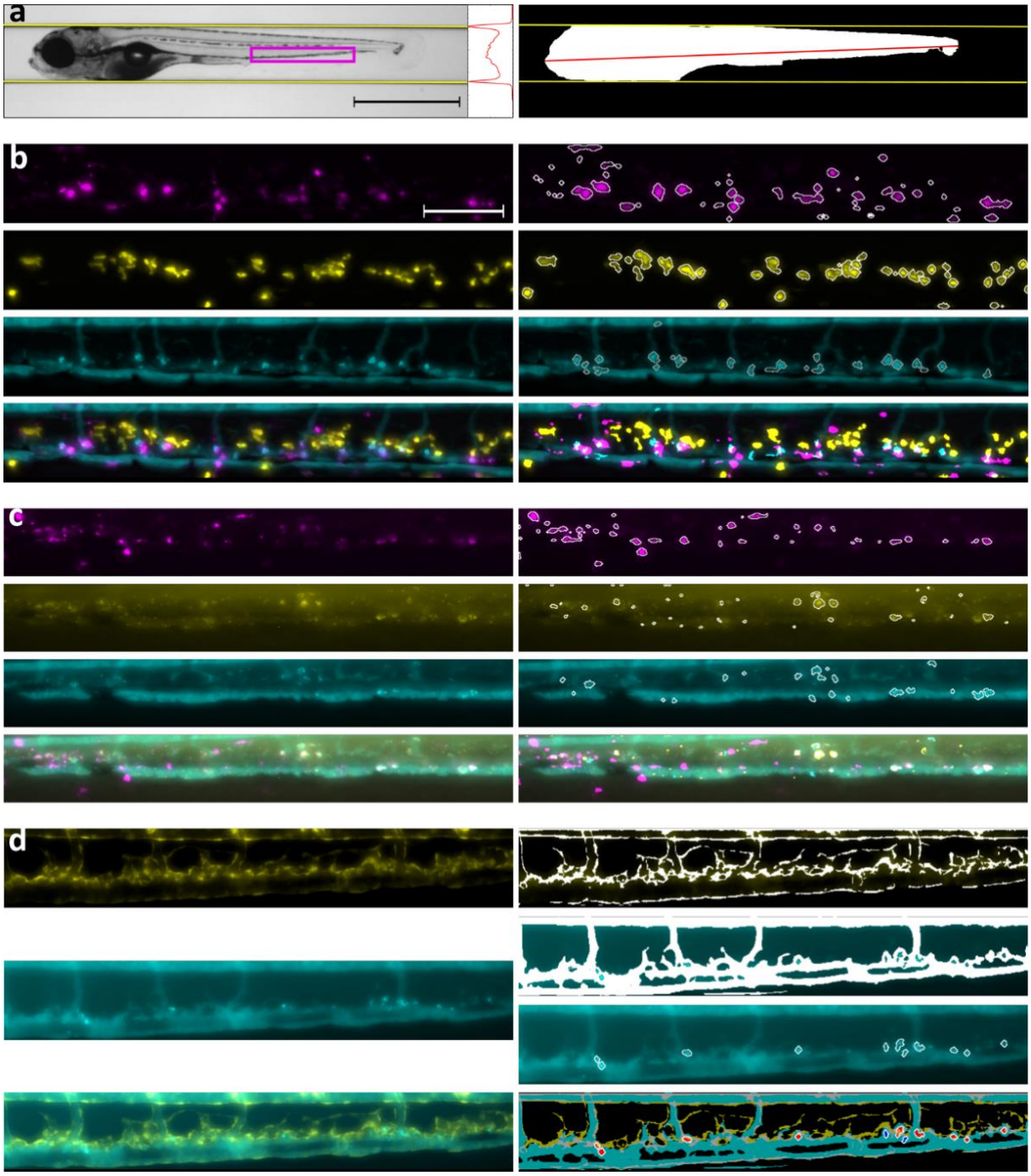


Figure 1. Raw data (left) and objective, semi-automated quantification (right) of body size and early-stage atherosclerosis in 10-day-old zebrafish larvae. **a**) Left: A bright field image of a zebrafish larva in lateral orientation with projection of all intensity values to the y-axis. The two distinct 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).

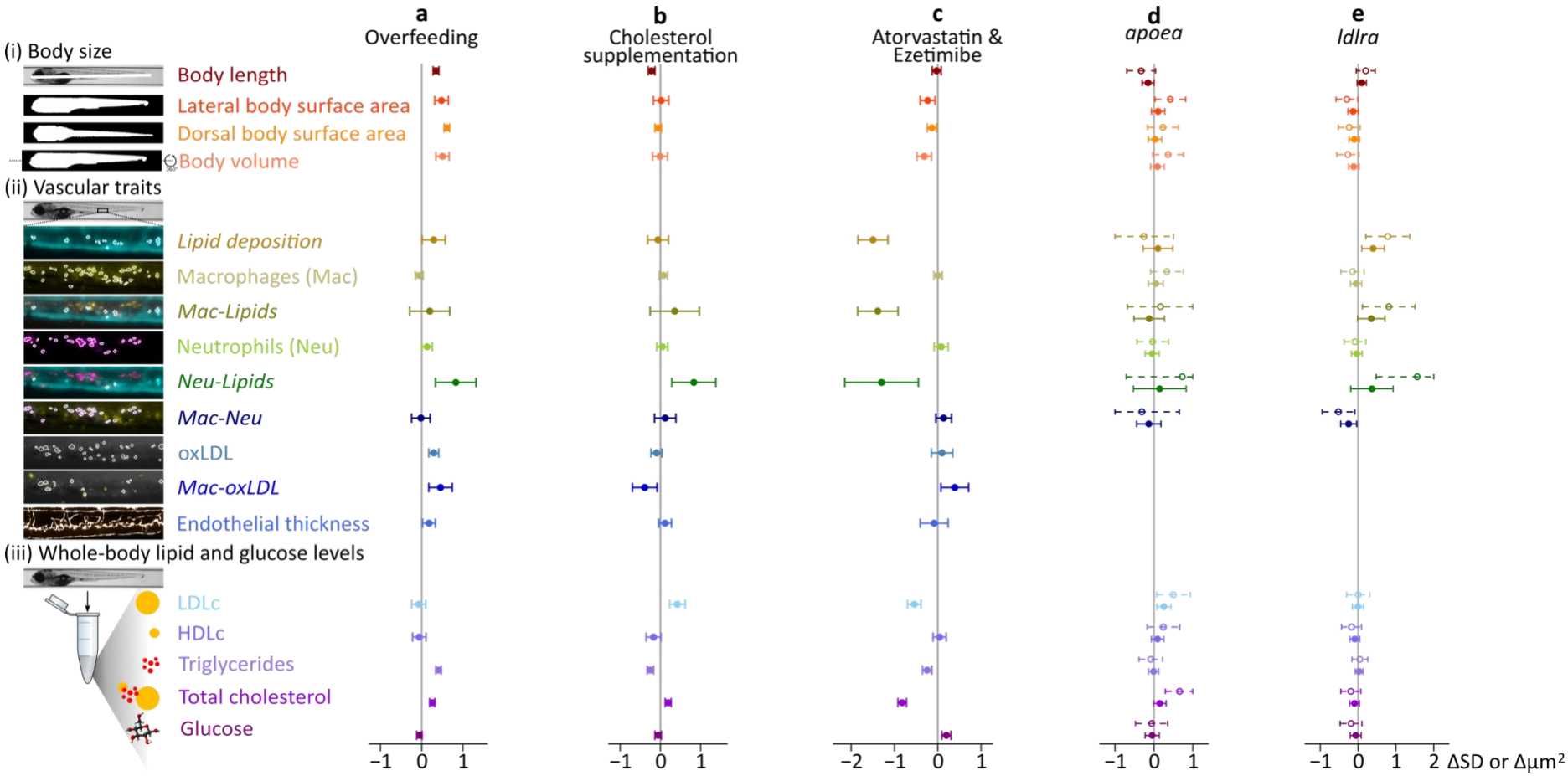


Figure 2. The effect of overfeeding, cholesterol supplementation, treatment with atorvastatin and ezetimibe and mutations in *apoea* and *ldlra* on body size (**i**), vascular atherogenic traits (**ii**) and whole-body lipid and glucose levels (**iii**). Across **a-e**, dorsal and lateral body surface 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.

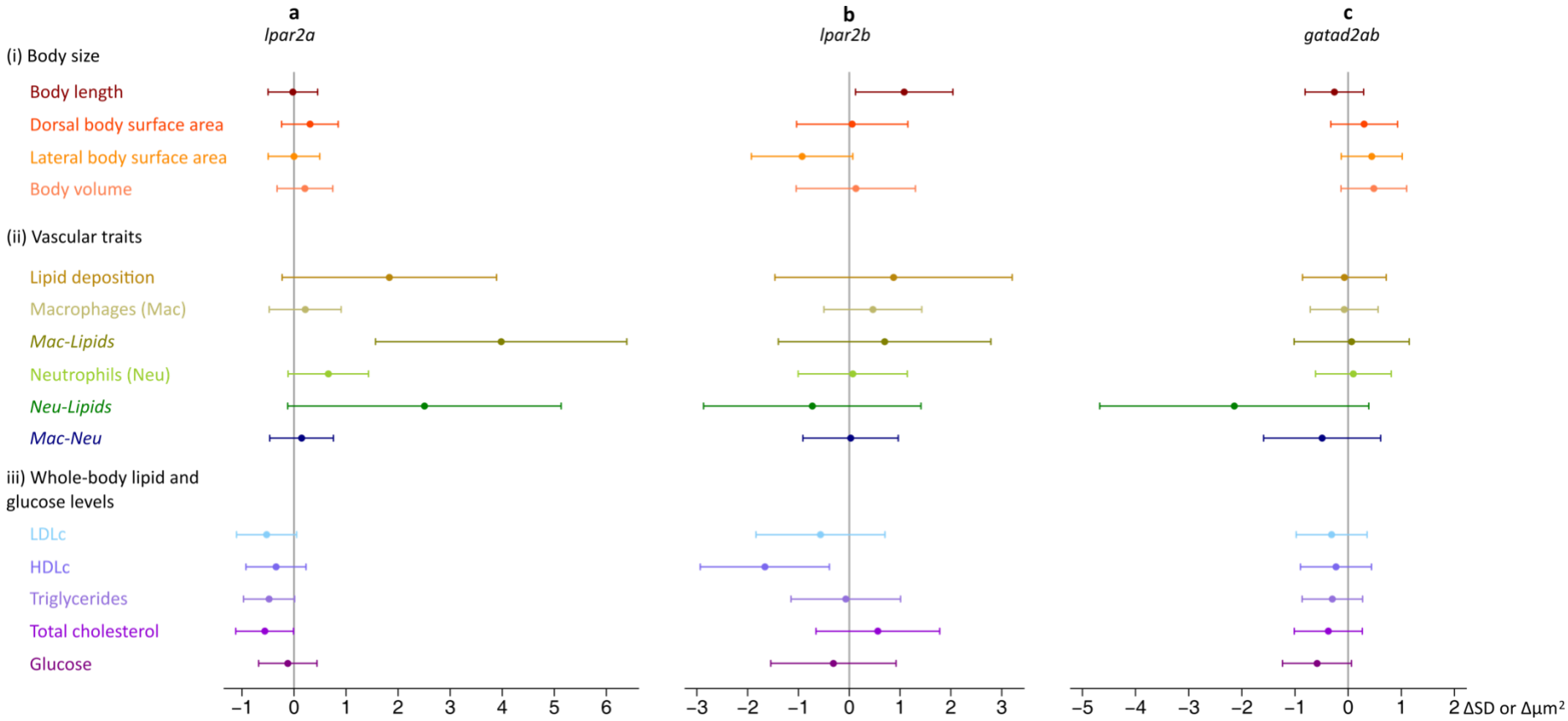


Figure 3. The mutually adjusted effect of mutations in zebrafish orthologues of *LPAR2* and *GATAD2A* on body size (**i**), vascular atherogenic traits (**ii**) and whole-body lipid and glucose levels (**iii**) using an additive model. Dorsal and lateral body surface area and body volume were normalized 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.

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	377	4420	227
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	377	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	376	1.4×10^6	1.7×10^5
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	368	3.8×10^8	6.5×10^7
Whole-body lipid and glucose levels													
LDL cholesterol (μg)		564	0.04	0.04	567	0.12	0.08	339	0.18	0.12	378	0.56	0.40
HDL cholesterol (μg)		549	0.06	0.02	564	0.06	0.04	339	0.15	0.05	378	0.19	0.06
Triglyceride levels (μg)		2123	0.93	0.80	1005	0.61	0.51	339	1.10	0.82	378	0.96	0.70
Total cholesterol levels (μg)		2123	0.29	0.17	1005	0.36	0.18	339	0.45	0.21	378	0.23	0.09
Glucose (μg)		2128	0.92	0.66	1008	0.38	0.42	339	0.30	0.16	378	0.60	0.45
Vascular atherogenic traits													
Lipid deposition (μm^2)	-	*1954*	*0*	*36*	*837*	*0*	*20*	*272*	*43*	*133*	*184*	*44*	*137*
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	223	1813	730
Infiltration by neutrophils (μm^2)	*Tg:mpo-EGFP*	*494*	*1545*	*2116*	404	2438	873	330	1050	911	234	2026	922
Co-localizing macrophages and lipids (μm^2)	*Tg:mpeg1-mCherry*	*917*	*0*	*10*	*605*	*0*	*0*	*269*	*1*	*13*	*173*	*8*	*36*
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*	*177*	*0*	*3*
Co-localizing macrophages and neutrophils (μm^2)	*Tg:mpeg1-mCherry & Tg:mpo-EGFP*	*488*	*140*	*306*	394	139	124	*327*	*25*	*68*	*220*	*65*	*87*
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 FIGURES

Supplementary Figure 1 - The effect of overfeeding, cholesterol supplementation and treatment with atorvastatin and ezetimibe on body size (p57)

Supplementary Figure 2 - The effect of overfeeding, cholesterol supplementation and treatment with atorvastatin and ezetimibe on whole-body lipid and glucose levels (p58)

Supplementary Figure 3 - The effect of overfeeding, cholesterol supplementation and treatment with atorvastatin and ezetimibe on vascular atherogenic traits (p59-60)

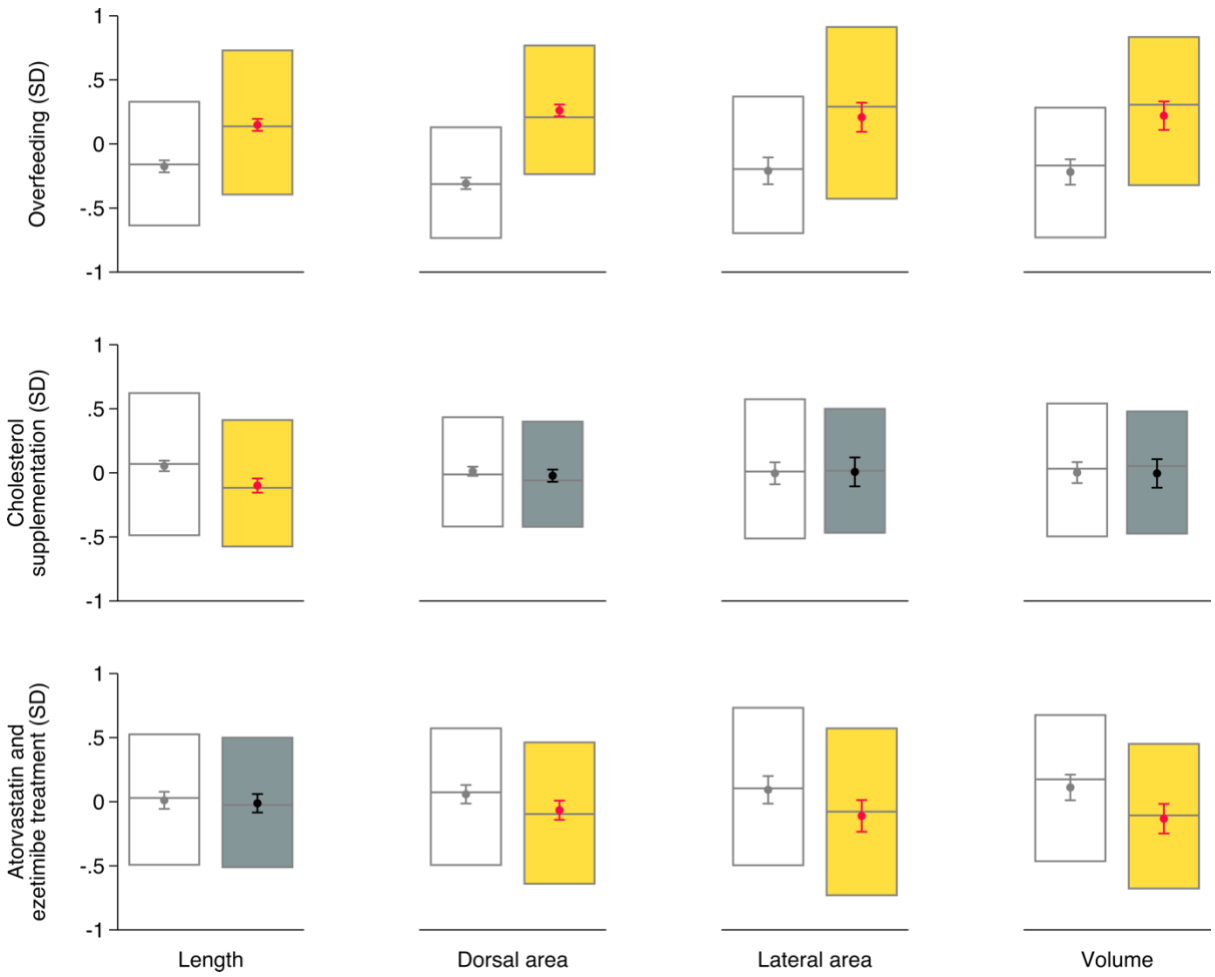
Supplementary Figure 4 - Food intake as a function of dietary or drug treatment intervention (p61)

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 (p62)

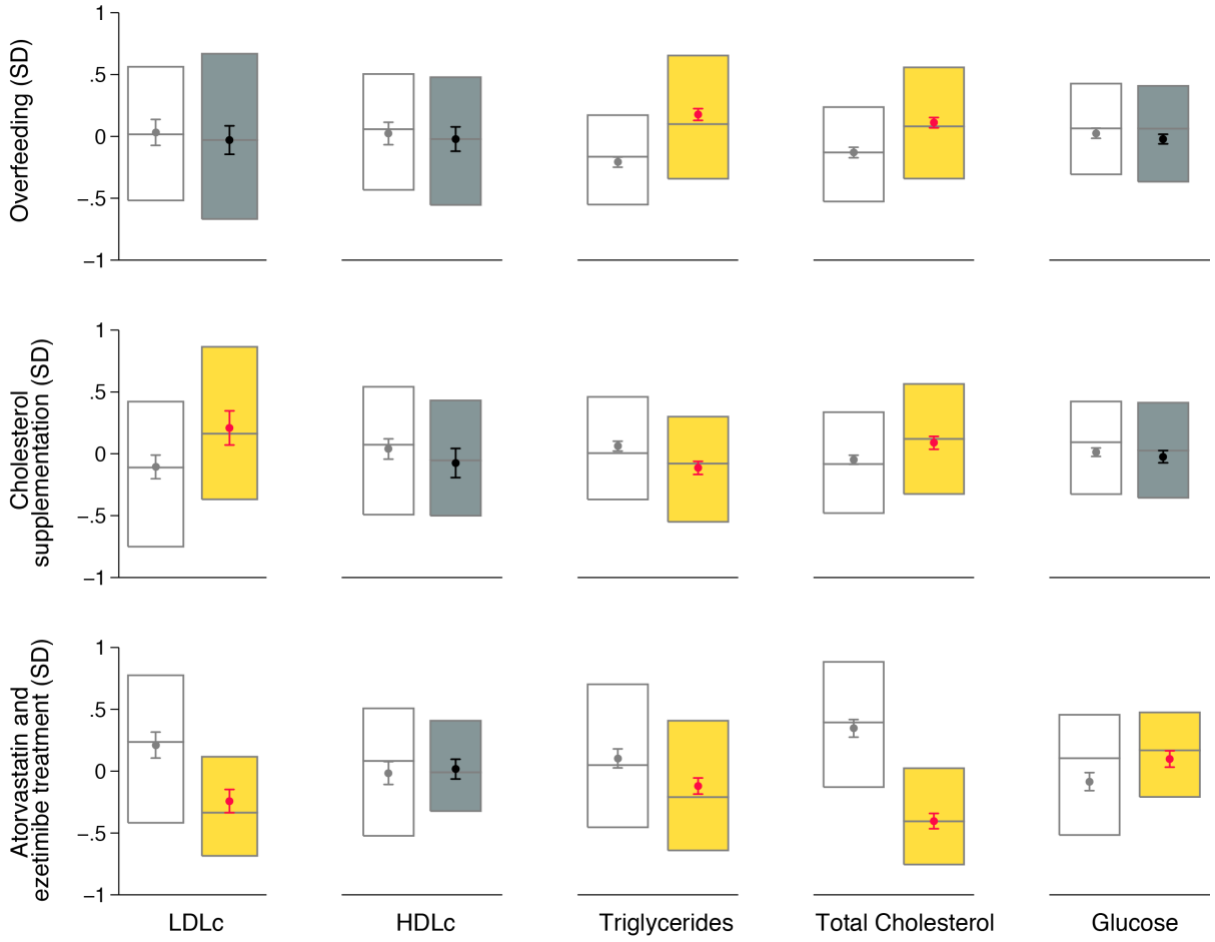
Supplementary Figure 6 - The effect of mutations in *apoea*, *apoeb, apobb.1 and ldlra* on body size, vascular atherogenic traits and whole-body lipid and glucose levels (p63-64)

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 (p65)

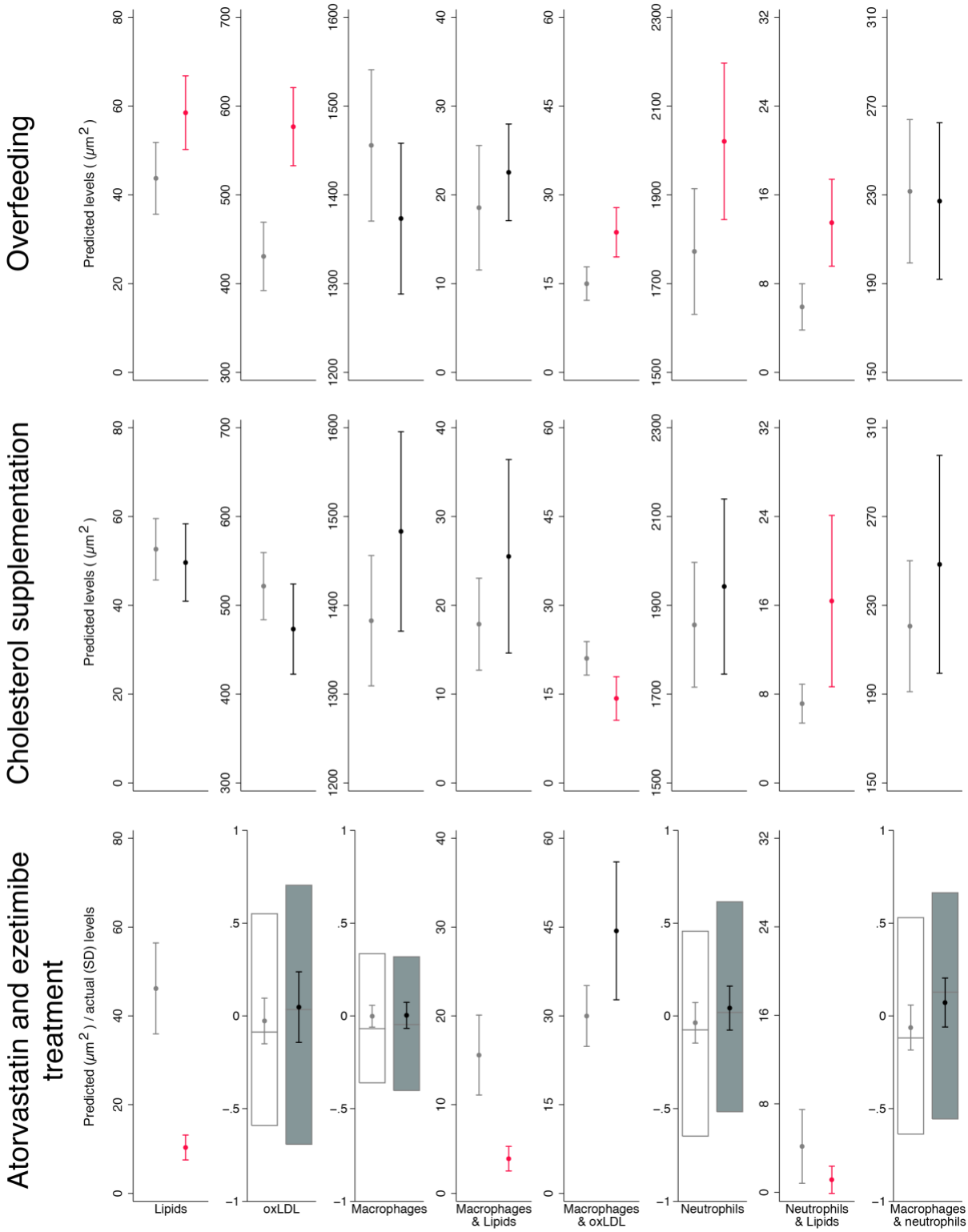
Supplementary Figure 8 - The association of vascular atherogenic traits with whole-body lipid and glucose levels in data from the dietary, drug treatment and genetic intervention for proof-of-concept genes combined (p66-67)



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 $P<0.05$.

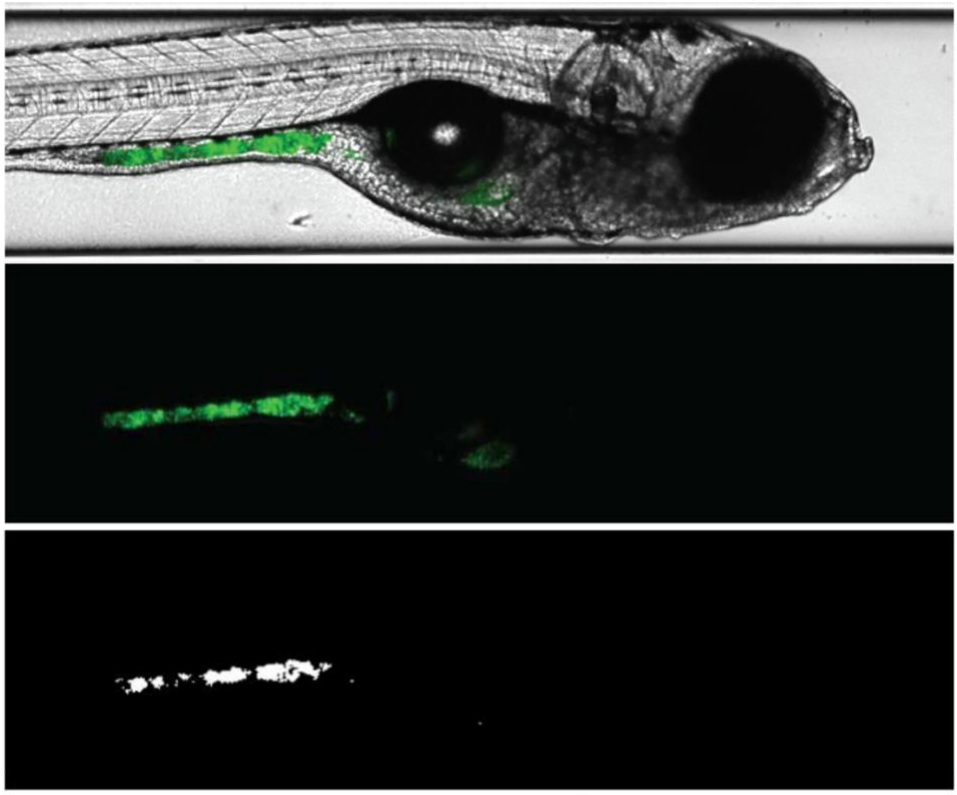


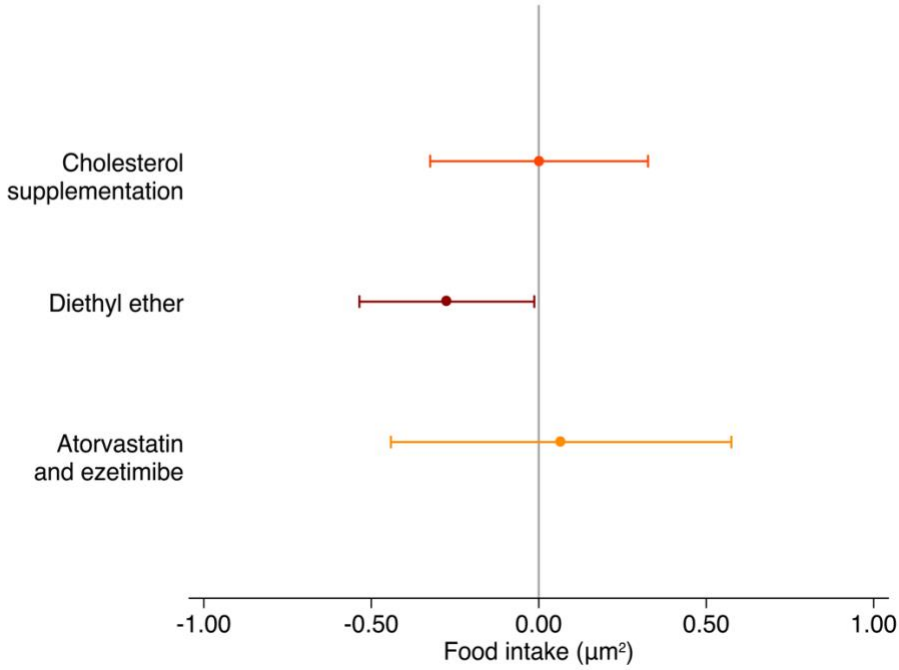
Supplementary Figure 2. The effect of overfeeding (**top**), cholesterol supplementation (**middle**) and treatment with atorvastatin and ezetimibe (**bottom**) on whole-body lipid and glucose levels. Dots and whiskers show mean and 95% confidence interval (CI); boxes show median and inter quantile range. 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 $P<0.05$.



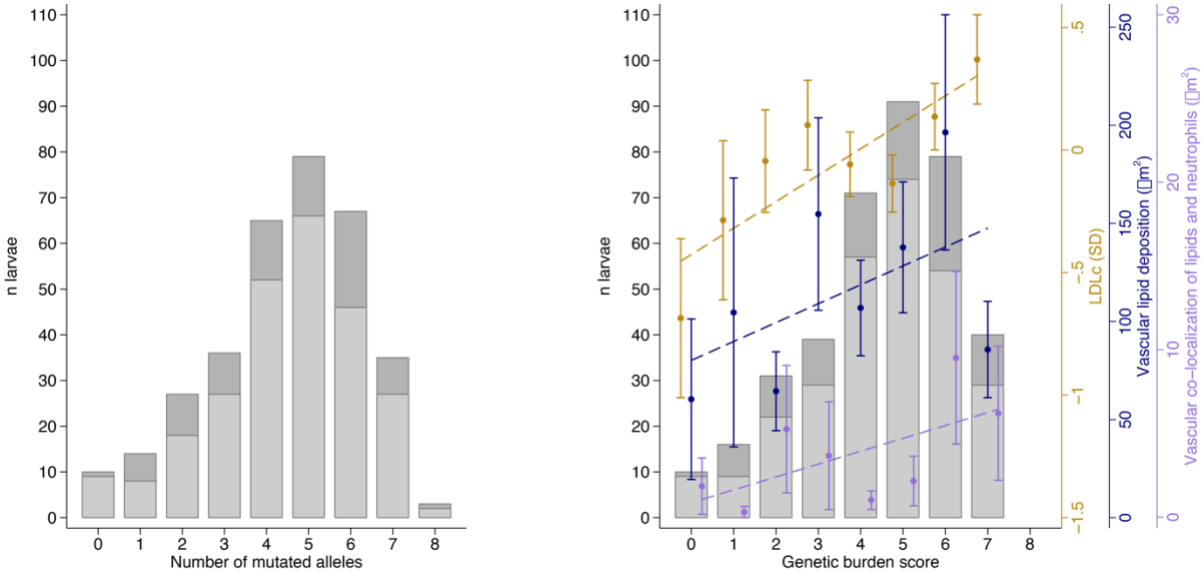
Supplementary Figure 3. The effect of overfeeding (**top**), cholesterol supplementation (**middle**) and treatment with atorvastatin and ezetimibe (**bottom**) on vascular atherogenic traits. Outcomes showing effect estimate and 95% CI for predicted values have been analyzed using negative binomial 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 $P<0.05$.

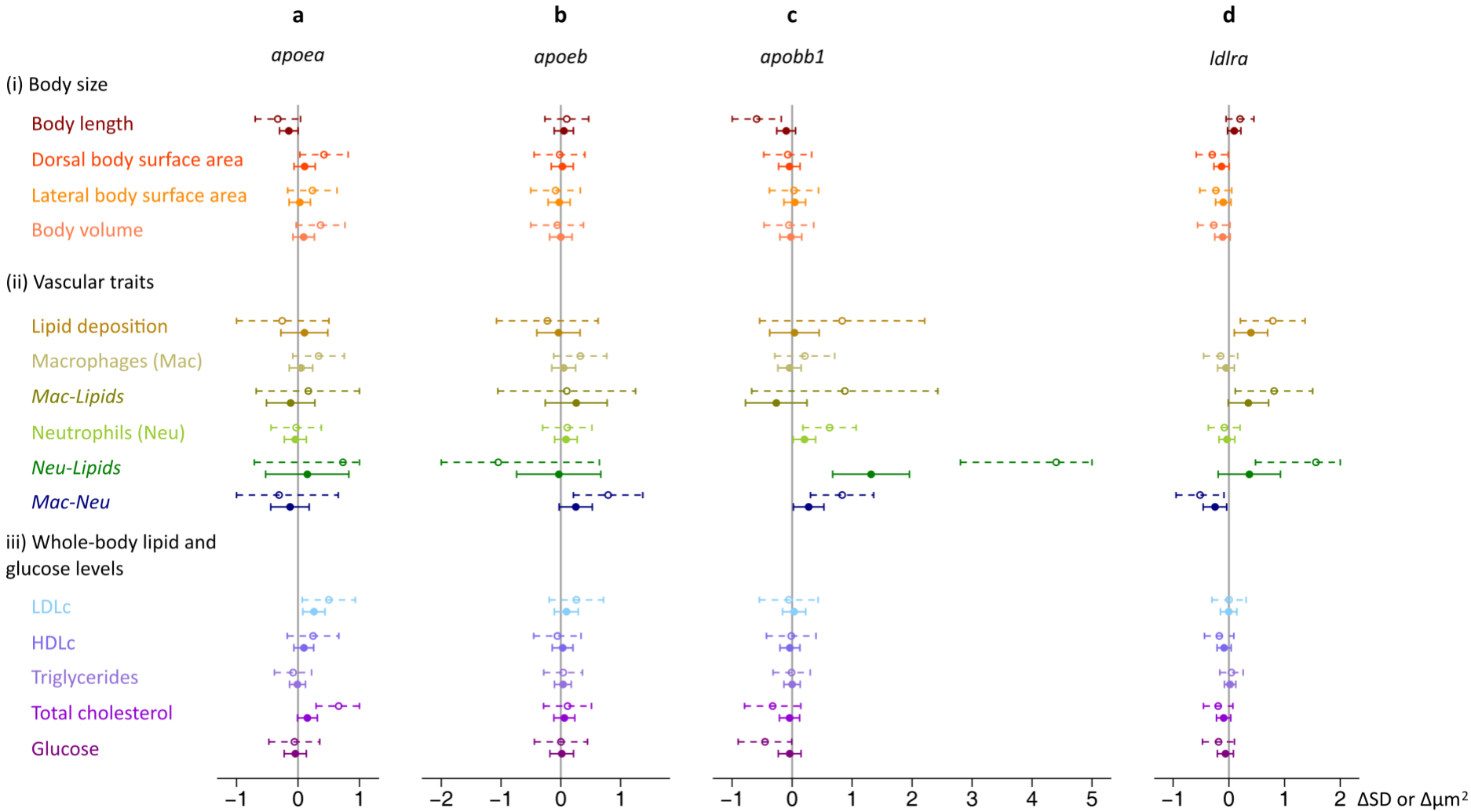




Supplementary Figure 4. Food intake as a function of dietary or drug treatment intervention. Mixing fluorescently labelled tracers in with standard dry food, standard dry food enriched with 4% extra cholesterol using diethyl ether, standard dry food treated with diethyl ether, and standard dry food enriched 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.

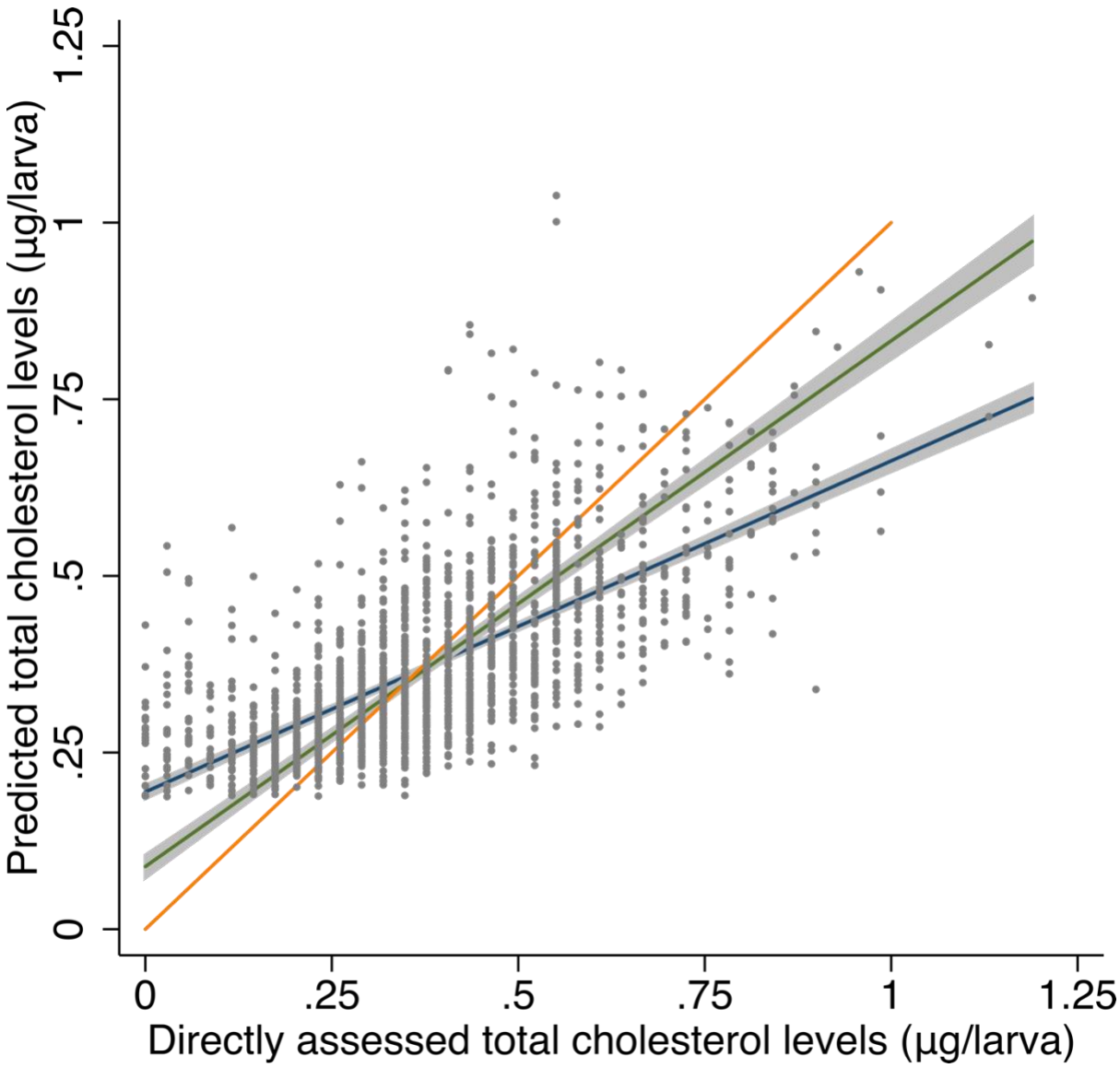


Supplementary Figure 5. Histogram of the number of mutated alleles and genetic burden score across *apoea*, *apoeb*, *apobb.1* and *ldlra* and association of whole-body LDL cholesterol levels, vascular lipid deposition and vascular co-localization of lipids and neutrophils with the genetic burden score. **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 in data from larvae with two mutated alleles in *apoba*, *apobb.2* and *ldlrb*, i.e: 1) LDLc (n=258, in gold), 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=204, in blue); and 3) vascular co-localization of lipids and neutrophils (n=204, in purple), 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.

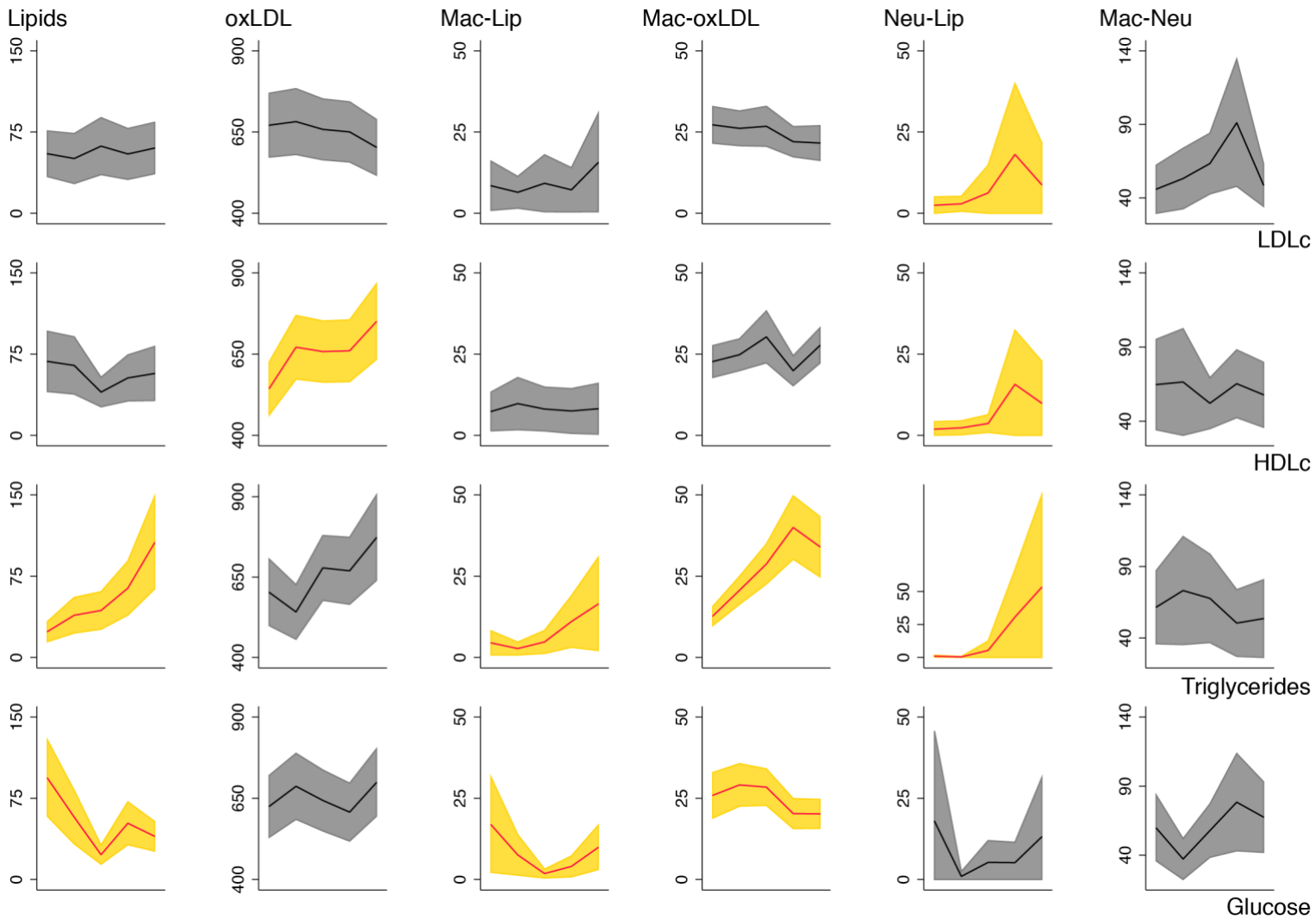


Supplementary Figure 6. The effect of mutations in *apoea*, *apoeb, apobb.1 and ldlra* on body size (**i**), vascular atherogenic traits (**ii**) and whole-body lipid and glucose levels (**iii**). Dorsal and lateral body surface area and body volume were normalized for body length before the analysis; 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 - 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 (chr 19 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 2 - 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 3 - 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 4 - 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 4**

		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 4**

		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 4**

		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 4**

		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 5 - 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 5**

	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 5**

	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 6 - 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 7 - 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 8 - 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 8**

		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 8**

		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 9 - 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 10 - 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 11 - 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)		Exon	Strand	GC (%)	Self-complementarity	Off-targets				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
			Chr	Pos					0	1	2	3							
	apoea	**GGCTCTCTCCTGCGCGTAAG**	**19**	**10,856,063**	**3 of 4**	**-**	**65**	**0**	**0**	**0**	**0**	**0**	**0.42**	**54**	**yes**	**high**	**AGCACACTGATCTCTGACAGC**	**GATCCTTCGCCTCCTCCATG**	**160**
		GGATGAGCCAAGAAGCCGCT	19	10,855,768	2 of 4	+	60	2	0	0	0	0	0.52	37	yes	moderate	TCCGTTTTGACTTTGCAGGC	GAGCTGAGTGGCCTTGATGT	155
	apoeb	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**
		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
	apoba	**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
		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
	apobb.1	**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
		GAGCCAGTTCAGTGGGCTG	20	31,273,334	11 of 27	-	60	2	0	0	0	22	0.47	38	no	moderate	GCAGAGAGGTGCTAATGAAGGT	TGTATACTCACTCCCCGGTCTC	222
APOB		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
	apobb.2	**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
		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
	ldlrb	**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
		GgGTCACGTTAGAGCTCTGA	6	102,589	1 of 5	-	55	0	0	0	0	0	0.52	61	no	no	TTCTGCTCAGAGAGGGAGAATC	GATCAGTGAAACTCACCGGTTC	182
LDLR		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 12 - 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 (wildtype reference)**	**430**	**1079 ± 766**
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	41M11D67M	91	861 ± 515
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCTGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M8D60M	67	873 ± 498
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCGCGCGAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	48M5D66M	50	726 ± 397
	ATGATGGACAGCATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	2M4S47M11D67M	30	735 ± 344
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCTCCAAACGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M1S3I67M	29	698 ± 293
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCAGAGGAGGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	50M2S1M1S1M1S1I63M	15	782 ± 366
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCCCCTCTCTCGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	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
	ATGATGGAGCTGCAAATGTACAGAGATGATCTGCACTCCAAACTGGCCCGCGCAGGAGAGAGCCCAGAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	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
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S40M13D80M	11	596 ± 279
	TTGTGATTAACTTAGTTTGGTATAAAGTTCAGAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCTGTTGATAGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	75M7D4M1I79M	9	409 ± 291
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCAGGCTCGTAGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	31M1S38M6D7M2S1M1I79M	8	660 ± 346
	TTGTGATTAACTTAGTTTGGTATAAAGTTCACAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	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
	TTGTGATTAACTTAGTTTGGTATAAAGTTCAGAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCCCAGGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	71M5D89M	1	2044
	TTGTGATTAACTTAGTTTGGTATAAAGTTCAGAGTCTCTTCTCACCTCTTGTAGGCTGCCAGGCTCGTAGCTGATGCCCCTCAGCCCAGATGGGAGGAGATGGTGGACCGTTTCTGGCAGTATGTGTCTGAACTCAACACACAAACTGACGGCA	69M11D85M	1	1032
apoba	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTATCTATGAATGGGAGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M11I3S43M1S25M	122	666 ± 434
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	58M15D42M1S25M	119	782 ± 674
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTAGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	64M5D46M1S25M	91	742 ± 433
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	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
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCATCAACAACTTTTATGAATGGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	68M14I1S1M1S70M	5	497 ± 382
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTTCACAGCTAGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M7I46M1S25M	4	666 ± 97
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGGCTCTATCTGGGGGGCAATGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M9I1M1S44M1S25M	3	590 ± 32
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	69M9D37M1S25M	3	517 ± 460
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTACAAAATAATGGCCAGCTGCCCCTTAA	57M13D45M1S25M	2	816 ± 240
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTACACTGTTGATGTTCCCAATTACATTGCTAAGTATAAAATAATGGCCAGCTGCCCCTTAA	65M16D60M	2	681 ± 57
	CCATGTTGGGTGTAGCAGAGCTGTCAGCTAAGATGAACAGCAACTTTTATGAATGGGAGGGCTCTATCTATCTTTTATGAATGGGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAGTATAAAATAATGGCCAGCTGCCCCTTAA	68M13I1M2S70M	1	1120
apobb.1	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTACCAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	160M1I24M	252	772 ± 562
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTACCAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTGTTCGATTTCTCACTCA	**184M (wildtype reference)**	**213**	**750 ± 617**
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTACAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTGTTCGATTTCTCACTCA	50M1S1M1S1M10I1M1S104M1I24M	101	639 ± 427
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	44M7D109M1I24M	73	651 ± 346
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGTAAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTTGTTCGATTTCTCACTCA	49M2D109M1I24M	24	444 ± 206
	CTTCCGTGACACCATGCAGAAGACCATTAACTATGCAGCTGACAAAGGGGCAATGACATTATGCAGAGCATGTTCCCAACCCTATGGAATAACATCAAAATGCAAAAGGTCTATAAAATAGAGTTTATTCTTTATTTCCACACTGATGGCATCTTTTTTTGTTCGATTTCTCACTCA	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 (wildtype reference)**	**21**	**437 ± 240**
	GTCTTTATTATTTCCAGAGCCAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	21M16D145M	18	704 ± 578
	GTCTTTATTATTTCCAGAGCCATCCTTGCTAGCTTGCTCAGCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGCAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	26M16I156M	13	508 ± 367
	GTCTTTATTATTTCCAGAGCCATCCAGACAACCAGACAACCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	25M7S3M2S2M1S142M	9	467 ± 183
	GTCTTTATTATTTCCAGAGCTCAGCTAATCAGGAGCAACCAGACCTGCAAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	18M11D153M	6	751 ± 461
	GTCTTTATTATTTCCAGAGCCATCTTTCTTGCTCAGCTAATCAGGAGCAACCAGACCTGCAACTACAAGTTTGACAAAGAGCAGGAGCACATGACCTCTGCTATTTGCACCGAAAAACATGTTCTTGTGCCCTTTTCACACAAGTAAGCATCAATGTTAGAAACTTTGTTTAGAGATCTGCCT	24M1I1S157M	5	22 ± 35

Continued **Supplementary Table 12**

Zebrafish orthologue	Sequence	Annotation	Number of alleles	mean ± SD number of reads
	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 (wildtype reference)**	**241**	**1176 ± 838**
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCACTACAGTAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	134M1S2M1S2I1S45M	159	982 ± 595
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCATGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	140M1D43M	119	1179 ± 722
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTATGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S128M	64	888 ± 609
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	139M1I45M	53	937 ± 655
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTATGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S78M8D42M	47	891 ± 617
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	134M8D42M	42	832 ± 397
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	132M6D46M	21	741 ± 441
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTGATTCACGGCAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S80M7I2S46M	7	528 ± 324
	GAGGCGTGTTTGTTTAGTTTTTTAAATATCAGCATAGTTTGGAATAATTAGCGTATGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAAGTGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	25M1S29M1S83M1I45M	4	395 ± 245
	GAGGCGTGTTTGTTTAGTTTTTTAAGTATCAGCATAGTTTGGAATAATTAGCGTACGGCACCCTTAGTCAAGGAGAATGTGTCACTTACAGTATTTCTCCTTCCAACAGGTGCCTTGACTTGTGATTCACGGCAGTATCAATGTGGCAATGGAAAGTGCATCACGGCGAGATGGGTGTGTGATG	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
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCACGAAGAATCGCAGAATCCGAGAATCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	72M20I1S102M	16	297 ± 208
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCTCTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCACTAACGTGACGCTGATGGAGCCCCGGGTCGGCGCTCGGCTCGTCTGCTCG	72M14I52M1S33M1S16M	15	303 ± 287
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCCGCCTCTCTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCTCTAACGTGACGCTGATGGAGCCCCGGGTCGGCGTTCGGCTCGTCTGCTCG	68M1D1S1M1S103M	12	143 ± 116
	CCGGAGCCCCGCCCCCCGCGGCTTCATTCAAATGCTCGGCTTCTGCTCAGAGAGGGAGAATCTCTCGCAGAATCCGCTCCCGGTACAGAACAGCATCTCTATCCGCCCTCAGAGCACTAACGTGACGCTGATGGAGCCCCGGGTCGGCGCTCGGCTCGTCTGCTCG	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 (wildtype reference)**	**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 standrard deviation for the number of reads that were observed for the sequence.

Supplementary Table 13 - 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	CCAGGCTCGTAGCCTGTTCCAGGC TGATGCCCCTCAGCCC/-	-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
		23,961,550	23,961,550	T/C	0	missense variant	moderate	68
apoeb	16	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 13**

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
ldlrb	6	102,545	102,546	CG/TT	0	upstream gene variant	modifier	120
		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	GCTCGCAGAATCCGCTCCCGGTAC AGAACAGCATCTCTATCCGCCCTC AGAGCTCTAACGTGACGCT/-	-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 14 - 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 15 - The effect of a genetic burden score on body size

		Body length (n=256)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	0.008	0.029	7.79E-01	-0.048	0.065
	time of day (in hours since 9AM)	-0.033	0.044	4.58E-01	-0.119	0.054
	intercept	-0.158	0.256	5.38E-01	-0.659	0.344
random factors	***variance by batch***	*0.469*	*0.136*	-	*0.266*	*0.827*
	residual	*0.751*	*0.034*	-	*0.688*	*0.821*

		Dorsal body surface area (n=256)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	-0.034	0.033	2.90E-01	-0.098	0.029
	time of day (in hours since 9AM)	0.069	0.050	1.65E-01	-0.028	0.167
	intercept	-0.075	0.291	7.96E-01	-0.646	0.496
random factors	***variance by batch***	*0.540*	*0.153*	-	*0.310*	*0.943*
	residual	*0.849*	*0.038*	-	*0.777*	*0.927*

		Lateral body surface area (n=252)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	-0.037	0.033	2.54E-01	-0.102	0.027
	time of day (in hours since 9AM)	0.026	0.050	6.04E-01	-0.072	0.123
	intercept	0.031	0.289	9.14E-01	-0.534	0.597
random factors	***variance by batch***	*0.520*	*0.148*	-	*0.297*	*0.909*
	residual	*0.844*	*0.038*	-	*0.773*	*0.923*

		Body volume (n=248)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	-0.035	0.033	2.93E-01	-0.100	0.030
	time of day (in hours since 9AM)	0.068	0.051	1.82E-01	-0.032	0.167
	intercept	-0.108	0.293	7.14E-01	-0.683	0.467
random factors	***variance by batch***	*0.526*	*0.151*	-	*0.300*	*0.924*
	residual	*0.844*	*0.039*	-	*0.772*	*0.923*

A genetic burden score was calculated by summing the dosage scores for *apoea* , *apoeb* , *apobb.1* and *ldlra* in larvae that carried two mutated alleles in *apoba* , *apobb.2* and *ldlrb* . 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 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 16 - The effect of a genetic burden score on whole-body lipid and glucose levels

		LDL cholesterol levels (n=284)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	0.075	0.035	3.11E-02	0.007	0.143
	time of day (in hours since 9AM)	0.007	0.044	8.75E-01	-0.079	0.093
	intercept	-0.375	0.222	9.14E-02	-0.810	0.060
random factors	***variance by batch***	*0.050*	*0.195*	-	*0.000*	*101.926*
	residual	*0.975*	*0.042*	-	*0.896*	*1.060*

		HDL cholesterol levels (n=284)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	-0.017	0.030	5.66E-01	-0.076	0.042
	time of day (in hours since 9AM)	-0.026	0.044	5.56E-01	-0.111	0.060
	intercept	0.185	0.295	5.31E-01	-0.394	0.764
random factors	***variance by batch***	*0.612*	*0.168*	-	*0.357*	*1.048*
	residual	*0.822*	*0.035*	-	*0.756*	*0.894*

		Triglyceride levels (n=284)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	0.016	0.024	5.19E-01	-0.032	0.063
	time of day (in hours since 9AM)	-0.089	0.036	1.25E-02	-0.159	-0.019
	intercept	0.010	0.315	9.74E-01	-0.608	0.628
random factors	***variance by batch***	*0.765*	*0.196*	-	*0.463*	*1.264*
	residual	*0.662*	*0.028*	-	*0.609*	*0.720*

		Total cholesterol levels (n=284)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	-0.005	0.031	8.79E-01	-0.064	0.055
	time of day (in hours since 9AM)	0.082	0.044	6.37E-02	-0.005	0.169
	intercept	-0.177	0.304	5.60E-01	-0.773	0.419
random factors	***variance by batch***	*0.639*	*0.189*	-	*0.358*	*1.140*
	residual	*0.834*	*0.036*	-	*0.767*	*0.906*

		Glucose levels (n=284)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	**genetic burden score**	-0.037	0.034	2.78E-01	-0.104	0.030
	time of day (in hours since 9AM)	0.016	0.048	7.35E-01	-0.078	0.111
	intercept	0.067	0.270	8.03E-01	-0.462	0.597
random factors	***variance by batch***	*0.420*	*0.137*	-	*0.222*	*0.795*
	residual	*0.932*	*0.040*	-	*0.858*	*1.014*

A genetic burden score was calculated by summing the dosage scores for *apoea* , *apoeb* , *apobb.1* and *ldlra* in larvae carrying two mutated alleles in *apoba* , *apobb.2* and *ldlrb* . 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 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 vascular atherogenic traits

		Vascular lipid deposition														
		Model 1 (n=225)					Model 2 (n=202)					Model 3 (n=202)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	genetic burden score	0.200	0.066	2.45E-03	0.071	0.329	0.175	0.067	9.29E-03	0.043	0.307	0.134	0.065	3.75E-02	0.008	0.261
	time of day (in hours since 9AM)	-0.008	0.105	9.37E-01	-0.213	0.197	-0.051	0.136	7.08E-01	-0.317	0.215	-0.128	0.125	3.08E-01	-0.373	0.118
	body length (in SD)	-	-	-	-	-	-0.426	0.143	2.95E-03	-0.706	-0.145	-0.214	0.143	1.35E-01	-0.494	0.066
	dorsal body surface area (in SD)	-	-	-	-	-	0.145	0.172	3.99E-01	-0.192	0.482	0.276	0.163	9.00E-02	-0.043	0.596
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.130	0.100	1.91E-01	-0.326	0.065
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.049	0.149	7.41E-01	-0.242	0.340
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.696	0.174	6.56E-05	0.354	1.037
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.238	0.124	5.47E-02	-0.480	0.005
	batch 1	4.540	0.988	4.37E-06	2.603	6.477	4.570	1.049	1.32E-05	2.514	6.626	4.887	1.059	3.95E-06	2.811	6.962
	batch 2	2.804	0.981	4.25E-03	0.882	4.727	2.516	1.035	1.51E-02	0.487	4.545	3.091	1.090	4.56E-03	0.955	5.227
	batch 3	3.487	1.002	5.04E-04	1.522	5.452	3.315	1.038	1.41E-03	1.280	5.349	3.462	1.034	8.17E-04	1.435	5.489
	batch 4	3.842	1.152	8.52E-04	1.584	6.100	3.191	1.128	4.68E-03	0.980	5.402	3.534	1.062	8.78E-04	1.452	5.617
	batch 5	4.300	0.973	9.81E-06	2.394	6.207	4.125	1.066	1.08E-04	2.036	6.214	3.473	1.037	8.15E-04	1.440	5.506
	batch 6	4.622	0.980	2.40E-06	2.701	6.542	4.793	1.060	6.09E-06	2.716	6.870	3.947	1.060	1.96E-04	1.870	6.024
	batch 7	3.554	1.022	5.04E-04	1.552	5.556	3.816	1.120	6.56E-04	1.621	6.011	3.685	1.092	7.44E-04	1.544	5.826
	intercept	0.010	1.019	9.92E-01	-1.987	2.007	0.313	1.118	7.79E-01	-1.878	2.505	0.862	1.093	4.30E-01	-1.280	3.004

		Vascular infiltration by macrophages														
		Model 1 (n=276)					Model 2 (n=248)					Model 3 (n=248)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	genetic burden score	-0.001	0.033	9.84E-01	-0.065	0.064	-0.010	0.035	7.88E-01	-0.079	0.060	-0.011	0.036	7.68E-01	-0.081	0.060
	time of day (in hours since 9AM)	0.037	0.047	4.36E-01	-0.056	0.129	0.030	0.054	5.76E-01	-0.075	0.135	0.035	0.053	5.16E-01	-0.070	0.139
	body length (in SD)	-	-	-	-	-	0.050	0.082	5.43E-01	-0.110	0.209	0.052	0.082	5.30E-01	-0.109	0.212
	dorsal body surface area (in SD)	-	-	-	-	-	-0.032	0.070	6.49E-01	-0.168	0.105	-0.030	0.071	6.70E-01	-0.168	0.108
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.045	0.065	4.84E-01	-0.081	0.172
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.120	0.076	1.11E-01	-0.028	0.268
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.046	0.092	6.16E-01	-0.134	0.226
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.001	0.065	9.84E-01	-0.126	0.128
	intercept	-0.103	0.282	7.14E-01	-0.656	0.450	-0.039	0.299	8.97E-01	-0.625	0.547	-0.042	0.293	8.86E-01	-0.616	0.532
random factors	*variance by batch*	0.507	0.142	-	0.292	0.879	0.514	0.152	-	0.289	0.917	0.477	0.147	-	0.261	0.872
	residual	0.884	0.038	-	0.812	0.962	0.903	0.041	-	0.825	0.987	0.899	0.041	-	0.822	0.983

continued **Supplementary Table 17**

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=223)					Model 2 (n=200)					Model 3 (n=200)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	genetic burden score	0.201	0.084	1.69E-02	0.036	0.367	0.157	0.093	9.35E-02	-0.026	0.340	0.151	0.097	1.20E-01	-0.039	0.341
	time of day (in hours since 9AM)	0.182	0.115	1.14E-01	-0.044	0.407	0.215	0.133	1.05E-01	-0.045	0.476	0.200	0.149	1.81E-01	-0.093	0.493
	body length (in SD)	-	-	-	-	-	-0.496	0.205	1.55E-02	-0.898	-0.094	-0.290	0.229	2.05E-01	-0.740	0.159
	dorsal body surface area (in SD)	-	-	-	-	-	0.343	0.185	6.38E-02	-0.020	0.706	0.387	0.194	4.63E-02	0.006	0.768
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.455	0.218	3.70E-02	-0.883	-0.027
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.250	0.188	1.84E-01	-0.119	0.619
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.736	0.264	5.26E-03	0.219	1.253
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.141	0.175	4.22E-01	-0.485	0.203
	batch 1	2.942	0.958	2.12E-03	1.065	4.819	2.465	1.090	2.37E-02	0.328	4.601	3.042	1.224	1.30E-02	0.642	5.441
	batch 2	2.264	1.185	5.61E-02	-0.059	4.587	1.927	1.300	1.38E-01	-0.621	4.476	1.637	1.287	2.04E-01	-0.887	4.160
	batch 3	2.123	0.952	2.58E-02	0.257	3.990	1.555	1.068	1.45E-01	-0.538	3.649	2.019	1.036	5.12E-02	-0.010	4.049
	batch 4	3.401	1.148	3.06E-03	1.151	5.652	2.145	1.189	7.12E-02	-0.185	4.475	2.264	1.097	3.90E-02	0.114	4.414
	batch 5	2.901	0.986	3.27E-03	0.968	4.834	1.988	1.182	9.26E-02	-0.329	4.305	1.410	1.096	1.98E-01	-0.737	3.557
	batch 6	2.558	0.957	7.53E-03	0.682	4.435	2.305	1.148	4.47E-02	0.055	4.555	1.858	1.168	1.12E-01	-0.432	4.148
	batch 7	1.166	1.163	3.16E-01	-1.114	3.445	0.506	1.329	7.04E-01	-2.098	3.109	0.807	1.305	5.36E-01	-1.750	3.364
	intercept	-1.574	1.059	1.37E-01	-3.651	0.502	-0.994	1.165	3.94E-01	-3.278	1.290	-0.865	1.147	4.51E-01	-3.113	1.383

		Vascular infiltration by neutrophils														
		Model 1 (n=278)					Model 2 (n=250)					Model 3 (n=250)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	genetic burden score	0.014	0.032	6.66E-01	-0.049	0.077	0.036	0.034	2.91E-01	-0.030	0.101	0.042	0.034	2.14E-01	-0.025	0.110
	time of day (in hours since 9AM)	0.038	0.045	4.00E-01	-0.051	0.127	0.013	0.050	7.96E-01	-0.085	0.111	0.017	0.050	7.25E-01	-0.080	0.115
	body length (in SD)	-	-	-	-	-	-0.125	0.075	9.81E-02	-0.272	0.023	-0.101	0.076	1.82E-01	-0.250	0.048
	dorsal body surface area (in SD)	-	-	-	-	-	0.069	0.065	2.86E-01	-0.058	0.196	0.094	0.066	1.52E-01	-0.035	0.223
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.012	0.060	8.44E-01	-0.129	0.106
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.063	0.071	3.79E-01	-0.077	0.203
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.121	0.083	1.43E-01	-0.283	0.041
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.023	0.062	7.12E-01	-0.098	0.144
	intercept	-0.150	0.246	5.41E-01	-0.632	0.331	-0.156	0.252	5.34E-01	-0.650	0.337	-0.215	0.249	3.87E-01	-0.704	0.273
random factors	*variance by batch*	0.347	0.103	-	0.194	0.622	0.318	0.102	-	0.170	0.595	0.288	0.095	-	0.151	0.549
	residual	0.876	0.038	-	0.805	0.953	0.871	0.040	-	0.797	0.952	0.868	0.039	-	0.794	0.948

continued **Supplementary Table 17**

		Vascular co-localization of lipids with neutrophils														
		Model 1 (n=225)					Model 2 (n=202)					Model 3 (n=202)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	genetic burden score	0.296	0.104	4.56E-03	0.092	0.501	0.350	0.107	1.06E-03	0.141	0.560	0.218	0.120	6.99E-02	-0.018	0.454
	time of day (in hours since 9AM)	0.169	0.179	3.43E-01	-0.181	0.520	0.148	0.245	5.44E-01	-0.331	0.628	-0.033	0.234	8.87E-01	-0.493	0.426
	body length (in SD)	-	-	-	-	-	-1.248	0.268	3.35E-06	-1.774	-0.722	-0.729	0.325	2.51E-02	-1.366	-0.091
	dorsal body surface area (in SD)	-	-	-	-	-	0.214	0.295	4.68E-01	-0.365	0.793	0.257	0.271	3.44E-01	-0.275	0.789
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.133	0.304	6.61E-01	-0.462	0.728
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.409	0.312	1.89E-01	-0.202	1.020
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.307	0.341	1.27E-04	0.639	1.976
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.341	0.237	1.49E-01	-0.806	0.123
	batch 1	18.790	0.715	3.44E-152	17.388	20.191	20.130	1.152	2.41E-68	17.871	22.388	20.158	1.309	1.66E-53	17.592	22.723
	batch 2	16.246	0.871	1.11E-77	14.539	17.952	17.684	1.211	2.50E-48	15.311	20.056	17.534	1.386	1.14E-36	14.817	20.251
	batch 3	17.020	0.829	1.05E-93	15.395	18.644	18.478	1.136	1.68E-59	16.252	20.704	18.268	1.088	3.11E-63	16.135	20.401
	batch 4	18.402	0.837	3.03E-107	16.763	20.042	18.915	1.092	2.97E-67	16.775	21.054	19.669	1.059	4.69E-77	17.594	21.744
	batch 5	18.463	0.745	9.71E-136	17.004	19.923	19.939	1.198	3.29E-62	17.591	22.287	18.469	1.030	5.98E-72	16.451	20.487
	batch 6	18.887	0.810	2.14E-120	17.301	20.474	20.121	0.934	5.49E-103	18.291	21.951	18.714	0.977	9.07E-82	16.799	20.629
	batch 7	16.512	1.134	5.03E-48	14.289	18.734	19.883	1.680	2.48E-32	16.591	23.175	18.795	1.445	1.06E-38	15.964	21.626
	intercept	-18.814	0.776	5.63E-130	-20.334	-17.294	-20.886	1.028	8.92E-92	-22.901	-18.871	-19.098	1.197	2.59E-57	-21.444	-16.752

		Vascular co-localization of macrophages with neutrophils														
		Model 1 (n=276)					Model 2 (n=248)					Model 3 (n=248)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	genetic burden score	-0.042	0.048	3.80E-01	-0.136	0.052	-0.034	0.055	5.33E-01	-0.142	0.073	-0.043	0.054	4.31E-01	-0.149	0.064
	time of day (in hours since 9AM)	0.161	0.067	1.69E-02	0.029	0.293	0.139	0.079	7.72E-02	-0.015	0.293	0.116	0.080	1.44E-01	-0.040	0.273
	body length (in SD)	-	-	-	-	-	0.102	0.131	4.37E-01	-0.156	0.360	0.046	0.136	7.34E-01	-0.220	0.312
	dorsal body surface area (in SD)	-	-	-	-	-	0.240	0.120	4.48E-02	0.006	0.475	0.201	0.127	1.15E-01	-0.049	0.450
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.172	0.103	9.71E-02	-0.031	0.374
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.085	0.114	4.60E-01	-0.309	0.140
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.006	0.139	9.66E-01	-0.278	0.267
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.034	0.091	7.04E-01	-0.143	0.212
	batch 1	0.649	0.620	2.95E-01	-0.565	1.863	0.634	0.643	3.24E-01	-0.626	1.894	0.889	0.648	1.70E-01	-0.381	2.158
	batch 2	0.517	0.776	5.05E-01	-1.003	2.038	0.618	0.770	4.22E-01	-0.891	2.126	0.769	0.725	2.88E-01	-0.651	2.189
	batch 3	-0.666	0.648	3.03E-01	-1.936	0.603	-0.622	0.665	3.49E-01	-1.925	0.681	-0.431	0.662	5.15E-01	-1.728	0.865
	batch 4	1.069	0.688	1.20E-01	-0.278	2.417	1.214	0.716	9.02E-02	-0.190	2.618	1.270	0.717	7.66E-02	-0.136	2.676
	batch 5	0.212	0.625	7.34E-01	-1.012	1.437	0.081	0.664	9.03E-01	-1.221	1.383	0.363	0.676	5.91E-01	-0.961	1.688
	batch 6	-1.356	0.647	3.60E-02	-2.624	-0.088	-1.733	0.700	1.33E-02	-3.104	-0.361	-1.591	0.707	2.44E-02	-2.976	-0.206
	batch 7	-0.194	0.698	7.81E-01	-1.562	1.174	-0.523	0.758	4.90E-01	-2.009	0.963	-0.314	0.838	7.08E-01	-1.956	1.329
	intercept	3.477	0.665	1.72E-07	2.174	4.781	3.596	0.701	2.87E-07	2.223	4.970	3.497	0.681	2.84E-07	2.162	4.832

A genetic burden score was calculated by summing the dosage scores for *apoea* , *apoeb* , *apobb.1* and *ldlra* in larvae carrying two mutated alleles in *apoba* , *apobb.2* and *ldlrb* . 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 infiltration by macrophages and neutrophils). Model 1: adjusted for time of day 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 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 two vs. zero mutated alleles in *apoea* , *apoeb* , *apobb.1* or *ldlra* on body size

		Body length																			
		apoea					*apoeb*					*apobb.1*					*ldlra*				
		77 vs. 29 larvae with 2 vs 0 mutated alleles					26 vs. 169 larvae with 2 vs. 0 mutated alleles					110 vs. 16 larvae with 2 vs. 0 mutated alleles					77 vs. 121 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	-0.329	0.189	8.13E-02	-0.698	0.041	0.098	0.187	5.99E-01	-0.268	0.465	-0.590	0.209	4.64E-03	-0.999	-0.182	0.201	0.127	1.15E-01	-0.049	0.451
	apoea	-	-	-	-	-	-0.089	0.092	3.37E-01	-0.269	0.092	-0.173	0.117	1.40E-01	-0.403	0.057	-0.180	0.087	3.97E-02	-0.351	-0.009
	apoeb	0.086	0.128	4.99E-01	-0.164	0.337	-	-	-	-	-	0.047	0.111	6.68E-01	-0.169	0.264	0.128	0.092	1.63E-01	-0.052	0.308
	apobb.1	-0.163	0.121	1.79E-01	-0.401	0.075	-0.042	0.099	6.69E-01	-0.237	0.152	-	-	-	-	-	-0.176	0.091	5.29E-02	-0.354	0.002
	ldlra	0.102	0.099	3.00E-01	-0.091	0.295	0.085	0.072	2.41E-01	-0.057	0.227	0.119	0.094	2.05E-01	-0.065	0.304	-	-	-	-	-
	time of day (in hours since 9AM)	-0.050	0.065	4.36E-01	-0.177	0.076	0.024	0.050	6.33E-01	-0.073	0.121	0.052	0.062	4.02E-01	-0.070	0.174	-0.040	0.048	4.00E-01	-0.134	0.053
	intercept	-0.091	0.338	7.87E-01	-0.754	0.572	-0.386	0.261	1.40E-01	-0.897	0.126	-0.434	0.308	1.58E-01	-1.037	0.169	-0.163	0.263	5.35E-01	-0.680	0.353
random factors	*variance by batch*	0.460	0.150	-	0.242	0.873	0.345	0.115	-	0.180	0.662	0.384	0.130	-	0.198	0.744	0.404	0.123	-	0.223	0.733
	residual	0.736	0.053	-	0.640	0.847	0.751	0.039	-	0.678	0.831	0.757	0.049	-	0.666	0.860	0.748	0.038	-	0.677	0.828

		Dorsal body surface area																			
		77 vs. 29 larvae with 2 vs 0 mutated alleles					26 vs. 169 larvae with 2 vs. 0 mutated alleles					110 vs. 16 larvae with 2 vs. 0 mutated alleles					77 vs. 121 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	0.233	0.204	2.53E-01	-0.167	0.633	-0.089	0.212	6.75E-01	-0.504	0.326	0.032	0.209	8.79E-01	-0.378	0.442	-0.234	0.146	1.09E-01	-0.520	0.052
	apoea	-	-	-	-	-	-0.003	0.105	9.77E-01	-0.208	0.202	0.018	0.119	8.78E-01	-0.215	0.251	0.061	0.100	5.41E-01	-0.135	0.258
	apoeb	-0.109	0.138	4.27E-01	-0.380	0.161	-	-	-	-	-	-0.163	0.111	1.44E-01	-0.381	0.056	-0.031	0.105	7.65E-01	-0.238	0.175
	apobb.1	0.172	0.131	1.89E-01	-0.085	0.428	0.017	0.113	8.81E-01	-0.204	0.237	-	-	-	-	-	0.040	0.104	7.00E-01	-0.164	0.244
	ldlra	-0.116	0.106	2.74E-01	-0.325	0.092	-0.104	0.082	2.05E-01	-0.265	0.057	0.048	0.095	6.09E-01	-0.137	0.234	-	-	-	-	-
	time of day (in hours since 9AM)	0.148	0.070	3.60E-02	0.010	0.285	0.068	0.057	2.40E-01	-0.045	0.180	0.005	0.064	9.40E-01	-0.121	0.131	0.074	0.056	1.83E-01	-0.035	0.183
	intercept	-0.361	0.378	3.40E-01	-1.103	0.380	-0.043	0.326	8.96E-01	-0.683	0.597	0.142	0.347	6.81E-01	-0.538	0.823	-0.082	0.330	8.05E-01	-0.728	0.565
random factors	*variance by batch*	0.567	0.191	-	0.293	1.096	0.545	0.163	-	0.303	0.978	0.573	0.176	-	0.314	1.048	0.593	0.174	-	0.333	1.056
	residual	0.793	0.057	-	0.688	0.913	0.849	0.044	-	0.767	0.940	0.757	0.049	-	0.666	0.860	0.857	0.044	-	0.775	0.948

		Lateral body surface area																			
		76 vs. 28 larvae with 2 vs. 0 mutated alleles					25 vs. 168 larvae with 2 vs. 0 mutated alleles					108 vs. 16 larvae with 2 vs. 0 mutated alleles					75 vs. 119 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	0.422	0.201	3.55E-02	0.029	0.815	-0.022	0.216	9.19E-01	-0.446	0.402	-0.074	0.204	7.17E-01	-0.474	0.326	-0.298	0.146	4.15E-02	-0.584	-0.011
	apoea	-	-	-	-	-	0.069	0.105	5.10E-01	-0.137	0.276	0.003	0.116	9.79E-01	-0.225	0.231	0.126	0.100	2.10E-01	-0.071	0.323
	apoeb	0.028	0.136	8.40E-01	-0.240	0.295	-	-	-	-	-	-0.134	0.109	2.20E-01	-0.348	0.080	0.014	0.107	8.95E-01	-0.195	0.223
	apobb.1	0.023	0.130	8.57E-01	-0.231	0.278	-0.006	0.113	9.61E-01	-0.228	0.217	-	-	-	-	-	-0.033	0.105	7.53E-01	-0.239	0.173
	ldlra	-0.143	0.106	1.76E-01	-0.350	0.064	-0.161	0.083	5.21E-02	-0.324	0.001	0.028	0.093	7.62E-01	-0.154	0.211	-	-	-	-	-
	time of day (in hours since 9AM)	0.056	0.069	4.19E-01	-0.080	0.192	0.067	0.058	2.43E-01	-0.046	0.180	-0.049	0.063	4.36E-01	-0.174	0.075	0.016	0.056	7.79E-01	-0.094	0.125
	intercept	-0.320	0.370	3.87E-01	-1.044	0.405	-0.096	0.322	7.67E-01	-0.727	0.536	0.305	0.345	3.77E-01	-0.372	0.982	-0.014	0.340	9.67E-01	-0.681	0.653
random factors	*variance by batch*	0.536	0.188	-	0.269	1.068	0.498	0.148	-	0.279	0.891	0.581	0.184	-	0.313	1.080	0.612	0.183	-	0.340	1.100
	residual	0.779	0.057	-	0.675	0.899	0.853	0.044	-	0.770	0.944	0.738	0.049	-	0.649	0.840	0.853	0.044	-	0.771	0.945

		Body volume																			
		72 vs. 28 larvae with 2 vs. 0 mutated alleles					24 vs. 165 larvae with 2 vs. 0 mutated alleles					106 vs. 15 larvae with 2 vs. 0 mutated alleles					73 vs. 117 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	0.366	0.202	6.99E-02	-0.030	0.762	-0.062	0.225	7.83E-01	-0.503	0.379	-0.054	0.211	7.99E-01	-0.468	0.360	-0.270	0.149	6.96E-02	-0.562	0.022
	apoea	-	-	-	-	-	0.075	0.109	4.91E-01	-0.139	0.288	0.047	0.118	6.89E-01	-0.185	0.279	0.102	0.102	3.19E-01	-0.098	0.302
	apoeb	-0.035	0.142	8.07E-01	-0.313	0.243	-	-	-	-	-	-0.140	0.111	2.06E-01	-0.357	0.077	0.002	0.109	9.85E-01	-0.212	0.216
	apobb.1	0.077	0.135	5.68E-01	-0.187	0.340	-0.008	0.119	9.47E-01	-0.240	0.224	-	-	-	-	-	-0.024	0.108	8.21E-01	-0.236	0.187
	ldlra	-0.114	0.108	2.94E-01	-0.326	0.099	-0.135	0.085	1.14E-01	-0.302	0.032	0.032	0.095	7.35E-01	-0.155	0.219	-	-	-	-	-
	time of day (in hours since 9AM)	0.142	0.073	5.07E-02	0.000	0.285	0.097	0.060	1.06E-01	-0.021	0.215	0.013	0.066	8.42E-01	-0.117	0.144	0.067	0.058	2.45E-01	-0.046	0.180
	intercept	-0.527	0.378	1.64E-01	-1.268	0.214	-0.191	0.330	5.62E-01	-0.839	0.456	0.064	0.348	8.54E-01	-0.617	0.745	-0.141	0.343	6.80E-01	-0.813	0.531
random factors	*variance by batch*	0.530	0.197	-	0.256	1.097	0.499	0.151	-	0.276	0.905	0.564	0.185	-	0.296	1.072	0.602	0.182	-	0.333	1.089
	residual	0.782	0.059	-	0.675	0.906	0.866	0.046	-	0.781	0.960	0.741	0.050	-	0.650	0.845	0.858	0.045	-	0.774	0.952

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 in larvae carrying two mutated alleles in *apoba* , *apobb.2* and *ldlrb* . 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 three 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 19 - The effect of two vs. zero mutated alleles in *apoea* , *apoeb* , *apobb.1* or *ldlra* on whole-body lipid and glucose levels

		apoea					*apoeb*					*apobb.1*					*ldlra*				
		LDL cholesterol levels																			
		84 vs. 33 larvae with 2 vs 0 mutated alleles					**27 vs. 188 larvae with 2 vs 0 mutated alleles**					**119 vs. 17 larvae with 2 vs 0 mutated alleles**					**83 vs. 139 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**	0.501	0.220	2.32E-02	0.069	0.933	0.260	0.231	2.61E-01	-0.193	0.713	-0.056	0.250	8.23E-01	-0.545	0.434	0.004	0.156	9.78E-01	-0.302	0.310
	apoea	-	-	-	-	-	0.295	0.109	6.83E-03	0.081	0.509	0.253	0.134	5.95E-02	-0.010	0.515	0.217	0.104	3.65E-02	0.014	0.420
	apoeb	0.226	0.158	1.53E-01	-0.084	0.536	-	-	-	-	-	0.045	0.127	7.24E-01	-0.205	0.295	0.094	0.114	4.07E-01	-0.129	0.317
	apobb.1	-0.004	0.154	9.79E-01	-0.305	0.297	0.031	0.120	7.94E-01	-0.203	0.266	-	-	-	-	-	0.058	0.113	6.08E-01	-0.163	0.279
	ldlra	-0.175	0.125	1.63E-01	-0.420	0.071	-0.005	0.088	9.52E-01	-0.179	0.168	0.019	0.110	8.65E-01	-0.197	0.235	-	-	-	-	-
	time of day (in hours since 9AM)	-0.004	0.067	9.49E-01	-0.135	0.127	0.016	0.050	7.53E-01	-0.082	0.114	0.051	0.062	4.08E-01	-0.070	0.173	0.006	0.051	9.03E-01	-0.093	0.105
	intercept	-0.459	0.349	1.89E-01	-1.144	0.225	-0.594	0.263	2.41E-02	-1.109	-0.078	-0.539	0.301	7.33E-02	-1.128	0.051	-0.459	0.260	7.74E-02	-0.969	0.050
random factors	***variance by batch***	*0.000*	*0.000*	-	*0.000*	-	*0.000*	*0.000*	-	*0.000*	*0.068*	*0.000*	*0.000*	-	*0.000*	*0.000*	*0.000*	*0.000*	-	*0.000*	*0.006*
	residual	*0.994*	*0.065*	-	*0.875*	*1.130*	*0.974*	*0.047*	-	*0.886*	*1.071*	*0.953*	*0.058*	-	*0.846*	*1.073*	*0.984*	*0.047*	-	*0.897*	*1.080*
		HDL cholesterol levels																			
		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**	0.245	0.214	2.53E-01	-0.175	0.664	-0.058	0.202	7.75E-01	-0.454	0.339	-0.014	0.211	9.45E-01	-0.428	0.399	-0.174	0.134	1.96E-01	-0.437	0.090
	apoea	-	-	-	-	-	0.132	0.097	1.74E-01	-0.058	0.323	0.067	0.119	5.73E-01	-0.167	0.301	0.078	0.091	3.96E-01	-0.101	0.256
	apoeb	0.132	0.146	3.65E-01	-0.154	0.417	-	-	-	-	-	-0.011	0.113	9.25E-01	-0.233	0.211	0.014	0.097	8.88E-01	-0.177	0.205
	apobb.1	-0.205	0.139	1.42E-01	-0.478	0.069	-0.055	0.105	5.99E-01	-0.261	0.151	-	-	-	-	-	0.014	0.097	8.83E-01	-0.175	0.204
	ldlra	-0.110	0.114	3.36E-01	-0.333	0.114	-0.047	0.077	5.43E-01	-0.198	0.104	-0.109	0.097	2.61E-01	-0.298	0.081	-	-	-	-	-
	time of day (in hours since 9AM)	-0.016	0.070	8.25E-01	-0.153	0.122	-0.050	0.050	3.23E-01	-0.149	0.049	-0.020	0.061	7.41E-01	-0.141	0.100	-0.047	0.048	3.34E-01	-0.142	0.048
	intercept	0.116	0.383	7.61E-01	-0.635	0.868	0.265	0.310	3.93E-01	-0.343	0.872	0.187	0.346	5.90E-01	-0.492	0.865	0.190	0.306	5.35E-01	-0.410	0.790
random factors	***variance by batch***	*0.501*	*0.178*	-	*0.250*	*1.004*	*0.541*	*0.157*	-	*0.306*	*0.957*	*0.570*	*0.177*	-	*0.309*	*1.049*	*0.562*	*0.163*	-	*0.318*	*0.991*
	residual	*0.889*	*0.061*	-	*0.778*	*1.017*	*0.831*	*0.041*	-	*0.754*	*0.915*	*0.797*	*0.050*	-	*0.704*	*0.901*	*0.822*	*0.040*	-	*0.748*	*0.904*
		Triglyceride levels																			
		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**	-0.082	0.155	5.95E-01	-0.385	0.221	0.037	0.165	8.22E-01	-0.287	0.362	-0.009	0.158	9.56E-01	-0.318	0.301	0.047	0.107	6.62E-01	-0.162	0.256
	apoea	-	-	-	-	-	-0.059	0.080	4.55E-01	-0.216	0.097	-0.076	0.090	3.96E-01	-0.253	0.100	0.012	0.073	8.67E-01	-0.130	0.155
	apoeb	0.018	0.103	8.61E-01	-0.184	0.221	-	-	-	-	-	-0.024	0.085	7.76E-01	-0.191	0.143	-0.017	0.077	8.21E-01	-0.169	0.134
	apobb.1	-0.084	0.099	3.94E-01	-0.278	0.109	0.024	0.086	7.83E-01	-0.145	0.192	-	-	-	-	-	0.012	0.077	8.72E-01	-0.138	0.163
	ldlra	0.120	0.081	1.37E-01	-0.038	0.279	0.027	0.063	6.74E-01	-0.097	0.150	0.061	0.072	3.99E-01	-0.081	0.203	-	-	-	-	-
	time of day (in hours since 9AM)	-0.106	0.052	4.16E-02	-0.208	-0.004	-0.063	0.042	1.34E-01	-0.145	0.019	-0.058	0.047	2.12E-01	-0.150	0.033	-0.100	0.039	1.03E-02	-0.177	-0.024
	intercept	0.061	0.360	8.66E-01	-0.645	0.766	-0.011	0.341	9.75E-01	-0.678	0.657	0.007	0.345	9.84E-01	-0.670	0.683	0.112	0.322	7.29E-01	-0.520	0.743
random factors	***variance by batch***	*0.748*	*0.200*	-	*0.443*	*1.262*	*0.778*	*0.202*	-	*0.469*	*1.293*	*0.768*	*0.201*	-	*0.459*	*1.283*	*0.745*	*0.194*	-	*0.448*	*1.240*
	residual	*0.627*	*0.042*	-	*0.549*	*0.716*	*0.678*	*0.033*	-	*0.616*	*0.747*	*0.595*	*0.037*	-	*0.527*	*0.673*	*0.652*	*0.031*	-	*0.593*	*0.716*
		Total cholesterol levels																			
		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**	0.660	0.187	4.15E-04	0.294	1.027	0.113	0.204	5.82E-01	-0.288	0.513	-0.325	0.239	1.74E-01	-0.793	0.144	-0.192	0.135	1.54E-01	-0.456	0.072
	apoea	-	-	-	-	-	0.175	0.098	7.42E-02	-0.017	0.368	0.189	0.128	1.41E-01	-0.063	0.440	0.159	0.092	8.21E-02	-0.020	0.339
	apoeb	0.249	0.127	5.05E-02	-0.001	0.498	-	-	-	-	-	0.088	0.122	4.72E-01	-0.151	0.327	0.074	0.098	4.47E-01	-0.117	0.266
	apobb.1	-0.074	0.122	5.44E-01	-0.313	0.165	0.003	0.106	9.76E-01	-0.205	0.212	-	-	-	-	-	-0.031	0.097	7.50E-01	-0.221	0.159
	ldlra	-0.185	0.100	6.33E-02	-0.381	0.010	-0.104	0.078	1.84E-01	-0.257	0.049	-0.153	0.105	1.47E-01	-0.360	0.054	-	-	-	-	-
	time of day (in hours since 9AM)	0.120	0.061	5.15E-02	-0.001	0.240	0.083	0.051	1.04E-01	-0.017	0.184	0.080	0.060	1.80E-01	-0.037	0.196	0.093	0.049	5.46E-02	-0.002	0.189
	intercept	-0.660	0.334	4.82E-02	-1.315	-0.005	-0.336	0.322	2.97E-01	-0.968	0.296	-0.534	0.288	6.39E-02	-1.098	0.031	-0.386	0.306	2.08E-01	-0.986	0.214
random factors	***variance by batch***	*0.433*	*0.191*	-	*0.182*	*1.029*	*0.586*	*0.190*	-	*0.310*	*1.105*	*0.000*	*0.000*	-	*0.000*	*0.000*	*0.558*	*0.188*	-	*0.289*	*1.080*
	residual	*0.777*	*0.054*	-	*0.678*	*0.891*	*0.840*	*0.042*	-	*0.762*	*0.925*	*0.913*	*0.055*	-	*0.810*	*1.028*	*0.825*	*0.040*	-	*0.750*	*0.908*
		Glucose levels																			
		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**	-0.060	0.211	7.77E-01	-0.473	0.354	0.002	0.226	9.93E-01	-0.441	0.445	-0.454	0.228	4.68E-02	-0.901	-0.006	-0.186	0.147	2.04E-01	-0.474	0.101
	apoea	-	-	-	-	-	-0.045	0.108	6.79E-01	-0.257	0.168	-0.003	0.127	9.79E-01	-0.253	0.246	-0.041	0.099	6.77E-01	-0.236	0.153
	apoeb	0.250	0.146	8.77E-02	-0.037	0.536	-	-	-	-	-	-0.074	0.122	5.40E-01	-0.313	0.164	0.078	0.106	4.62E-01	-0.130	0.287
	apobb.1	-0.148	0.140	2.94E-01	-0.423	0.128	-0.045	0.118	7.00E-01	-0.276	0.185	-	-	-	-	-	-0.016	0.105	8.82E-01	-0.222	0.191
	ldlra	-0.267	0.115	2.01E-02	-0.491	-0.042	0.026	0.086	7.64E-01	-0.143	0.195	-0.060	0.104	5.63E-01	-0.264	0.143	-	-	-	-	-
	time of day (in hours since 9AM)	-0.007	0.068	9.15E-01	-0.140	0.125	-0.002	0.055	9.65E-01	-0.111	0.106	0.035	0.064	5.83E-01	-0.090	0.160	0.039	0.051	4.52E-01	-0.062	0.139
	intercept	-0.067	0.353	8.50E-01	-0.758	0.625	-0.027	0.308	9.30E-01	-0.631	0.577	-0.031	0.322	9.23E-01	-0.662	0.600	-0.159	0.277	5.65E-01	-0.703	0.384
random factors	***variance by batch***	*0.306*	*0.164*	-	*0.107*	*0.875*	*0.414*	*0.144*	-	*0.209*	*0.819*	*0.351*	*0.156*	-	*0.147*	*0.839*	*0.328*	*0.135*	-	*0.146*	*0.736*
	residual	*0.899*	*0.062*	-	*0.786*	*1.030*	*0.932*	*0.046*	-	*0.846*	*1.027*	*0.864*	*0.055*	-	*0.763*	*0.977*	*0.902*	*0.044*	-	*0.820*	*0.992*

All outcomes were normalized for protein level using residuals and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models in larvae carrying two mutated alleles in *apoba* , *apobb.2* and *ldlrb*. 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 three 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 vascular atherogenic traits

		apoea														
		Vascular lipid deposition														
		Model 1					**Model 2**					**Model 3**				
		70 vs. 23 larvae with 2 vs. 0 mutated alleles					**63 vs. 20 larvae with 2 vs. 0 mutated alleles**					**63 vs. 20 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.119	0.373	7.49E-01	-0.851	0.612	-0.257	0.387	5.07E-01	-1.015	0.502	-0.443	0.366	2.27E-01	-1.161	0.275
	apoeb	0.093	0.226	6.79E-01	-0.349	0.536	-0.061	0.242	8.00E-01	-0.536	0.413	-0.065	0.349	8.53E-01	-0.749	0.619
	apobb.1	0.210	0.213	3.23E-01	-0.207	0.627	-0.166	0.271	5.39E-01	-0.697	0.365	0.077	0.265	7.71E-01	-0.442	0.595
	ldlra	0.386	0.175	2.78E-02	0.042	0.729	0.517	0.199	9.32E-03	0.127	0.907	0.244	0.246	3.21E-01	-0.238	0.725
	body length (in SD)	-	-	-	-	-	-0.214	0.252	3.95E-01	-0.708	0.279	-0.011	0.282	9.70E-01	-0.563	0.541
	dorsal body surface area (in SD)	-	-	-	-	-	0.706	0.330	3.24E-02	0.059	1.353	0.600	0.352	8.87E-02	-0.091	1.291
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.196	0.205	3.40E-01	-0.598	0.207
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.010	0.226	9.65E-01	-0.453	0.433
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.573	0.252	2.28E-02	0.080	1.066
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.022	0.379	9.53E-01	-0.721	0.766
	time of day (in hours since 9AM)	0.193	0.124	1.20E-01	-0.050	0.436	0.084	0.197	6.71E-01	-0.302	0.470	0.005	0.188	9.80E-01	-0.364	0.373
	batch 2	-1.148	0.736	1.19E-01	-2.591	0.296	-0.972	0.890	2.75E-01	-2.717	0.773	-0.953	1.449	5.11E-01	-3.793	1.886
	batch 3	-0.446	0.626	4.76E-01	-1.673	0.780	-0.499	0.709	4.82E-01	-1.890	0.891	-0.703	0.924	4.46E-01	-2.514	1.107
	batch 4	0.371	0.985	7.07E-01	-1.561	2.302	-0.356	1.048	7.34E-01	-2.411	1.698	-0.377	0.960	6.95E-01	-2.258	1.505
	batch 5	0.189	0.596	7.51E-01	-0.979	1.357	-0.144	0.737	8.45E-01	-1.589	1.300	-1.056	1.093	3.34E-01	-3.199	1.087
	batch 6	-0.302	0.587	6.08E-01	-1.452	0.849	-0.994	0.760	1.91E-01	-2.483	0.495	-1.886	1.146	9.97E-02	-4.132	0.360
	batch 7	-0.766	0.718	2.86E-01	-2.172	0.641	-0.955	0.812	2.39E-01	-2.547	0.636	-1.770	1.228	1.50E-01	-4.178	0.637
	intercept	3.556	0.693	2.85E-07	2.198	4.914	4.440	1.045	2.15E-05	2.392	6.488	5.325	1.254	2.16E-05	2.868	7.782

		Vascular infiltration by macrophages														
		80 vs. 32 larvae with 2 vs. 0 mutated alleles					**73 vs. 28 larvae with 2 vs. 0 mutated alleles**					**73 vs. 28 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.421	0.203	3.82E-02	0.023	0.819	0.334	0.214	1.19E-01	-0.086	0.754	0.341	0.210	1.04E-01	-0.070	0.752
	apoeb	0.312	0.138	2.41E-02	0.041	0.583	0.387	0.147	8.32E-03	0.100	0.674	0.379	0.146	9.53E-03	0.093	0.666
	apobb.1	-0.209	0.132	1.14E-01	-0.468	0.050	-0.252	0.141	7.30E-02	-0.528	0.024	-0.264	0.140	5.93E-02	-0.538	0.010
	ldlra	-0.017	0.108	8.74E-01	-0.229	0.194	-0.017	0.113	8.81E-01	-0.238	0.204	0.013	0.116	9.14E-01	-0.214	0.239
	body length (in SD)	-	-	-	-	-	-0.274	0.118	2.04E-02	-0.506	-0.042	-0.246	0.114	3.09E-02	-0.470	-0.023
	dorsal body surface area (in SD)	-	-	-	-	-	-0.027	0.101	7.89E-01	-0.226	0.171	0.017	0.104	8.67E-01	-0.187	0.222
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.036	0.092	6.99E-01	-0.217	0.145
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.217	0.099	2.86E-02	0.023	0.412
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.062	0.125	6.18E-01	-0.306	0.182
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.117	0.103	2.56E-01	-0.319	0.085
	time of day (in hours since 9AM)	0.071	0.067	2.87E-01	-0.060	0.202	0.070	0.074	3.48E-01	-0.076	0.215	0.090	0.071	2.07E-01	-0.050	0.229
	intercept_random	-0.665	0.361	6.57E-02	-1.373	0.043	-0.752	0.366	3.98E-02	-1.468	-0.035	-0.843	0.347	1.52E-02	-1.523	-0.162
random factors	***variance by batch***	*0.471*	*0.164*	-	*0.238*	*0.932*	*0.401*	*0.169*	-	*0.176*	*0.915*	*0.298*	*0.160*	-	*0.104*	*0.854*
	residual	*0.827*	*0.058*	-	*0.722*	*0.948*	*0.824*	*0.061*	-	*0.712*	*0.953*	*0.804*	*0.060*	-	*0.694*	*0.931*

		Vascular co-localization of lipids with macrophages														
		68 vs. 23 larvae with 2 vs. 0 mutated alleles					**61 vs. 20 larvae with 2 vs. 0 mutated alleles**					**61 vs. 20 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.380	0.430	3.76E-01	-0.462	1.222	0.168	0.433	6.98E-01	-0.681	1.018	0.033	0.415	9.37E-01	-0.781	0.846
	apoeb	0.001	0.286	9.98E-01	-0.560	0.562	0.166	0.309	5.90E-01	-0.439	0.772	0.679	0.374	6.92E-02	-0.053	1.411
	apobb.1	-0.066	0.443	8.81E-01	-0.934	0.801	-0.402	0.341	2.38E-01	-1.070	0.266	-0.507	0.329	1.24E-01	-1.153	0.139
	ldlra	0.586	0.275	3.35E-02	0.046	1.126	0.404	0.247	1.02E-01	-0.080	0.888	0.142	0.296	6.32E-01	-0.439	0.722
	body length (in SD)	-	-	-	-	-	-0.541	0.350	1.23E-01	-1.227	0.146	-0.859	0.413	3.75E-02	-1.669	-0.050
	dorsal body surface area (in SD)	-	-	-	-	-	0.836	0.370	2.37E-02	0.112	1.560	0.386	0.407	3.44E-01	-0.413	1.184
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.628	0.307	4.08E-02	-1.230	-0.026
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.505	0.309	1.03E-01	-0.101	1.112
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.376	0.380	3.23E-01	-0.370	1.121
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.987	0.449	2.81E-02	-1.867	-0.106
	time of day (in hours since 9AM)	0.205	0.180	2.56E-01	-0.148	0.557	0.218	0.226	3.34E-01	-0.224	0.661	0.373	0.246	1.29E-01	-0.108	0.854
	batch 2	-0.148	1.197	9.02E-01	-2.495	2.199	0.121	1.206	9.20E-01	-2.241	2.484	-2.841	1.797	1.14E-01	-6.362	0.681
	batch 3	-0.694	0.732	3.43E-01	-2.129	0.741	-0.711	0.765	3.53E-01	-2.211	0.790	-0.778	1.290	5.47E-01	-3.307	1.751
	batch 4	0.460	1.037	6.58E-01	-1.573	2.492	-0.489	0.997	6.24E-01	-2.443	1.465	-0.436	1.277	7.33E-01	-2.939	2.066
	batch 5	0.434	0.716	5.44E-01	-0.969	1.838	-0.336	0.806	6.77E-01	-1.915	1.243	-0.908	1.513	5.49E-01	-3.873	2.058
	batch 6	-0.847	0.898	3.46E-01	-2.606	0.913	-1.037	0.853	2.24E-01	-2.708	0.634	-1.016	1.540	5.09E-01	-4.034	2.001
	batch 7	-3.443	1.126	2.22E-03	-5.649	-1.237	-4.481	1.035	1.48E-05	-6.508	-2.453	-2.972	1.492	4.64E-02	-5.898	-0.047
	intercept	1.501	1.033	1.46E-01	-0.523	3.525	1.782	1.117	1.10E-01	-0.407	3.971	0.712	1.627	6.61E-01	-2.476	3.900

		Vascular infiltration by neutrophils														
		82 vs. 32 larvae with 2 vs. 0 mutated alleles					**75 vs. 28 larvae with 2 vs. 0 mutated alleles**					**75 vs. 28 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.037	0.204	8.58E-01	-0.437	0.364	-0.030	0.209	8.84E-01	-0.439	0.378	-0.048	0.207	8.15E-01	-0.455	0.358
	apoeb	0.058	0.139	6.77E-01	-0.214	0.330	0.126	0.142	3.75E-01	-0.152	0.403	0.159	0.143	2.65E-01	-0.121	0.439
	apobb.1	0.136	0.134	3.08E-01	-0.126	0.399	0.096	0.138	4.87E-01	-0.175	0.366	0.067	0.136	6.25E-01	-0.200	0.333
	ldlra	-0.145	0.110	1.86E-01	-0.359	0.070	-0.110	0.111	3.21E-01	-0.327	0.107	-0.097	0.113	3.90E-01	-0.320	0.125
	body length (in SD)	-	-	-	-	-	-0.280	0.112	1.23E-02	-0.500	-0.061	-0.249	0.110	2.41E-02	-0.465	-0.033
	dorsal body surface area (in SD)	-	-	-	-	-	0.120	0.097	2.15E-01	-0.070	0.311	0.189	0.102	6.26E-02	-0.010	0.389
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.017	0.087	8.43E-01	-0.153	0.188
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.072	0.098	4.66E-01	-0.121	0.264
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.183	0.119	1.24E-01	-0.417	0.050
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.140	0.101	1.69E-01	-0.339	0.059
	time of day (in hours since 9AM)	0.012	0.067	8.57E-01	-0.118	0.142	-0.021	0.072	7.75E-01	-0.161	0.120	-0.022	0.070	7.57E-01	-0.159	0.115
	intercept_random	0.002	0.352	9.96E-01	-0.688	0.691	-0.015	0.345	9.64E-01	-0.692	0.662	-0.098	0.341	7.73E-01	-0.766	0.569
random factors	***variance by batch***	*0.402*	*0.142*	-	*0.201*	*0.805*	*0.314*	*0.138*	-	*0.133*	*0.744*	*0.302*	*0.134*	-	*0.127*	*0.719*
	residual	*0.847*	*0.058*	-	*0.740*	*0.969*	*0.817*	*0.059*	-	*0.708*	*0.942*	*0.794*	*0.058*	-	*0.688*	*0.915*

		Vascular co-localization of lipids with neutrophils														
		66 vs. 23 larvae with 2 vs. 0 mutated alleles					**59 vs. 20 larvae with 2 vs. 0 mutated alleles**					**59 vs. 20 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.140	0.789	8.59E-01	-1.686	1.406	0.729	0.735	3.21E-01	-0.712	2.170	0.761	1.033	4.61E-01	-1.264	2.787
	apoeb	-0.337	0.552	5.41E-01	-1.419	0.745	-0.619	0.426	1.46E-01	-1.453	0.216	-1.291	0.511	1.15E-02	-2.292	-0.290
	apobb.1	1.307	0.547	1.68E-02	0.236	2.379	2.028	0.544	1.91E-04	0.963	3.094	2.399	0.616	9.86E-05	1.192	3.607
	ldlra	0.295	0.424	4.88E-01	-0.537	1.126	0.262	0.365	4.73E-01	-0.454	0.978	0.000	0.377	1.00E+00	-0.740	0.740
	body length (in SD)	-	-	-	-	-	-1.626	0.530	2.15E-03	-2.665	-0.588	-1.038	0.619	9.35E-02	-2.251	0.175
	dorsal body surface area (in SD)	-	-	-	-	-	-1.141	0.522	2.88E-02	-2.164	-0.118	-1.475	0.658	2.50E-02	-2.764	-0.185
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.692	0.482	1.51E-01	-1.636	0.252
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.937	0.562	9.57E-02	-0.165	2.038
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.525	0.473	1.26E-03	0.598	2.452
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.620	0.424	1.44E-01	-0.211	1.451
	time of day (in hours since 9AM)	0.618	0.245	1.17E-02	0.137	1.098	1.432	0.309	3.60E-06	0.826	2.038	1.187	0.395	2.68E-03	0.412	1.962
	batch 2	-2.088	1.503	1.65E-01	-5.033	0.858	1.298	1.702	4.46E-01	-2.039	4.635	2.820	2.384	2.37E-01	-1.852	7.492
	batch 3	-4.032	1.537	8.70E-03	-7.044	-1.020	-2.003	1.203	9.60E-02	-4.361	0.355	-0.267	1.932	8.90E-01	-4.053	3.518
	batch 4	-0.786	1.875	6.75E-01	-4.461	2.890	-0.654	1.810	7.18E-01	-4.201	2.894	1.016	2.299	6.58E-01	-3.490	5.522
	batch 5	-1.841	1.468	2.10E-01	-4.718	1.036	0.430	1.000	6.67E-01	-1.530	2.390	1.365	2.093	5.14E-01	-2.737	5.466
	batch 6	-5.464	1.673	1.09E-03	-8.743	-2.185	-28.393	1.571	5.46E-73	-31.473	-25.314	-25.452	2.698	4.00E-21	-30.741	-20.164
	intercept	0.343	1.639	8.34E-01	-2.870	3.556	-5.746	1.399	4.02E-05	-8.488	-3.003	-5.140	1.931	7.77E-03	-8.925	-1.356

		Vascular co-localization of macrophages with neutrophils														
		80 vs. 32 larvae with 2 vs. 0 mutated alleles					**73 vs. 28 larvae with 2 vs. 0 mutated alleles**					**73 vs. 28 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.094	0.376	8.03E-01	-0.832	0.644	-0.310	0.492	5.28E-01	-1.274	0.654	-0.625	0.546	2.53E-01	-1.695	0.446
	apoeb	0.415	0.198	3.59E-02	0.027	0.803	0.674	0.224	2.68E-03	0.234	1.114	0.850	0.242	4.40E-04	0.376	1.324
	apobb.1	0.113	0.188	5.47E-01	-0.255	0.482	0.170	0.227	4.52E-01	-0.274	0.615	0.069	0.242	7.77E-01	-0.405	0.543
	ldlra	-0.472	0.175	6.89E-03	-0.814	-0.130	-0.525	0.199	8.28E-03	-0.914	-0.135	-0.467	0.208	2.49E-02	-0.874	-0.059
	body length (in SD)	-	-	-	-	-	0.054	0.204	7.91E-01	-0.346	0.454	-0.004	0.177	9.82E-01	-0.352	0.344
	dorsal body surface area (in SD)	-	-	-	-	-	0.330	0.252	1.90E-01	-0.163	0.823	0.420	0.265	1.13E-01	-0.100	0.939
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.022	0.147	8.84E-01	-0.310	0.267
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.138	0.167	4.10E-01	-0.189	0.465
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.417	0.204	4.08E-02	-0.816	-0.017
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.499	0.200	1.26E-02	-0.891	-0.107
	time of day (in hours since 9AM)	0.138	0.113	2.21E-01	-0.083	0.359	-0.024	0.154	8.74E-01	-0.325	0.277	0.040	0.150	7.87E-01	-0.253	0.334
	batch 1	0.009	0.795	9.91E-01	-1.549	1.566	0.472	0.938	6.15E-01	-1.366	2.310	0.062	1.118	9.56E-01	-2.129	2.252
	batch 2	0.060	0.960	9.50E-01	-1.822	1.942	-0.121	0.965	9.00E-01	-2.011	1.770	-1.573	0.986	1.11E-01	-3.505	0.359
	batch 3	-1.499	0.910	9.96E-02	-3.283	0.285	-1.436	0.973	1.40E-01	-3.342	0.470	-1.990	1.006	4.80E-02	-3.961	-0.018
	batch 4	0.041	0.851	9.62E-01	-1.628	1.710	0.199	0.905	8.26E-01	-1.576	1.973	-0.060	0.959	9.50E-01	-1.940	1.819
	batch 5	-0.352	0.888	6.92E-01	-2.092	1.388	-0.472	1.042	6.50E-01	-2.514	1.569	-0.746	1.031	4.69E-01	-2.766	1.274
	batch 6	-2.060	0.887	2.03E-02	-3.799	-0.321	-2.972	1.177	1.16E-02	-5.279	-0.664	-2.635	1.187	2.65E-02	-4.962	-0.308
	batch 7	-1.515	1.048	1.48E-01	-3.569	0.538	-1.927	1.246	1.22E-01	-4.369	0.515	-1.460	1.324	2.70E-01	-4.056	1.135
	intercept	3.814	0.824	3.70E-06	2.198	5.429	4.015	0.906	9.38E-06	2.239	5.790	3.784	0.906	2.97E-05	2.008	5.560

continued **Supplementary Table 20**

		apoeb														
		Vascular lipid deposition														
		Model 1					**Model 2**					**Model 3**				
		20 vs. 143 larvae with 2 vs. 0 mutated alleles					**19 vs. 127 larvae with 2 vs. 0 mutated alleles**					**19 vs. 127 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.089	0.422	8.33E-01	-0.915	0.738	-0.226	0.433	6.01E-01	-1.076	0.623	-0.036	0.381	9.24E-01	-0.783	0.710
	apoea	0.000	0.199	9.98E-01	-0.391	0.390	-0.085	0.212	6.88E-01	-0.500	0.330	-0.136	0.211	5.19E-01	-0.550	0.277
	apobb.1	0.511	0.179	4.23E-03	0.161	0.861	0.423	0.188	2.45E-02	0.054	0.791	0.300	0.171	8.00E-02	-0.036	0.636
	ldlra	0.267	0.151	7.72E-02	-0.029	0.563	0.341	0.158	3.13E-02	0.030	0.651	0.415	0.149	5.49E-03	0.122	0.707
	body length (in SD)	-	-	-	-	-	-0.346	0.178	5.22E-02	-0.695	0.003	-0.216	0.182	2.34E-01	-0.573	0.140
	dorsal body surface area (in SD)	-	-	-	-	-	0.166	0.162	3.06E-01	-0.152	0.483	0.358	0.160	2.48E-02	0.046	0.671
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.142	0.112	2.04E-01	-0.361	0.077
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.018	0.161	9.10E-01	-0.297	0.334
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.537	0.197	6.50E-03	0.150	0.923
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.426	0.135	1.67E-03	-0.691	-0.160
	time of day (in hours since 9AM)	-0.101	0.111	3.59E-01	-0.318	0.115	-0.117	0.152	4.39E-01	-0.414	0.180	-0.235	0.144	1.01E-01	-0.517	0.046
	batch 2	-1.626	0.531	2.22E-03	-2.667	-0.584	-1.929	0.598	1.27E-03	-3.101	-0.756	-1.988	0.551	3.08E-04	-3.067	-0.908
	batch 3	-1.216	0.471	9.91E-03	-2.140	-0.292	-1.520	0.455	8.41E-04	-2.413	-0.628	-1.378	0.495	5.33E-03	-2.348	-0.409
	batch 4	-1.305	0.603	3.05E-02	-2.487	-0.123	-1.718	0.548	1.73E-03	-2.793	-0.643	-0.918	0.543	9.11E-02	-1.982	0.147
	batch 5	-0.253	0.363	4.86E-01	-0.965	0.458	-0.470	0.427	2.71E-01	-1.306	0.366	-1.024	0.564	6.95E-02	-2.129	0.082
	batch 6	0.038	0.467	9.34E-01	-0.876	0.953	-0.126	0.505	8.03E-01	-1.117	0.864	-1.103	0.588	6.07E-02	-2.256	0.049
	batch 7	-0.620	0.480	1.96E-01	-1.562	0.321	-0.602	0.584	3.03E-01	-1.747	0.543	-0.488	0.761	5.21E-01	-1.980	1.003
	intercept	5.150	0.643	1.16E-15	3.889	6.410	5.533	0.763	4.03E-13	4.038	7.028	5.887	0.843	2.80E-12	4.236	7.538

		Vascular infiltration by macrophages														
		26 vs. 183 larvae with 2 vs. 0 mutated alleles					**25 vs. 164 larvae with 2 vs. 0 mutated alleles**					**25 vs. 164 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.285	0.216	1.88E-01	-0.139	0.708	0.324	0.226	1.52E-01	-0.120	0.767	0.340	0.225	1.30E-01	-0.101	0.780
	apoea	-0.058	0.105	5.82E-01	-0.263	0.148	-0.074	0.113	5.13E-01	-0.296	0.148	-0.076	0.113	5.04E-01	-0.297	0.146
	apobb.1	-0.078	0.112	4.86E-01	-0.297	0.141	-0.054	0.119	6.51E-01	-0.288	0.180	-0.053	0.118	6.53E-01	-0.285	0.179
	ldlra	-0.067	0.082	4.17E-01	-0.228	0.095	-0.095	0.088	2.79E-01	-0.267	0.077	-0.094	0.088	2.83E-01	-0.266	0.078
	body length (in SD)	-	-	-	-	-	0.045	0.093	6.28E-01	-0.138	0.228	0.068	0.095	4.73E-01	-0.118	0.253
	dorsal body surface area (in SD)	-	-	-	-	-	-0.016	0.079	8.42E-01	-0.171	0.139	-0.003	0.079	9.74E-01	-0.158	0.153
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.018	0.073	8.09E-01	-0.125	0.160
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.186	0.086	3.15E-02	0.016	0.355
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.022	0.102	8.26E-01	-0.178	0.223
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.010	0.073	8.93E-01	-0.153	0.133
	time of day (in hours since 9AM)	0.047	0.054	3.84E-01	-0.059	0.152	0.030	0.061	6.21E-01	-0.090	0.151	0.040	0.061	5.14E-01	-0.080	0.159
	intercept_random	-0.294	0.323	3.63E-01	-0.926	0.339	-0.252	0.344	4.64E-01	-0.926	0.422	-0.297	0.337	3.79E-01	-0.958	0.364
random factors	***variance by batch***	*0.539*	*0.156*	-	*0.306*	*0.951*	*0.555*	*0.167*	-	*0.308*	*1.000*	*0.507*	*0.157*	-	*0.276*	*0.932*
	residual	*0.877*	*0.044*	-	*0.796*	*0.968*	*0.894*	*0.047*	-	*0.806*	*0.991*	*0.885*	*0.047*	-	*0.798*	*0.981*

		Vascular co-localization of lipids with macrophages														
		19 vs. 142 larvae with 2 vs. 0 mutated alleles					**18 vs. 126 larvae with 2 vs. 0 mutated alleles**					**18 vs. 126 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.204	0.555	7.13E-01	-0.883	1.291	0.098	0.588	8.67E-01	-1.053	1.250	0.821	0.560	1.43E-01	-0.276	1.918
	apoea	-0.292	0.223	1.91E-01	-0.730	0.146	-0.320	0.218	1.43E-01	-0.748	0.108	-0.384	0.268	1.52E-01	-0.910	0.141
	apobb.1	0.494	0.282	7.93E-02	-0.058	1.046	0.122	0.284	6.66E-01	-0.434	0.679	-0.330	0.263	2.10E-01	-0.846	0.186
	ldlra	0.349	0.204	8.67E-02	-0.050	0.748	0.530	0.204	9.18E-03	0.131	0.929	0.800	0.254	1.65E-03	0.302	1.298
	body length (in SD)	-	-	-	-	-	-0.693	0.236	3.29E-03	-1.155	-0.231	-0.486	0.256	5.73E-02	-0.988	0.015
	dorsal body surface area (in SD)	-	-	-	-	-	0.405	0.188	3.15E-02	0.036	0.773	0.580	0.230	1.16E-02	0.129	1.031
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.621	0.224	5.50E-03	-1.059	-0.182
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.172	0.287	5.49E-01	-0.390	0.735
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.729	0.325	2.49E-02	0.092	1.366
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.644	0.271	1.74E-02	-1.174	-0.113
	time of day (in hours since 9AM)	0.192	0.134	1.51E-01	-0.070	0.454	0.175	0.162	2.79E-01	-0.142	0.492	0.010	0.182	9.56E-01	-0.346	0.366
	batch 2	-0.634	0.867	4.64E-01	-2.333	1.065	-0.943	1.010	3.50E-01	-2.923	1.036	-3.196	0.975	1.05E-03	-5.108	-1.284
	batch 3	-1.078	0.526	4.05E-02	-2.108	-0.047	-1.697	0.524	1.19E-03	-2.724	-0.671	-1.796	0.862	3.72E-02	-3.487	-0.106
	batch 4	-0.222	0.703	7.53E-01	-1.600	1.157	-0.972	0.672	1.48E-01	-2.289	0.344	-0.379	0.959	6.93E-01	-2.258	1.501
	batch 5	-0.238	0.439	5.89E-01	-1.098	0.623	-0.780	0.537	1.46E-01	-1.833	0.273	-1.811	1.098	9.92E-02	-3.964	0.342
	batch 6	-0.450	0.523	3.90E-01	-1.475	0.576	-0.774	0.554	1.62E-01	-1.861	0.312	-3.320	1.180	4.91E-03	-5.633	-1.007
	batch 7	-1.403	1.067	1.89E-01	-3.494	0.689	-2.049	1.021	4.48E-02	-4.051	-0.048	-2.600	1.328	5.02E-02	-5.202	0.003
	intercept	1.575	0.819	5.44E-02	-0.030	3.180	1.994	0.825	1.57E-02	0.376	3.611	2.590	1.284	4.38E-02	0.072	5.107

		Vascular infiltration by neutrophils														
		27 vs. 184 larvae with 2 vs. 0 mutated alleles					**26 vs. 165 larvae with 2 vs. 0 mutated alleles**					**26 vs. 165 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.027	0.207	8.95E-01	-0.378	0.432	0.107	0.211	6.11E-01	-0.306	0.520	0.116	0.209	5.77E-01	-0.292	0.525
	apoea	-0.085	0.100	3.94E-01	-0.281	0.111	-0.042	0.105	6.90E-01	-0.247	0.164	-0.031	0.105	7.71E-01	-0.236	0.175
	apobb.1	0.162	0.108	1.32E-01	-0.049	0.373	0.217	0.112	5.24E-02	-0.002	0.436	0.222	0.110	4.46E-02	0.005	0.438
	ldlra	-0.009	0.079	9.13E-01	-0.164	0.147	-0.027	0.082	7.42E-01	-0.189	0.134	-0.014	0.082	8.64E-01	-0.175	0.147
	body length (in SD)	-	-	-	-	-	-0.046	0.083	5.78E-01	-0.210	0.117	0.001	0.084	9.87E-01	-0.163	0.166
	dorsal body surface area (in SD)	-	-	-	-	-	0.081	0.070	2.49E-01	-0.057	0.219	0.111	0.070	1.14E-01	-0.027	0.249
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.026	0.066	6.97E-01	-0.155	0.104
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.167	0.078	3.35E-02	0.013	0.320
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.085	0.084	3.09E-01	-0.250	0.079
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.076	0.067	2.59E-01	-0.056	0.207
	time of day (in hours since 9AM)	0.046	0.050	3.51E-01	-0.051	0.144	0.036	0.055	5.13E-01	-0.072	0.143	0.054	0.054	3.11E-01	-0.051	0.160
	intercept_random	-0.160	0.266	5.48E-01	-0.681	0.362	-0.215	0.275	4.33E-01	-0.753	0.323	-0.313	0.271	2.49E-01	-0.845	0.219
random factors	***variance by batch***	*0.289*	*0.100*	-	*0.146*	*0.570*	*0.261*	*0.103*	-	*0.120*	*0.566*	*0.202*	*0.089*	-	*0.085*	*0.480*
	residual	*0.852*	*0.042*	-	*0.773*	*0.938*	*0.846*	*0.044*	-	*0.763*	*0.937*	*0.837*	*0.044*	-	*0.756*	*0.927*

		Vascular co-localization of lipids with neutrophils														
		20 vs. 138 larvae with 2 vs. 0 mutated alleles					**19 vs. 122 larvae with 2 vs. 0 mutated alleles**					**19 vs. 122 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.641	1.196	5.92E-01	-2.985	1.703	-1.046	0.862	2.25E-01	-2.737	0.644	-0.932	0.948	3.26E-01	-2.789	0.926
	apoea	0.159	0.352	6.51E-01	-0.530	0.849	0.232	0.375	5.36E-01	-0.502	0.967	-0.590	0.608	3.31E-01	-1.781	0.601
	apobb.1	1.246	0.299	3.08E-05	0.660	1.832	1.324	0.344	1.20E-04	0.649	1.998	0.939	0.439	3.25E-02	0.078	1.800
	ldlra	0.157	0.325	6.30E-01	-0.481	0.794	0.573	0.302	5.77E-02	-0.019	1.164	0.514	0.307	9.44E-02	-0.088	1.117
	body length (in SD)	-	-	-	-	-	-1.738	0.380	4.92E-06	-2.483	-0.992	-1.259	0.454	5.56E-03	-2.148	-0.369
	dorsal body surface area (in SD)	-	-	-	-	-	-0.195	0.270	4.70E-01	-0.723	0.333	-0.149	0.302	6.21E-01	-0.742	0.443
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.019	0.312	9.51E-01	-0.631	0.593
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.470	0.526	3.71E-01	-0.561	1.501
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.573	0.498	1.60E-03	0.596	2.550
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.297	0.389	4.45E-01	-1.059	0.465
	time of day (in hours since 9AM)	-0.020	0.190	9.18E-01	-0.392	0.353	0.427	0.261	1.02E-01	-0.084	0.938	0.163	0.319	6.08E-01	-0.461	0.788
	batch 2	-1.868	0.943	4.75E-02	-3.715	-0.020	-1.496	1.211	2.17E-01	-3.869	0.877	-3.163	1.334	1.78E-02	-5.779	-0.548
	batch 3	-1.783	0.902	4.82E-02	-3.552	-0.014	-2.134	0.787	6.72E-03	-3.678	-0.591	-3.521	0.860	4.27E-05	-5.207	-1.835
	batch 4	-0.585	1.152	6.12E-01	-2.843	1.674	-2.068	0.939	2.76E-02	-3.908	-0.228	-1.018	1.455	4.84E-01	-3.869	1.834
	batch 5	-0.346	0.588	5.56E-01	-1.498	0.806	-0.349	0.671	6.03E-01	-1.664	0.965	-3.162	1.263	1.23E-02	-5.639	-0.686
	batch 6	1.311	0.853	1.24E-01	-0.360	2.983	0.450	0.874	6.07E-01	-1.263	2.163	-2.706	1.479	6.72E-02	-5.605	0.192
	intercept	1.119	1.283	3.83E-01	-1.395	3.633	-1.102	1.138	3.33E-01	-3.333	1.129	2.173	1.743	2.12E-01	-1.242	5.589

		Vascular co-localization of macrophages with neutrophils														
		26 vs. 183 larvae with 2 vs. 0 mutated alleles					**25 vs. 164 larvae with 2 vs. 0 mutated alleles**					**25 vs. 164 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.742	0.287	9.61E-03	0.180	1.304	0.790	0.296	7.57E-03	0.210	1.370	0.799	0.287	5.37E-03	0.236	1.361
	apoea	-0.047	0.136	7.31E-01	-0.313	0.219	-0.102	0.147	4.88E-01	-0.389	0.186	-0.091	0.150	5.47E-01	-0.385	0.204
	apobb.1	0.176	0.139	2.06E-01	-0.097	0.449	0.210	0.137	1.24E-01	-0.058	0.479	0.215	0.138	1.20E-01	-0.056	0.486
	ldlra	-0.346	0.116	2.92E-03	-0.573	-0.118	-0.313	0.112	5.22E-03	-0.533	-0.093	-0.315	0.112	4.94E-03	-0.535	-0.095
	body length (in SD)	-	-	-	-	-	0.317	0.136	1.99E-02	0.050	0.583	0.327	0.145	2.40E-02	0.043	0.611
	dorsal body surface area (in SD)	-	-	-	-	-	0.503	0.136	2.15E-04	0.237	0.770	0.504	0.147	6.09E-04	0.216	0.792
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.003	0.122	9.82E-01	-0.243	0.237
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.044	0.118	7.10E-01	-0.188	0.275
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.074	0.145	6.11E-01	-0.359	0.211
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.035	0.097	7.17E-01	-0.155	0.226
	time of day (in hours since 9AM)	0.162	0.073	2.74E-02	0.018	0.306	0.080	0.088	3.60E-01	-0.091	0.252	0.082	0.091	3.69E-01	-0.097	0.261
	batch 1	0.966	0.603	1.09E-01	-0.216	2.148	0.975	0.650	1.33E-01	-0.298	2.248	0.888	0.669	1.84E-01	-0.423	2.199
	batch 2	1.081	0.708	1.27E-01	-0.308	2.469	1.282	0.716	7.34E-02	-0.121	2.686	1.188	0.708	9.35E-02	-0.200	2.576
	batch 3	-0.081	0.647	9.00E-01	-1.348	1.186	0.047	0.689	9.45E-01	-1.303	1.397	0.011	0.725	9.88E-01	-1.411	1.432
	batch 4	1.363	0.623	2.87E-02	0.142	2.584	1.543	0.647	1.70E-02	0.276	2.811	1.470	0.688	3.26E-02	0.122	2.818
	batch 5	0.790	0.600	1.88E-01	-0.386	1.966	0.405	0.644	5.30E-01	-0.858	1.668	0.473	0.697	4.98E-01	-0.894	1.840
	batch 6	-0.497	0.649	4.44E-01	-1.768	0.775	-1.269	0.697	6.85E-02	-2.635	0.096	-1.168	0.766	1.27E-01	-2.670	0.333
	batch 7	0.492	0.726	4.97E-01	-0.930	1.915	-0.381	0.826	6.44E-01	-2.000	1.237	-0.326	0.947	7.30E-01	-2.183	1.530
	intercept	2.323	0.636	2.58E-04	1.077	3.568	2.700	0.669	5.50E-05	1.388	4.012	2.673	0.675	7.39E-05	1.351	3.996

continued **Supplementary Table 20**

		apobb.1														
		Vascular lipid deposition														
		Model 1					**Model 2**					**Model 3**				
		90 vs. 13 larvae with 2 vs. 0 mutated alleles					**81 vs. 12 larvae with 2 vs. 0 mutated alleles**					**81 vs. 12 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.839	0.499	9.24E-02	-0.138	1.817	0.834	0.702	2.34E-01	-0.541	2.209	0.486	0.582	4.04E-01	-0.655	1.627
	apoea	0.366	0.314	2.45E-01	-0.250	0.981	0.363	0.396	3.59E-01	-0.413	1.139	0.207	0.306	4.99E-01	-0.393	0.807
	apoeb	-0.191	0.337	5.71E-01	-0.851	0.469	0.010	0.373	9.79E-01	-0.722	0.742	-0.042	0.311	8.92E-01	-0.652	0.567
	ldlra	0.453	0.254	7.40E-02	-0.044	0.950	0.346	0.289	2.31E-01	-0.220	0.913	0.363	0.257	1.57E-01	-0.140	0.867
	body length (in SD)	-	-	-	-	-	0.013	0.241	9.58E-01	-0.460	0.485	0.294	0.232	2.05E-01	-0.160	0.747
	dorsal body surface area (in SD)	-	-	-	-	-	0.414	0.345	2.31E-01	-0.263	1.091	0.464	0.324	1.52E-01	-0.170	1.099
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.383	0.217	7.73E-02	-0.807	0.042
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.153	0.238	5.21E-01	-0.620	0.314
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.788	0.267	3.21E-03	0.264	1.312
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.646	0.198	1.13E-03	-1.034	-0.257
	time of day (in hours since 9AM)	-0.150	0.141	2.86E-01	-0.426	0.126	-0.251	0.220	2.53E-01	-0.682	0.180	-0.306	0.173	7.65E-02	-0.645	0.033
	batch 2	-1.805	0.878	3.97E-02	-3.525	-0.085	-2.008	1.161	8.38E-02	-4.285	0.268	-1.959	0.772	1.11E-02	-3.472	-0.447
	batch 3	-1.713	0.986	8.24E-02	-3.646	0.220	-1.816	1.217	1.36E-01	-4.200	0.569	-2.017	0.715	4.76E-03	-3.418	-0.616
	batch 4	-0.586	1.034	5.71E-01	-2.612	1.441	-0.803	1.304	5.38E-01	-3.358	1.752	-0.626	0.802	4.35E-01	-2.198	0.946
	batch 5	-0.340	0.695	6.25E-01	-1.702	1.023	-0.784	0.977	4.22E-01	-2.698	1.131	-1.569	0.677	2.06E-02	-2.896	-0.241
	batch 6	-0.003	0.855	9.98E-01	-1.678	1.673	-0.111	1.211	9.27E-01	-2.484	2.262	-1.083	0.837	1.95E-01	-2.724	0.557
	batch 7	-1.265	1.007	2.09E-01	-3.239	0.710	-1.813	1.309	1.66E-01	-4.378	0.752	-2.130	0.864	1.37E-02	-3.822	-0.437
	intercept	5.420	1.278	2.22E-05	2.915	7.924	5.873	1.680	4.74E-04	2.580	9.166	6.483	1.167	2.75E-08	4.196	8.769

		Vascular infiltration by macrophages														
		113 vs. 17 larvae with 2 vs. 0 mutated alleles					**104 vs. 16 larvae with 2 vs. 0 mutated alleles**					**104 vs. 16 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.140	0.232	5.47E-01	-0.315	0.596	0.210	0.255	4.09E-01	-0.289	0.709	0.258	0.254	3.10E-01	-0.240	0.756
	apoea	0.050	0.133	7.05E-01	-0.211	0.312	0.046	0.143	7.47E-01	-0.234	0.326	0.024	0.141	8.65E-01	-0.253	0.300
	apoeb	0.185	0.125	1.40E-01	-0.061	0.431	0.178	0.133	1.79E-01	-0.081	0.438	0.185	0.130	1.55E-01	-0.070	0.440
	ldlra	-0.100	0.107	3.51E-01	-0.310	0.110	-0.111	0.113	3.24E-01	-0.332	0.110	-0.079	0.113	4.85E-01	-0.301	0.143
	body length (in SD)	-	-	-	-	-	-0.011	0.114	9.25E-01	-0.234	0.213	0.008	0.114	9.42E-01	-0.215	0.231
	dorsal body surface area (in SD)	-	-	-	-	-	-0.219	0.108	4.19E-02	-0.430	-0.008	-0.169	0.111	1.28E-01	-0.387	0.049
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.062	0.095	5.15E-01	-0.125	0.249
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.151	0.115	1.87E-01	-0.073	0.376
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.125	0.127	3.26E-01	-0.375	0.125
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.171	0.097	7.90E-02	-0.020	0.362
	time of day (in hours since 9AM)	0.021	0.067	7.53E-01	-0.111	0.153	0.016	0.075	8.33E-01	-0.131	0.162	0.020	0.074	7.88E-01	-0.124	0.164
	intercept_random	-0.170	0.351	6.28E-01	-0.859	0.518	-0.154	0.364	6.73E-01	-0.867	0.559	-0.197	0.352	5.76E-01	-0.887	0.493
random factors	***variance by batch***	*0.470*	*0.160*	-	*0.241*	*0.914*	*0.418*	*0.161*	-	*0.197*	*0.889*	*0.323*	*0.147*	-	*0.132*	*0.788*
	residual	*0.874*	*0.056*	-	*0.771*	*0.991*	*0.889*	*0.060*	-	*0.779*	*1.014*	*0.877*	*0.059*	-	*0.769*	*1.001*

		Vascular co-localization of lipids with macrophages														
		88 vs. 13 larvae with 2 vs. 0 mutated alleles					**79 vs. 12 larvae with 2 vs. 0 mutated alleles**					**79 vs. 12 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	1.156	0.769	1.33E-01	-0.351	2.664	0.878	0.791	2.67E-01	-0.672	2.429	0.378	0.645	5.58E-01	-0.887	1.643
	apoea	-0.134	0.401	7.38E-01	-0.920	0.652	-0.312	0.424	4.62E-01	-1.143	0.519	0.025	0.304	9.34E-01	-0.571	0.621
	apoeb	0.069	0.459	8.81E-01	-0.831	0.968	0.620	0.662	3.49E-01	-0.677	1.917	0.127	0.352	7.19E-01	-0.564	0.817
	ldlra	0.549	0.327	9.30E-02	-0.092	1.190	0.262	0.449	5.59E-01	-0.618	1.143	0.691	0.298	2.06E-02	0.106	1.276
	body length (in SD)	-	-	-	-	-	-0.190	0.454	6.76E-01	-1.079	0.700	0.737	0.397	6.32E-02	-0.040	1.514
	dorsal body surface area (in SD)	-	-	-	-	-	0.807	0.551	1.43E-01	-0.274	1.888	1.042	0.499	3.67E-02	0.064	2.019
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-1.397	0.353	7.53E-05	-2.088	-0.705
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.057	0.352	8.70E-01	-0.747	0.632
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.161	0.470	7.32E-01	-0.759	1.081
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.231	0.375	5.38E-01	-0.965	0.504
	time of day (in hours since 9AM)	0.044	0.197	8.24E-01	-0.342	0.430	-0.073	0.309	8.15E-01	-0.679	0.534	-0.156	0.254	5.38E-01	-0.654	0.341
	batch 2	-0.654	1.322	6.21E-01	-3.246	1.938	-0.979	1.169	4.02E-01	-3.271	1.313	-3.004	0.989	2.39E-03	-4.943	-1.066
	batch 3	-1.443	1.182	2.22E-01	-3.760	0.873	-1.243	1.016	2.21E-01	-3.234	0.749	-2.620	1.137	2.12E-02	-4.848	-0.392
	batch 4	1.149	1.182	3.31E-01	-1.168	3.467	0.535	1.539	7.28E-01	-2.481	3.552	-0.019	1.043	9.85E-01	-2.064	2.025
	batch 5	-0.656	0.928	4.80E-01	-2.476	1.164	-2.090	1.050	4.64E-02	-4.147	-0.033	-2.500	1.438	8.22E-02	-5.319	0.319
	batch 6	-0.202	1.049	8.47E-01	-2.258	1.854	-0.669	1.002	5.04E-01	-2.632	1.295	-1.333	1.802	4.60E-01	-4.865	2.199
	batch 7	-0.460	1.042	6.59E-01	-2.501	1.582	-1.453	1.033	1.60E-01	-3.478	0.572	-2.518	1.401	7.23E-02	-5.265	0.228
	intercept	1.948	1.735	2.62E-01	-1.453	5.348	2.476	1.501	9.91E-02	-0.466	5.418	3.800	2.000	5.75E-02	-0.121	7.720

		Vascular infiltration by neutrophils														
		115 vs. 17 larvae with 2 vs. 0 mutated alleles					**106 vs. 16 larvae with 2 vs. 0 mutated alleles**					**106 vs. 16 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	0.542	0.213	1.10E-02	0.124	0.960	0.623	0.226	5.92E-03	0.179	1.067	0.634	0.226	4.95E-03	0.192	1.076
	apoea	-0.036	0.121	7.64E-01	-0.272	0.200	-0.053	0.125	6.70E-01	-0.299	0.192	-0.051	0.125	6.87E-01	-0.296	0.195
	apoeb	0.160	0.114	1.63E-01	-0.064	0.384	0.261	0.117	2.57E-02	0.032	0.490	0.258	0.115	2.53E-02	0.032	0.483
	ldlra	-0.160	0.098	1.04E-01	-0.352	0.033	-0.194	0.100	5.31E-02	-0.391	0.003	-0.161	0.100	1.09E-01	-0.357	0.036
	body length (in SD)	-	-	-	-	-	-0.078	0.100	4.37E-01	-0.275	0.119	-0.053	0.100	5.95E-01	-0.249	0.143
	dorsal body surface area (in SD)	-	-	-	-	-	0.183	0.094	5.22E-02	-0.002	0.368	0.218	0.097	2.56E-02	0.027	0.409
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.054	0.080	5.03E-01	-0.211	0.104
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.044	0.102	6.66E-01	-0.156	0.245
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.227	0.112	4.39E-02	-0.447	-0.006
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.091	0.087	2.95E-01	-0.079	0.261
	time of day (in hours since 9AM)	-0.065	0.061	2.90E-01	-0.184	0.055	-0.125	0.066	6.03E-02	-0.255	0.005	-0.113	0.065	8.40E-02	-0.241	0.015
	intercept_random	0.139	0.313	6.56E-01	-0.474	0.753	0.222	0.322	4.92E-01	-0.410	0.853	0.114	0.318	7.19E-01	-0.509	0.738
random factors	***variance by batch***	*0.391*	*0.131*	-	*0.202*	*0.754*	*0.376*	*0.139*	-	*0.182*	*0.777*	*0.327*	*0.128*	-	*0.152*	*0.705*
	residual	*0.804*	*0.051*	-	*0.710*	*0.911*	*0.791*	*0.053*	-	*0.694*	*0.901*	*0.779*	*0.052*	-	*0.684*	*0.887*

		Vascular co-localization of lipids with neutrophils														
		88 vs. 13 larvae with 2 vs. 0 mutated alleles					**79 vs. 12 larvae with 2 vs. 0 mutated alleles**					**79 vs. 12 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	4.029	0.521	1.04E-14	3.008	5.050	4.405	0.816	6.70E-08	2.806	6.004	4.828	1.103	1.20E-05	2.666	6.989
	apoea	-1.083	0.428	1.14E-02	-1.921	-0.244	-1.173	0.757	1.22E-01	-2.657	0.312	-0.642	0.523	2.20E-01	-1.667	0.383
	apoeb	0.551	0.397	1.65E-01	-0.226	1.329	0.059	0.552	9.15E-01	-1.023	1.141	-0.292	0.456	5.22E-01	-1.186	0.602
	ldlra	0.540	0.353	1.26E-01	-0.151	1.232	0.329	0.420	4.34E-01	-0.495	1.152	0.350	0.454	4.40E-01	-0.538	1.239
	body length (in SD)	-	-	-	-	-	-1.572	0.590	7.70E-03	-2.727	-0.416	-1.035	0.532	5.15E-02	-2.077	0.007
	dorsal body surface area (in SD)	-	-	-	-	-	-0.917	0.600	1.27E-01	-2.093	0.260	-0.950	0.745	2.02E-01	-2.410	0.509
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-1.115	0.426	8.83E-03	-1.949	-0.280
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-1.095	0.578	5.81E-02	-2.228	0.037
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.304	0.696	6.62E-01	-1.060	1.669
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.255	0.396	5.19E-01	-0.520	1.030
	time of day (in hours since 9AM)	-0.361	0.172	3.58E-02	-0.698	-0.024	0.735	0.420	8.01E-02	-0.088	1.559	0.260	0.367	4.79E-01	-0.459	0.979
	batch 2	-2.529	0.792	1.41E-03	-4.082	-0.976	-2.049	1.316	1.20E-01	-4.629	0.531	-2.542	1.614	1.15E-01	-5.707	0.622
	batch 3	-4.658	0.819	1.28E-08	-6.263	-3.053	-5.569	1.240	7.02E-06	-7.999	-3.140	-5.928	1.548	1.29E-04	-8.962	-2.893
	batch 4	2.760	0.954	3.81E-03	0.890	4.630	-0.060	1.831	9.74E-01	-3.649	3.530	-0.909	1.811	6.16E-01	-4.459	2.641
	batch 5	-1.116	0.581	5.45E-02	-2.254	0.021	-2.926	1.143	1.05E-02	-5.167	-0.686	-3.596	1.547	2.01E-02	-6.628	-0.564
	batch 6	1.246	0.729	8.74E-02	-0.183	2.674	0.949	0.973	3.30E-01	-0.959	2.857	-0.599	1.929	7.56E-01	-4.380	3.182
	intercept	1.122	0.981	2.53E-01	-0.802	3.045	-1.484	1.706	3.85E-01	-4.828	1.860	1.124	2.387	6.38E-01	-3.555	5.803

		Vascular co-localization of macrophages with neutrophils														
		113 vs. 17 larvae with 2 vs. 0 mutated alleles					**104 vs. 16 larvae with 2 vs. 0 mutated alleles**					**104 vs. 16 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.615	0.265	2.02E-02	0.096	1.134	0.833	0.269	1.95E-03	0.306	1.361	0.784	0.264	3.00E-03	0.266	1.301
	apoea	-0.119	0.192	5.34E-01	-0.496	0.257	-0.217	0.218	3.20E-01	-0.644	0.210	-0.255	0.206	2.15E-01	-0.659	0.149
	apoeb	0.376	0.155	1.54E-02	0.072	0.681	0.475	0.162	3.31E-03	0.158	0.791	0.404	0.161	1.23E-02	0.088	0.720
	ldlra	-0.393	0.132	2.88E-03	-0.651	-0.134	-0.446	0.130	6.34E-04	-0.701	-0.190	-0.415	0.137	2.45E-03	-0.683	-0.146
	body length (in SD)	-	-	-	-	-	0.276	0.161	8.69E-02	-0.040	0.591	0.234	0.158	1.40E-01	-0.077	0.544
	dorsal body surface area (in SD)	-	-	-	-	-	0.424	0.213	4.62E-02	0.007	0.842	0.381	0.213	7.33E-02	-0.036	0.798
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.042	0.157	7.89E-01	-0.349	0.265
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.207	0.170	2.22E-01	-0.540	0.125
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.383	0.165	2.03E-02	-0.706	-0.060
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.008	0.135	9.52E-01	-0.274	0.257
	time of day (in hours since 9AM)	0.141	0.090	1.18E-01	-0.036	0.317	0.020	0.103	8.44E-01	-0.182	0.222	0.023	0.098	8.11E-01	-0.169	0.216
	batch 1	-1.012	0.804	2.09E-01	-2.588	0.565	-0.849	0.852	3.19E-01	-2.518	0.820	-0.977	0.880	2.67E-01	-2.703	0.748
	batch 2	-0.926	0.880	2.92E-01	-2.651	0.798	-1.015	0.876	2.47E-01	-2.733	0.702	-1.247	0.895	1.64E-01	-3.001	0.508
	batch 3	-2.270	0.818	5.54E-03	-3.874	-0.666	-2.309	0.848	6.48E-03	-3.971	-0.646	-2.458	0.853	3.94E-03	-4.129	-0.787
	batch 4	-0.373	0.789	6.37E-01	-1.919	1.174	-0.280	0.810	7.29E-01	-1.869	1.308	-0.386	0.804	6.31E-01	-1.962	1.191
	batch 5	-1.315	0.790	9.59E-02	-2.864	0.233	-1.795	0.856	3.60E-02	-3.472	-0.117	-1.365	0.861	1.13E-01	-3.052	0.322
	batch 6	-2.655	0.806	9.80E-04	-4.234	-1.076	-3.619	0.869	3.10E-05	-5.322	-1.916	-3.241	0.869	1.91E-04	-4.943	-1.539
	batch 7	-1.617	0.987	1.01E-01	-3.552	0.318	-2.300	1.129	4.16E-02	-4.512	-0.088	-2.423	1.140	3.36E-02	-4.658	-0.188
	intercept	4.589	0.858	8.78E-08	2.908	6.270	5.197	0.922	1.75E-08	3.389	7.004	5.144	0.896	9.60E-09	3.387	6.901

continued **Supplementary Table 20**

		ldlrb														
		Vascular lipid deposition														
		Model 1					**Model 2**					**Model 3**				
		62 vs. 109 larvae with 2 vs. 0 mutated alleles					**58 vs. 93 larvae with 2 vs. 0 mutated alleles**					**58 vs. 93 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.670	0.280	1.68E-02	0.121	1.220	0.787	0.297	8.02E-03	0.205	1.368	0.657	0.277	1.76E-02	0.115	1.200
	apoea	0.354	0.194	6.75E-02	-0.025	0.733	0.228	0.190	2.30E-01	-0.144	0.599	0.066	0.177	7.07E-01	-0.280	0.412
	apoeb	-0.257	0.208	2.16E-01	-0.665	0.150	-0.227	0.197	2.49E-01	-0.614	0.159	-0.149	0.202	4.62E-01	-0.545	0.248
	apobb.1	0.187	0.187	3.19E-01	-0.181	0.554	0.057	0.210	7.85E-01	-0.354	0.469	0.065	0.190	7.31E-01	-0.307	0.437
	body length (in SD)	-	-	-	-	-	-0.401	0.155	9.89E-03	-0.706	-0.096	-0.224	0.143	1.18E-01	-0.504	0.057
	dorsal body surface area (in SD)	-	-	-	-	-	0.212	0.186	2.55E-01	-0.153	0.577	0.325	0.170	5.57E-02	-0.008	0.658
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.098	0.113	3.86E-01	-0.318	0.123
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.033	0.179	8.53E-01	-0.317	0.383
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.620	0.197	1.64E-03	0.234	1.006
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.264	0.153	8.44E-02	-0.564	0.036
	time of day (in hours since 9AM)	0.030	0.117	7.98E-01	-0.200	0.260	-0.076	0.136	5.76E-01	-0.343	0.191	-0.133	0.126	2.90E-01	-0.380	0.114
	batch 2	-2.357	0.552	1.94E-05	-3.439	-1.276	-2.818	0.645	1.27E-05	-4.083	-1.553	-2.289	0.638	3.36E-04	-3.540	-1.038
	batch 3	-1.619	0.418	1.07E-04	-2.438	-0.800	-1.798	0.446	5.51E-05	-2.672	-0.924	-1.905	0.497	1.27E-04	-2.879	-0.931
	batch 4	-1.219	0.766	1.12E-01	-2.721	0.284	-1.954	0.618	1.56E-03	-3.164	-0.743	-1.801	0.531	6.93E-04	-2.841	-0.760
	batch 5	-0.469	0.367	2.01E-01	-1.188	0.250	-0.876	0.440	4.65E-02	-1.738	-0.014	-1.537	0.608	1.14E-02	-2.728	-0.346
	batch 6	-0.351	0.464	4.50E-01	-1.259	0.558	-0.372	0.555	5.03E-01	-1.460	0.716	-1.369	0.739	6.39E-02	-2.817	0.079
	batch 7	-1.027	0.508	4.33E-02	-2.024	-0.031	-0.914	0.618	1.39E-01	-2.126	0.298	-1.293	0.768	9.22E-02	-2.798	0.212
	intercept	5.142	0.645	1.61E-15	3.877	6.407	5.717	0.752	2.83E-14	4.244	7.190	6.271	0.804	6.13E-15	4.695	7.846
		Vascular infiltration by macrophages														
		81 vs. 135 larvae with 2 vs. 0 mutated alleles					**75 vs. 117 larvae with 2 vs. 0 mutated alleles**					**75 vs. 117 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.081	0.144	5.74E-01	-0.364	0.202	-0.147	0.156	3.46E-01	-0.453	0.159	-0.165	0.155	2.87E-01	-0.470	0.139
	apoea	0.071	0.100	4.77E-01	-0.125	0.266	0.029	0.109	7.94E-01	-0.186	0.243	0.022	0.109	8.36E-01	-0.190	0.235
	apoeb	0.090	0.105	3.90E-01	-0.116	0.296	0.122	0.113	2.78E-01	-0.099	0.344	0.135	0.111	2.24E-01	-0.083	0.352
	apobb.1	-0.106	0.104	3.08E-01	-0.311	0.098	-0.085	0.112	4.49E-01	-0.304	0.135	-0.085	0.110	4.40E-01	-0.300	0.130
	body length (in SD)	-	-	-	-	-	0.010	0.093	9.14E-01	-0.172	0.193	0.028	0.095	7.66E-01	-0.157	0.213
	dorsal body surface area (in SD)	-	-	-	-	-	0.007	0.077	9.29E-01	-0.144	0.158	0.024	0.077	7.53E-01	-0.126	0.174
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.048	0.071	4.98E-01	-0.091	0.187
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.205	0.087	1.84E-02	0.035	0.376
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.084	0.106	4.27E-01	-0.123	0.291
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.091	0.077	2.36E-01	-0.241	0.059
	time of day (in hours since 9AM)	0.008	0.052	8.86E-01	-0.095	0.110	-0.018	0.059	7.58E-01	-0.135	0.098	0.000	0.058	9.95E-01	-0.115	0.114
	intercept_random	-0.146	0.305	6.32E-01	-0.743	0.451	-0.063	0.324	8.46E-01	-0.699	0.573	-0.112	0.318	7.25E-01	-0.736	0.512
random factors	***variance by batch***	*0.486*	*0.144*	-	*0.272*	*0.868*	*0.501*	*0.157*	-	*0.271*	*0.926*	*0.477*	*0.154*	-	*0.253*	*0.898*
	residual	*0.879*	*0.043*	-	*0.798*	*0.967*	*0.902*	*0.047*	-	*0.815*	*1.000*	*0.884*	*0.046*	-	*0.798*	*0.980*
		Vascular co-localization of lipids with macrophages														
		61 vs. 108 larvae with 2 vs. 0 mutated alleles					**57 vs. 92 larvae with 2 vs. 0 mutated alleles**					**57 vs. 92 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	0.821	0.366	2.48E-02	0.104	1.538	0.811	0.355	2.21E-02	0.116	1.506	0.800	0.374	3.24E-02	0.067	1.533
	apoea	0.144	0.212	4.96E-01	-0.271	0.560	0.043	0.210	8.37E-01	-0.369	0.456	-0.009	0.206	9.66E-01	-0.413	0.395
	apoeb	0.098	0.237	6.80E-01	-0.368	0.563	0.147	0.272	5.90E-01	-0.387	0.680	0.408	0.249	1.01E-01	-0.080	0.895
	apobb.1	0.240	0.284	3.98E-01	-0.317	0.798	-0.176	0.252	4.86E-01	-0.669	0.318	-0.232	0.244	3.40E-01	-0.710	0.245
	body length (in SD)	-	-	-	-	-	-0.788	0.234	7.40E-04	-1.246	-0.330	-0.624	0.211	3.15E-03	-1.038	-0.210
	dorsal body surface area (in SD)	-	-	-	-	-	0.382	0.197	5.17E-02	-0.003	0.768	0.462	0.189	1.46E-02	0.091	0.833
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.157	0.174	3.67E-01	-0.499	0.184
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.443	0.234	5.84E-02	-0.016	0.901
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.555	0.263	3.50E-02	0.039	1.071
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.276	0.198	1.62E-01	-0.663	0.111
	time of day (in hours since 9AM)	0.187	0.143	1.92E-01	-0.094	0.468	0.061	0.160	7.05E-01	-0.254	0.375	0.080	0.151	5.94E-01	-0.215	0.376
	batch 2	-3.331	0.605	3.60E-08	-4.516	-2.146	-4.385	0.776	1.58E-08	-5.906	-2.865	-4.025	0.763	1.30E-07	-5.519	-2.530
	batch 3	-1.124	0.492	2.24E-02	-2.089	-0.160	-1.433	0.523	6.09E-03	-2.457	-0.409	-0.962	0.674	1.54E-01	-2.283	0.359
	batch 4	0.155	0.853	8.56E-01	-1.517	1.827	-1.279	0.639	4.52E-02	-2.530	-0.027	-0.783	0.796	3.25E-01	-2.344	0.777
	batch 5	-0.358	0.461	4.37E-01	-1.261	0.546	-0.777	0.540	1.50E-01	-1.835	0.282	-0.979	0.852	2.50E-01	-2.649	0.691
	batch 6	-0.769	0.509	1.31E-01	-1.766	0.229	-0.775	0.569	1.74E-01	-1.891	0.341	-1.279	0.950	1.78E-01	-3.141	0.582
	batch 7	-1.852	0.937	4.81E-02	-3.688	-0.016	-2.092	0.881	1.76E-02	-3.819	-0.364	-1.573	1.123	1.61E-01	-3.773	0.627
	intercept	1.539	0.766	4.44E-02	0.038	3.040	2.383	0.860	5.57E-03	0.698	4.068	1.845	1.027	7.26E-02	-0.169	3.859
		Vascular infiltration by neutrophils														
		82 vs. 136 larvae with 2 vs. 0 mutated alleles					**76 vs. 118 larvae with 2 vs. 0 mutated alleles**					**76 vs. 118 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	**2 vs. 0 mutated alleles**	-0.083	0.141	5.56E-01	-0.360	0.194	-0.083	0.146	5.69E-01	-0.368	0.203	-0.066	0.147	6.51E-01	-0.354	0.221
	apoea	-0.070	0.096	4.66E-01	-0.259	0.119	-0.060	0.100	5.48E-01	-0.257	0.136	-0.048	0.102	6.35E-01	-0.247	0.151
	apoeb	0.050	0.102	6.22E-01	-0.150	0.251	0.127	0.104	2.25E-01	-0.078	0.331	0.115	0.104	2.69E-01	-0.089	0.319
	apobb.1	0.149	0.102	1.43E-01	-0.051	0.348	0.147	0.104	1.56E-01	-0.056	0.351	0.154	0.103	1.37E-01	-0.049	0.356
	body length (in SD)	-	-	-	-	-	-0.185	0.083	2.54E-02	-0.348	-0.023	-0.146	0.086	8.90E-02	-0.315	0.022
	dorsal body surface area (in SD)	-	-	-	-	-	0.050	0.069	4.64E-01	-0.084	0.184	0.073	0.070	2.98E-01	-0.064	0.209
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.002	0.065	9.72E-01	-0.130	0.125
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.012	0.081	8.77E-01	-0.146	0.170
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.144	0.092	1.16E-01	-0.324	0.036
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.005	0.072	9.49E-01	-0.145	0.136
	time of day (in hours since 9AM)	-0.017	0.050	7.29E-01	-0.115	0.080	-0.047	0.053	3.78E-01	-0.151	0.057	-0.044	0.054	4.08E-01	-0.149	0.061
	intercept_random	0.042	0.267	8.76E-01	-0.483	0.566	0.005	0.266	9.85E-01	-0.516	0.526	-0.027	0.268	9.18E-01	-0.553	0.498
random factors	***variance by batch***	*0.318*	*0.103*	-	*0.168*	*0.601*	*0.267*	*0.098*	-	*0.130*	*0.547*	*0.256*	*0.093*	-	*0.125*	*0.523*
	residual	*0.864*	*0.042*	-	*0.785*	*0.950*	*0.847*	*0.044*	-	*0.765*	*0.937*	*0.841*	*0.043*	-	*0.760*	*0.931*
		Vascular co-localization of lipids with neutrophils														
		61 vs. 104 larvae with 2 vs. 0 mutated alleles					**57 vs. 88 larvae with 2 vs. 0 mutated alleles**					**57 vs. 88 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	1.172	0.511	2.19E-02	0.170	2.173	1.562	0.553	4.76E-03	0.478	2.647	0.963	0.582	9.78E-02	-0.177	2.104
	apoea	-0.891	0.380	1.90E-02	-1.635	-0.146	-0.646	0.374	8.40E-02	-1.379	0.087	-0.796	0.430	6.43E-02	-1.639	0.047
	apoeb	-0.373	0.365	3.07E-01	-1.090	0.343	-0.660	0.349	5.85E-02	-1.345	0.024	-0.783	0.379	3.87E-02	-1.525	-0.041
	apobb.1	1.452	0.307	2.33E-06	0.849	2.055	1.804	0.352	2.91E-07	1.115	2.493	1.762	0.347	3.83E-07	1.082	2.443
	body length (in SD)	-	-	-	-	-	-1.379	0.275	5.24E-07	-1.918	-0.841	-1.382	0.291	2.06E-06	-1.953	-0.812
	dorsal body surface area (in SD)	-	-	-	-	-	-0.270	0.247	2.74E-01	-0.753	0.213	-0.447	0.229	5.05E-02	-0.895	0.001
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.484	0.324	1.35E-01	-0.151	1.119
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.175	0.320	5.84E-01	-0.451	0.801
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.759	0.447	8.98E-02	-0.118	1.636
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.496	0.289	8.58E-02	-0.070	1.062
	time of day (in hours since 9AM)	-0.082	0.171	6.32E-01	-0.417	0.253	0.177	0.212	4.05E-01	-0.239	0.593	0.192	0.219	3.81E-01	-0.237	0.622
	batch 2	-37.447	0.951	0.00E+00	-39.311	-35.582	-35.743	1.012	3.98E-273	-37.727	-33.759	-35.061	0.869	0.00E+00	-36.765	-33.357
	batch 3	-3.957	0.764	2.26E-07	-5.456	-2.459	-3.929	0.683	8.70E-09	-5.267	-2.591	-4.637	0.868	9.08E-08	-6.337	-2.936
	batch 4	1.274	1.003	2.04E-01	-0.691	3.240	-0.418	0.871	6.31E-01	-2.126	1.289	-1.396	0.956	1.44E-01	-3.270	0.478
	batch 5	-0.470	0.586	4.23E-01	-1.619	0.679	-0.329	0.713	6.45E-01	-1.727	1.070	-2.251	1.041	3.07E-02	-4.292	-0.210
	batch 6	0.542	0.953	5.69E-01	-1.325	2.410	0.817	0.846	3.34E-01	-0.841	2.475	-0.482	1.134	6.71E-01	-2.706	1.741
	intercept	1.517	1.057	1.51E-01	-0.555	3.590	-0.105	1.143	9.27E-01	-2.345	2.135	1.615	1.438	2.61E-01	-1.203	4.433
		Vascular co-localization of macrophages with neutrophils														
		81 vs. 135 larvae with 2 vs. 0 mutated alleles					**75 vs. 117 larvae with 2 vs. 0 mutated alleles**					**75 vs. 117 larvae with 2 vs. 0 mutated alleles**				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	**2 vs. 0 mutated alleles**	-0.552	0.213	9.74E-03	-0.970	-0.133	-0.517	0.220	1.85E-02	-0.948	-0.087	-0.524	0.216	1.53E-02	-0.947	-0.100
	apoea	-0.046	0.150	7.60E-01	-0.341	0.249	-0.144	0.175	4.11E-01	-0.487	0.199	-0.175	0.173	3.13E-01	-0.515	0.165
	apoeb	0.311	0.141	2.78E-02	0.034	0.588	0.399	0.144	5.47E-03	0.118	0.681	0.389	0.143	6.61E-03	0.108	0.670
	apobb.1	0.130	0.139	3.50E-01	-0.142	0.402	0.149	0.137	2.78E-01	-0.120	0.418	0.142	0.135	2.92E-01	-0.122	0.405
	body length (in SD)	-	-	-	-	-	0.070	0.139	6.13E-01	-0.202	0.342	0.033	0.137	8.11E-01	-0.236	0.302
	dorsal body surface area (in SD)	-	-	-	-	-	0.358	0.139	1.02E-02	0.085	0.631	0.317	0.139	2.23E-02	0.045	0.589
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.169	0.114	1.36E-01	-0.053	0.392
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.073	0.124	5.58E-01	-0.170	0.316
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.009	0.152	9.54E-01	-0.307	0.290
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.023	0.106	8.29E-01	-0.185	0.231
	time of day (in hours since 9AM)	0.083	0.079	2.93E-01	-0.072	0.237	0.035	0.089	6.98E-01	-0.140	0.210	0.011	0.089	8.98E-01	-0.164	0.187
	batch 1	0.139	0.760	8.55E-01	-1.351	1.629	0.076	0.832	9.27E-01	-1.554	1.706	0.137	0.857	8.73E-01	-1.543	1.816
	batch 2	0.176	0.869	8.39E-01	-1.527	1.880	0.232	0.913	8.00E-01	-1.557	2.021	0.136	0.922	8.82E-01	-1.671	1.944
	batch 3	-0.957	0.809	2.37E-01	-2.543	0.630	-0.895	0.890	3.15E-01	-2.640	0.850	-0.820	0.902	3.63E-01	-2.587	0.948
	batch 4	0.431	0.775	5.79E-01	-1.089	1.951	0.487	0.830	5.57E-01	-1.139	2.114	0.508	0.848	5.49E-01	-1.153	2.169
	batch 5	-0.142	0.774	8.54E-01	-1.659	1.375	-0.349	0.869	6.88E-01	-2.054	1.355	-0.153	0.877	8.61E-01	-1.871	1.565
	batch 6	-1.482	0.787	5.97E-02	-3.024	0.061	-2.098	0.906	2.06E-02	-3.874	-0.323	-1.918	0.907	3.44E-02	-3.695	-0.141
	batch 7	-0.511	0.882	5.62E-01	-2.239	1.217	-1.122	1.031	2.76E-01	-3.142	0.898	-0.799	1.063	4.52E-01	-2.882	1.284
	intercept	3.637	0.790	4.11E-06	2.090	5.185	3.817	0.860	8.96E-06	2.132	5.502	3.824	0.865	9.85E-06	2.128	5.519

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 infiltration by macrophages and neutrophils). Associations were only examined in larvae with two mutated alleles in *apoba* , *apobb.2* and *ldlrb* . 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-induced mutations. Model 1: adjusted for the number of mutated alleles in the other three orthologues weighted by their predicted effect on protein function, as well as for time of day and batch; Model 2: additionally adjusted for body length and dorsal body surface area normalized for body length; Model 3: additionally adjusted for whole-body LDL cholesterol (LDLc), HDL cholesterol (HDLc), triglyceride and glucose levels normalized for protein levels. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 21 - The additive effect of mutated alleles in *apoea* , *apoeb* , *apobb.1* and *ldlra* on body size

		Body length (n=256)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.150	0.078	5.32E-02	-0.303	0.002
	apoeb	0.049	0.082	5.51E-01	-0.113	0.211
	apobb.1	-0.099	0.080	2.16E-01	-0.257	0.058
	ldlra	0.097	0.061	1.14E-01	-0.023	0.218
	time of day (in hours since 9AM)	-0.030	0.044	4.85E-01	-0.116	0.055
	intercept	-0.136	0.258	5.98E-01	-0.642	0.370
random factors	***variance by batch***	*0.454*	*0.131*	-	*0.258*	*0.798*
	residual	*0.740*	*0.033*	-	*0.678*	*0.809*

		Dorsal body surface area (n=256)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.029	0.089	7.48E-01	-0.146	0.203
	apoeb	-0.028	0.094	7.63E-01	-0.213	0.156
	apobb.1	0.044	0.092	6.27E-01	-0.135	0.224
	ldlra	-0.099	0.070	1.58E-01	-0.237	0.038
	time of day (in hours since 9AM)	0.064	0.050	2.00E-01	-0.034	0.162
	intercept	-0.094	0.304	7.56E-01	-0.690	0.501
random factors	***variance by batch***	*0.556*	*0.158*	-	*0.319*	*0.970*
	residual	*0.845*	*0.038*	-	*0.774*	*0.923*

		Lateral body surface area (n=252)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.107	0.088	2.24E-01	-0.066	0.280
	apoeb	0.023	0.094	8.07E-01	-0.162	0.208
	apobb.1	-0.046	0.091	6.13E-01	-0.226	0.133
	ldlra	-0.130	0.070	6.25E-02	-0.267	0.007
	time of day (in hours since 9AM)	0.023	0.050	6.45E-01	-0.075	0.120
	intercept	-0.069	0.300	8.17E-01	-0.658	0.519
random factors	***variance by batch***	*0.531*	*0.152*	-	*0.303*	*0.930*
	residual	*0.837*	*0.038*	-	*0.766*	*0.915*

		Body volume (n=248)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.091	0.089	3.09E-01	-0.084	0.266
	apoeb	-0.001	0.096	9.93E-01	-0.189	0.188
	apobb.1	-0.022	0.093	8.15E-01	-0.205	0.161
	ldlra	-0.115	0.071	1.06E-01	-0.253	0.024
	time of day (in hours since 9AM)	0.064	0.051	2.12E-01	-0.036	0.164
	intercept	-0.174	0.305	5.68E-01	-0.773	0.424
random factors	***variance by batch***	*0.539*	*0.155*	-	*0.307*	*0.948*
	residual	*0.839*	*0.038*	-	*0.767*	*0.917*

All outcomes were normalized for length using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models in larvae carrying two mutated alleles in *apoba* , *apobb.2* and *ldlrb*. Effects shown are for each additional mutated allele in *apoea* , *apoeb* , *apobb.1* and *ldlra,* 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 22 - The additive effect of mutated alleles in *apoea* , *apoeb* , *apobb.1* and *ldlra* on whole-body lipid and glucose levels

		LDL cholesterol levels				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.258	0.092	5.19E-03	0.077	0.439
	apoeb	0.091	0.102	3.76E-01	-0.110	0.292
	apobb.1	0.033	0.099	7.38E-01	-0.161	0.227
	ldlra	-0.004	0.075	9.61E-01	-0.151	0.143
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	0.009	0.043	8.37E-01	-0.076	0.094
	intercept	-0.442	0.237	6.27E-02	-0.907	0.023
random factors	***variation by batch***	*0.000*	*0.000*	-	*0.000*	
	residual	*0.968*	*0.041*	-	*0.892*	*1.051*

		HDL cholesterol levels				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.093	0.082	2.55E-01	-0.067	0.254
	apoeb	0.029	0.088	7.43E-01	-0.144	0.202
	apobb.1	-0.036	0.085	6.71E-01	-0.203	0.131
	ldlra	-0.085	0.065	1.90E-01	-0.213	0.042
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	-0.028	0.044	5.28E-01	-0.113	0.058
	intercept	0.111	0.302	7.14E-01	-0.482	0.703
random factors	***variation by batch***	*0.604*	*0.166*	-	*0.352*	*1.037*
	residual	*0.819*	*0.035*	-	*0.753*	*0.890*

		Triglyceride levels				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.009	0.066	8.87E-01	-0.140	0.121
	apoeb	0.034	0.072	6.39E-01	-0.107	0.174
	apobb.1	-0.001	0.069	9.93E-01	-0.136	0.134
	ldlra	0.023	0.053	6.58E-01	-0.080	0.127
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	-0.088	0.036	1.37E-02	-0.158	-0.018
	intercept	0.001	0.321	9.97E-01	-0.628	0.630
random factors	***variation by batch***	*0.763*	*0.196*	-	*0.461*	*1.262*
	residual	*0.662*	*0.028*	-	*0.609*	*0.719*

		Total cholesterol levels				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.152	0.083	6.67E-02	-0.010	0.314
	apoeb	0.059	0.089	5.12E-01	-0.117	0.234
	apobb.1	-0.043	0.086	6.20E-01	-0.211	0.126
	ldlra	-0.094	0.066	1.52E-01	-0.223	0.035
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	0.079	0.044	7.20E-02	-0.007	0.166
	intercept	-0.282	0.304	3.54E-01	-0.879	0.315
random factors	***variation by batch***	*0.606*	*0.182*	-	*0.336*	*1.093*
	residual	*0.828*	*0.035*	-	*0.761*	*0.900*

		Glucose levels				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.045	0.093	6.25E-01	-0.227	0.136
	apoeb	0.015	0.100	8.78E-01	-0.182	0.212
	apobb.1	-0.041	0.097	6.75E-01	-0.230	0.149
	ldlra	-0.062	0.074	4.02E-01	-0.207	0.083
	body length (in SD)	-	-	-	-	-
	dorsal body surface area (in SD)	-	-	-	-	-
	time of day (in hours since 9AM)	0.015	0.049	7.59E-01	-0.080	0.110
	intercept	0.025	0.284	9.29E-01	-0.532	0.583
random factors	***variation by batch***	*0.423*	*0.137*	-	*0.224*	*0.799*
	residual	*0.932*	*0.040*	-	*0.857*	*1.013*

All outcomes were normalized for protein level using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models in 284 larvae carrying two mutated alleles in *apoba* , *apobb.2* and *ldlrb* . Effects shown are for each additional mutated allele in *apoea* , *apoeb* , *apobb.1* and *ldlra* , 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 image-based vascular atherogenic traits

		Vascular lipid deposition														
		Model 1 (n=225)					Model 2 (n=202)					Model 3 (n=202)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	0.247	0.195	2.04E-01	-0.134	0.628	0.104	0.195	5.94E-01	-0.278	0.485	-0.053	0.188	7.79E-01	-0.421	0.316
	apoeb	-0.021	0.193	9.11E-01	-0.400	0.357	-0.040	0.185	8.30E-01	-0.402	0.322	-0.007	0.178	9.68E-01	-0.357	0.343
	apobb.1	0.171	0.185	3.55E-01	-0.191	0.533	0.039	0.210	8.53E-01	-0.373	0.451	0.135	0.173	4.37E-01	-0.205	0.474
	ldlra	0.326	0.146	2.51E-02	0.041	0.611	0.396	0.152	9.23E-03	0.098	0.695	0.298	0.136	2.91E-02	0.030	0.565
	body length (in SD)	-	-	-	-	-	-0.453	0.152	2.84E-03	-0.751	-0.156	-0.239	0.150	1.12E-01	-0.534	0.056
	dorsal body surface area (in SD)	-	-	-	-	-	0.167	0.166	3.13E-01	-0.157	0.491	0.294	0.157	6.18E-02	-0.014	0.602
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.113	0.104	2.79E-01	-0.317	0.091
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.060	0.147	6.84E-01	-0.229	0.349
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.708	0.172	3.73E-05	0.371	1.044
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.253	0.125	4.34E-02	-0.498	-0.008
	time of day (in hours since 9AM)	0.017	0.108	8.72E-01	-0.194	0.229	-0.013	0.136	9.23E-01	-0.280	0.253	-0.122	0.127	3.35E-01	-0.371	0.126
	batch 1	4.653	1.001	3.37E-06	2.690	6.615	4.598	1.072	1.80E-05	2.497	6.699	4.757	1.075	9.60E-06	2.651	6.864
	batch 2	2.936	1.001	3.34E-03	0.975	4.898	2.472	1.066	2.03E-02	0.384	4.561	2.958	1.119	8.22E-03	0.764	5.152
	batch 3	3.461	1.014	6.44E-04	1.473	5.449	3.111	1.058	3.29E-03	1.036	5.185	3.196	1.039	2.10E-03	1.159	5.232
	batch 4	3.748	1.120	8.18E-04	1.553	5.943	2.944	1.123	8.74E-03	0.743	5.144	3.411	1.075	1.51E-03	1.304	5.517
	batch 5	4.339	0.989	1.15E-05	2.401	6.278	3.975	1.089	2.63E-04	1.840	6.111	3.267	1.056	1.98E-03	1.197	5.338
	batch 6	4.524	0.998	5.77E-06	2.569	6.480	4.466	1.104	5.20E-05	2.303	6.629	3.680	1.084	6.87E-04	1.555	5.805
	batch 7	3.582	1.043	5.96E-04	1.537	5.627	3.668	1.143	1.33E-03	1.428	5.909	3.484	1.099	1.52E-03	1.331	5.638
	intercept	0.106	1.040	9.19E-01	-1.933	2.144	0.558	1.137	6.23E-01	-1.670	2.786	1.205	1.126	2.85E-01	-1.002	3.413

		Vascular infiltration by macrophages														
		Model 1 (n=276)					Model 2 (n=248)					Model 3 (n=248)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	0.068	0.090	4.51E-01	-0.108	0.243	0.048	0.097	6.19E-01	-0.142	0.239	0.041	0.098	6.77E-01	-0.151	0.232
	apoeb	0.033	0.096	7.31E-01	-0.156	0.222	0.047	0.102	6.43E-01	-0.152	0.247	0.045	0.101	6.56E-01	-0.154	0.244
	apobb.1	-0.074	0.093	4.23E-01	-0.256	0.108	-0.044	0.099	6.61E-01	-0.238	0.151	-0.039	0.099	6.95E-01	-0.233	0.155
	ldlra	-0.019	0.071	7.86E-01	-0.158	0.119	-0.052	0.076	4.92E-01	-0.201	0.097	-0.052	0.076	4.95E-01	-0.202	0.098
	body length (in SD)	-	-	-	-	-	0.052	0.082	5.25E-01	-0.109	0.214	0.054	0.083	5.12E-01	-0.108	0.217
	dorsal body surface area (in SD)	-	-	-	-	-	-0.033	0.070	6.37E-01	-0.170	0.104	-0.031	0.071	6.61E-01	-0.169	0.107
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.042	0.065	5.21E-01	-0.086	0.169
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.119	0.075	1.15E-01	-0.029	0.267
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.046	0.092	6.16E-01	-0.134	0.226
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.001	0.065	9.84E-01	-0.128	0.126
	time of day (in hours since 9AM)	0.038	0.047	4.16E-01	-0.054	0.131	0.028	0.054	5.99E-01	-0.077	0.134	0.033	0.054	5.39E-01	-0.072	0.138
	intercept	-0.157	0.293	5.92E-01	-0.732	0.418	-0.105	0.309	7.33E-01	-0.710	0.500	-0.106	0.303	7.27E-01	-0.700	0.488
random factors	***variation by batch***	*0.506*	*0.142*	*-*	*0.291*	*0.878*	*0.512*	*0.151*	*-*	*0.287*	*0.913*	*0.476*	*0.147*	*-*	*0.260*	*0.871*
	residual	*0.882*	*0.038*	*-*	*0.810*	*0.960*	*0.901*	*0.041*	*-*	*0.824*	*0.986*	*0.898*	*0.041*	*-*	*0.821*	*0.982*

continued **Supplementary Table 23**

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=223)					Model 2 (n=200)					Model 3 (n=200)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	-0.009	0.201	9.66E-01	-0.402	0.385	-0.121	0.201	5.46E-01	-0.514	0.272	-0.111	0.223	6.20E-01	-0.548	0.327
	apoeb	0.328	0.235	1.64E-01	-0.133	0.790	0.258	0.264	3.28E-01	-0.259	0.774	0.367	0.252	1.45E-01	-0.126	0.860
	apobb.1	-0.023	0.306	9.40E-01	-0.622	0.576	-0.264	0.262	3.13E-01	-0.776	0.249	-0.299	0.234	2.01E-01	-0.757	0.159
	ldlra	0.308	0.197	1.18E-01	-0.079	0.695	0.350	0.185	5.84E-02	-0.013	0.713	0.285	0.196	1.46E-01	-0.099	0.669
	body length (in SD)	-	-	-	-	-	-0.621	0.213	3.54E-03	-1.038	-0.204	-0.371	0.229	1.05E-01	-0.819	0.077
	dorsal body surface area (in SD)	-	-	-	-	-	0.327	0.171	5.61E-02	-0.009	0.662	0.431	0.184	1.92E-02	0.070	0.791
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.473	0.222	3.30E-02	-0.908	-0.038
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.340	0.198	8.64E-02	-0.049	0.729
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.664	0.264	1.18E-02	0.147	1.181
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.201	0.176	2.54E-01	-0.546	0.144
	time of day (in hours since 9AM)	0.214	0.128	9.44E-02	-0.037	0.465	0.272	0.144	5.86E-02	-0.010	0.553	0.252	0.164	1.25E-01	-0.069	0.573
	batch 1	2.865	0.982	3.53E-03	0.940	4.789	2.350	1.131	3.77E-02	0.133	4.567	2.414	1.270	5.72E-02	-0.074	4.902
	batch 2	1.763	1.172	1.32E-01	-0.534	4.060	1.151	1.297	3.75E-01	-1.391	3.694	0.574	1.340	6.68E-01	-2.052	3.200
	batch 3	1.890	0.974	5.24E-02	-0.020	3.799	1.183	1.104	2.84E-01	-0.980	3.346	1.527	1.090	1.61E-01	-0.610	3.665
	batch 4	3.140	1.155	6.57E-03	0.876	5.405	1.562	1.193	1.90E-01	-0.776	3.900	1.684	1.159	1.46E-01	-0.588	3.956
	batch 5	2.581	1.009	1.05E-02	0.603	4.560	1.594	1.225	1.93E-01	-0.807	3.994	0.929	1.157	4.22E-01	-1.339	3.198
	batch 6	2.182	1.005	2.99E-02	0.212	4.152	1.881	1.200	1.17E-01	-0.472	4.233	1.390	1.218	2.54E-01	-0.997	3.777
	batch 7	0.649	1.226	5.97E-01	-1.753	3.051	-0.192	1.374	8.89E-01	-2.885	2.501	0.082	1.345	9.51E-01	-2.553	2.718
	intercept	-1.433	1.056	1.75E-01	-3.504	0.637	-0.720	1.189	5.45E-01	-3.050	1.611	-0.560	1.146	6.25E-01	-2.807	1.686

		Vascular infiltration by neutrophils														
		Model 1 (n=278)					Model 2 (n=250)					Model 3 (n=250)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	-0.058	0.087	5.03E-01	-0.229	0.112	-0.045	0.092	6.23E-01	-0.225	0.135	-0.040	0.093	6.69E-01	-0.221	0.142
	apoeb	0.033	0.094	7.22E-01	-0.151	0.218	0.084	0.096	3.81E-01	-0.104	0.273	0.082	0.096	3.92E-01	-0.106	0.271
	apobb.1	0.165	0.091	7.01E-02	-0.014	0.344	0.205	0.095	2.97E-02	0.020	0.391	0.205	0.094	2.91E-02	0.021	0.390
	ldlra	-0.028	0.069	6.82E-01	-0.165	0.108	-0.034	0.072	6.39E-01	-0.176	0.108	-0.022	0.073	7.64E-01	-0.165	0.121
	body length (in SD)	-	-	-	-	-	-0.122	0.076	1.06E-01	-0.270	0.026	-0.101	0.076	1.86E-01	-0.250	0.049
	dorsal body surface area (in SD)	-	-	-	-	-	0.064	0.064	3.21E-01	-0.062	0.189	0.087	0.065	1.82E-01	-0.041	0.215
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.002	0.060	9.76E-01	-0.116	0.119
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.061	0.071	3.92E-01	-0.078	0.199
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.106	0.082	1.97E-01	-0.266	0.055
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.022	0.061	7.23E-01	-0.098	0.142
	time of day (in hours since 9AM)	0.031	0.045	4.93E-01	-0.058	0.120	0.003	0.050	9.59E-01	-0.095	0.100	0.008	0.049	8.77E-01	-0.089	0.105
	intercept	-0.137	0.255	5.90E-01	-0.637	0.362	-0.152	0.258	5.56E-01	-0.658	0.354	-0.197	0.257	4.44E-01	-0.701	0.307
random factors	***variation by batch***	*0.334*	*0.101*	-	*0.185*	*0.603*	*0.302*	*0.098*	-	*0.160*	*0.571*	*0.279*	*0.093*	-	*0.145*	*0.535*
	residual	*0.871*	*0.037*	-	*0.800*	*0.947*	*0.863*	*0.039*	-	*0.790*	*0.944*	*0.860*	*0.039*	-	*0.787*	*0.940*

continued **Supplementary Table 23**

		Vascular co-localization of lipids with neutrophils														
		Model 1 (n=217)					Model 2 (n=194)					Model 3 (n=194)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	0.210	0.334	5.30E-01	-0.445	0.865	0.150	0.346	6.65E-01	-0.528	0.827	-0.601	0.398	1.31E-01	-1.382	0.180
	apoeb	0.373	0.374	3.19E-01	-0.361	1.107	-0.035	0.359	9.21E-01	-0.740	0.669	-0.239	0.372	5.20E-01	-0.968	0.490
	apobb.1	1.050	0.291	3.16E-04	0.479	1.621	1.316	0.327	5.60E-05	0.676	1.957	1.050	0.349	2.60E-03	0.367	1.734
	ldlra	-0.002	0.304	9.95E-01	-0.597	0.594	0.367	0.285	1.99E-01	-0.192	0.926	0.184	0.267	4.90E-01	-0.339	0.708
	body length (in SD)	-	-	-	-	-	-1.364	0.274	6.37E-07	-1.901	-0.827	-0.831	0.321	9.59E-03	-1.460	-0.202
	dorsal body surface area (in SD)	-	-	-	-	-	0.140	0.279	6.17E-01	-0.408	0.687	0.063	0.251	8.02E-01	-0.429	0.555
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.270	0.271	3.20E-01	-0.262	0.801
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.408	0.346	2.38E-01	-0.270	1.086
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.635	0.353	3.65E-06	0.943	2.327
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.051	0.262	8.46E-01	-0.565	0.463
	time of day (in hours since 9AM)	0.051	0.170	7.65E-01	-0.282	0.384	0.266	0.230	2.47E-01	-0.185	0.716	-0.014	0.231	9.50E-01	-0.467	0.438
	batch 2	-1.816	0.925	4.95E-02	-3.629	-0.004	-1.417	1.243	2.54E-01	-3.853	1.020	-2.299	1.152	4.60E-02	-4.557	-0.041
	batch 3	-1.581	0.839	5.95E-02	-3.225	0.063	-1.956	0.715	6.21E-03	-3.357	-0.555	-3.239	0.753	1.71E-05	-4.716	-1.763
	batch 4	0.706	0.914	4.40E-01	-1.085	2.497	-0.899	0.773	2.45E-01	-2.414	0.615	-0.613	0.928	5.09E-01	-2.431	1.206
	batch 5	0.057	0.558	9.19E-01	-1.036	1.150	-0.281	0.613	6.46E-01	-1.483	0.920	-3.160	0.954	9.20E-04	-5.030	-1.291
	batch 6	1.154	0.822	1.60E-01	-0.457	2.764	0.791	0.801	3.23E-01	-0.779	2.361	-1.777	1.166	1.28E-01	-4.063	0.509
	batch 7	-1.626	1.079	1.32E-01	-3.741	0.490	0.093	1.175	9.37E-01	-2.210	2.395	-2.503	1.477	9.00E-02	-5.397	0.391
	intercept	-0.421	0.994	6.72E-01	-2.369	1.527	-1.365	1.070	2.02E-01	-3.462	0.732	2.455	1.439	8.80E-02	-0.366	5.275

		Vascular co-localization of macrophages with neutrophils														
		Model 1 (n=276)					Model 2 (n=248)					Model 3 (n=248)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	-0.077	0.136	5.72E-01	-0.345	0.190	-0.132	0.160	4.09E-01	-0.444	0.181	-0.179	0.162	2.69E-01	-0.496	0.139
	apoeb	0.229	0.136	9.15E-02	-0.037	0.495	0.249	0.142	7.93E-02	-0.029	0.527	0.207	0.144	1.51E-01	-0.076	0.490
	apobb.1	0.193	0.126	1.26E-01	-0.055	0.441	0.277	0.130	3.35E-02	0.022	0.532	0.269	0.126	3.24E-02	0.023	0.515
	ldlra	-0.240	0.107	2.47E-02	-0.449	-0.030	-0.249	0.108	2.05E-02	-0.461	-0.038	-0.237	0.104	2.31E-02	-0.441	-0.033
	body length (in SD)	-	-	-	-	-	0.095	0.127	4.53E-01	-0.153	0.344	0.043	0.129	7.36E-01	-0.209	0.296
	dorsal body surface area (in SD)	-	-	-	-	-	0.230	0.124	6.34E-02	-0.013	0.473	0.197	0.131	1.31E-01	-0.059	0.453
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.161	0.105	1.26E-01	-0.045	0.367
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.073	0.111	5.11E-01	-0.291	0.145
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.018	0.131	8.91E-01	-0.275	0.239
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.043	0.087	6.18E-01	-0.127	0.214
	time of day (in hours since 9AM)	0.161	0.069	1.95E-02	0.026	0.296	0.136	0.082	9.95E-02	-0.026	0.297	0.111	0.083	1.78E-01	-0.051	0.273
	batch 1	0.363	0.680	5.94E-01	-0.969	1.694	0.258	0.728	7.23E-01	-1.168	1.684	0.468	0.719	5.15E-01	-0.942	1.877
	batch 2	0.184	0.779	8.13E-01	-1.343	1.711	0.162	0.801	8.40E-01	-1.408	1.732	0.275	0.763	7.18E-01	-1.220	1.771
	batch 3	-0.997	0.726	1.69E-01	-2.419	0.425	-1.081	0.781	1.66E-01	-2.611	0.449	-0.929	0.769	2.27E-01	-2.436	0.577
	batch 4	0.850	0.724	2.41E-01	-0.570	2.269	0.894	0.763	2.41E-01	-0.601	2.390	0.931	0.764	2.23E-01	-0.566	2.427
	batch 5	-0.061	0.695	9.30E-01	-1.424	1.301	-0.310	0.765	6.86E-01	-1.810	1.190	-0.058	0.766	9.40E-01	-1.560	1.444
	batch 6	-1.462	0.707	3.88E-02	-2.848	-0.075	-1.935	0.789	1.42E-02	-3.482	-0.389	-1.814	0.791	2.19E-02	-3.364	-0.263
	batch 7	-0.464	0.773	5.48E-01	-1.978	1.051	-0.867	0.870	3.19E-01	-2.572	0.838	-0.702	0.936	4.53E-01	-2.536	1.132
	intercept	3.381	0.725	3.11E-06	1.960	4.803	3.613	0.779	3.50E-06	2.087	5.140	3.614	0.774	2.98E-06	2.098	5.130

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) in larvae carrying two mutated alleles in *apoba* , *apobb.2* and *ldlrb* . 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. Effects shown for *apoea* , *apoeb* , *apobb.1* and *ldlra* are for each additional mutated allele, weighed by the predicted effect on protein function. 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 and image quantification quality

	Debris included in the segmentation for body size				
	Model 1 (n=279)				
	OR	SE	*P*	lci	uci
apoea	1.027	0.357	9.39E-01	0.520	2.029
apoeb	1.029	0.468	9.51E-01	0.422	2.509
apobb.1	1.017	0.377	9.63E-01	0.492	2.103
ldlra	1.518	0.484	1.91E-01	0.812	2.837
time of day (in hours since 9AM)	0.999	0.167	9.93E-01	0.719	1.387
intercept	0.047	0.048	2.55E-03	0.007	0.343

	Many false positive lipid deposits																			
	Model 1 (n=250)					Model 2 (n=250)					Model 3 (n=250)					Model 4 (n=250)				
	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci	OR	SE	*P*	lci	uci
apoea	1.056	0.278	8.35E-01	0.630	1.770	1.264	0.363	4.14E-01	0.720	2.218	1.332	0.400	3.39E-01	0.740	2.400	1.531	0.476	1.71E-01	0.832	2.817
apoeb	0.966	0.263	9.00E-01	0.567	1.648	0.890	0.253	6.82E-01	0.510	1.553	0.877	0.256	6.53E-01	0.495	1.555	0.846	0.255	5.80E-01	0.469	1.529
apobb.1	0.876	0.243	6.33E-01	0.509	1.508	0.927	0.282	8.03E-01	0.510	1.684	1.041	0.327	8.97E-01	0.563	1.926	1.061	0.337	8.53E-01	0.569	1.979
ldlra	0.890	0.185	5.74E-01	0.592	1.337	0.825	0.184	3.89E-01	0.533	1.277	0.748	0.176	2.17E-01	0.471	1.186	0.797	0.194	3.52E-01	0.495	1.285
time of day (in hours since 9AM)	1.291	0.166	4.72E-02	1.003	1.662	1.164	0.160	2.72E-01	0.888	1.524	1.113	0.156	4.43E-01	0.846	1.465	1.090	0.157	5.48E-01	0.822	1.445
body length (in SD)	-	-	-	-	-	1.990	0.430	1.47E-03	1.302	3.041	1.697	0.381	1.83E-02	1.094	2.634	1.701	0.396	2.26E-02	1.077	2.684
dorsal body surface area (in SD)	-	-	-	-	-	1.874	0.339	5.11E-04	1.315	2.672	1.582	0.315	2.15E-02	1.070	2.338	1.551	0.312	2.94E-02	1.045	2.302
LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.637	0.125	2.16E-02	0.433	0.936
HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.870	0.179	4.99E-01	0.582	1.302
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.929	0.395	1.33E-03	1.292	2.881	1.848	0.390	3.68E-03	1.221	2.796
glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.045	0.181	7.99E-01	0.744	1.468	1.056	0.187	7.59E-01	0.746	1.494
intercept	0.127	0.084	1.87E-03	0.035	0.466	0.165	0.117	1.07E-02	0.042	0.659	0.183	0.131	1.78E-02	0.045	0.745	0.158	0.115	1.12E-02	0.038	0.658

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 qualtification pipeline. Associations were examined using logistic regression models in larvae carrying two mutated alleles in *apoba* , *apobb.2* and *ldlrb* . 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* , *apobb.1* 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 interval.

Supplementary Table 25 - The effect of gene x gene interactions on body size

		Body length									
		2 vs. 0 mutated alleles (n=47)					Additive model (n=256)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	-0.706	0.440	1.08E-01	-1.568	0.155	-0.246	0.140	7.95E-02	-0.520	0.029
	apobb.1	-0.725	0.588	2.18E-01	-1.878	0.429	-0.018	0.163	9.14E-01	-0.336	0.301
	ldlra	0.391	0.291	1.79E-01	-0.179	0.961	0.167	0.102	1.02E-01	-0.033	0.368
	apoea* x *apobb.1	-0.545	0.977	5.77E-01	-2.460	1.370	0.101	0.124	4.15E-01	-0.142	0.345
	apoea* x *ldlra	-0.087	0.620	8.88E-01	-1.303	1.128	0.021	0.089	8.11E-01	-0.152	0.195
	apobb.1* x *ldlra	-0.133	0.730	8.55E-01	-1.565	1.298	-0.124	0.094	1.86E-01	-0.308	0.060
	time of day (in hours since 9AM)	0.023	0.089	7.94E-01	-0.151	0.198	-0.040	0.044	3.62E-01	-0.127	0.046
	intercept	-0.239	0.358	5.04E-01	-0.940	0.462	-0.059	0.253	8.16E-01	-0.555	0.437
random factors	***variance by batch***	*0.204*	*0.225*	-	*0.024*	*1.773*	*0.450*	*0.131*	-	*0.255*	*0.795*
	residual	*0.766*	*0.088*	-	*0.611*	*0.961*	*0.738*	*0.033*	-	*0.675*	*0.806*

		Dorsal body surface area									
		2 vs. 0 mutated alleles (n=47)					Additive model (n=256)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	0.366	0.422	3.85E-01	-0.460	1.193	0.017	0.160	9.18E-01	-0.298	0.331
	apobb.1	0.555	0.528	2.93E-01	-0.479	1.589	0.101	0.186	5.86E-01	-0.263	0.466
	ldlra	-0.264	0.273	3.34E-01	-0.800	0.272	-0.150	0.117	2.00E-01	-0.380	0.079
	apoea* x *apobb.1	1.272	0.933	1.73E-01	-0.557	3.102	-0.084	0.142	5.57E-01	-0.363	0.196
	apoea* x *ldlra	-0.266	0.567	6.40E-01	-1.377	0.846	0.055	0.101	5.88E-01	-0.144	0.254
	apobb.1* x *ldlra	-0.673	0.657	3.06E-01	-1.961	0.615	0.003	0.107	9.74E-01	-0.207	0.214
	time of day (in hours since 9AM)	-0.024	0.087	7.86E-01	-0.195	0.147	0.066	0.051	1.92E-01	-0.033	0.166
	intercept	0.198	0.392	6.14E-01	-0.571	0.966	-0.133	0.298	6.55E-01	-0.717	0.451
random factors	***variance by batch***	*0.525*	*0.214*	-	*0.237*	*1.165*	*0.550*	*0.157*	-	*0.315*	*0.962*
	residual	*0.673*	*0.078*	-	*0.536*	*0.845*	*0.844*	*0.038*	-	*0.773*	*0.922*

		Lateral body surface area									
		2 vs. 0 mutated alleles (n=45)					Additive model (n=252)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	0.344	0.402	3.93E-01	-0.445	1.132	0.064	0.160	6.89E-01	-0.250	0.378
	apobb.1	0.681	0.512	1.84E-01	-0.323	1.685	-0.013	0.187	9.45E-01	-0.379	0.353
	ldlra	-0.333	0.264	2.06E-01	-0.850	0.183	-0.134	0.117	2.52E-01	-0.364	0.095
	apoea* x *apobb.1	0.100	0.911	9.12E-01	-1.684	1.885	-0.001	0.143	9.93E-01	-0.282	0.279
	apoea* x *ldlra	0.164	0.568	7.72E-01	-0.949	1.278	0.034	0.102	7.37E-01	-0.165	0.234
	apobb.1* x *ldlra	-0.876	0.635	1.68E-01	-2.122	0.369	-0.025	0.107	8.16E-01	-0.236	0.186
	time of day (in hours since 9AM)	-0.109	0.086	2.07E-01	-0.278	0.060	0.022	0.051	6.59E-01	-0.077	0.122
	intercept	0.475	0.378	2.08E-01	-0.265	1.216	-0.027	0.293	9.28E-01	-0.601	0.548
random factors	***variance by batch***	*0.467*	*0.206*	-	*0.197*	*1.106*	*0.528*	*0.151*	-	*0.301*	*0.927*
	residual	*0.645*	*0.076*	-	*0.511*	*0.813*	*0.837*	*0.038*	-	*0.766*	*0.915*

		Body volume									
		2 vs. 0 mutated alleles (n=42)					Additive model (n=248)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	0.294	0.403	4.66E-01	-0.496	1.083	0.052	0.163	7.48E-01	-0.267	0.372
	apobb.1	0.558	0.533	2.96E-01	-0.488	1.603	-0.009	0.189	9.62E-01	-0.379	0.361
	ldlra	-0.288	0.275	2.95E-01	-0.827	0.251	-0.140	0.120	2.43E-01	-0.375	0.095
	apoea* x *apobb.1	0.780	0.922	3.98E-01	-1.028	2.588	-0.011	0.147	9.39E-01	-0.299	0.276
	apoea* x *ldlra	-0.162	0.591	7.85E-01	-1.320	0.997	0.037	0.103	7.20E-01	-0.165	0.240
	apobb.1* x *ldlra	-0.930	0.678	1.70E-01	-2.259	0.398	-0.005	0.109	9.66E-01	-0.218	0.209
	time of day (in hours since 9AM)	0.015	0.093	8.68E-01	-0.166	0.197	0.064	0.052	2.17E-01	-0.037	0.165
	intercept	0.069	0.377	8.55E-01	-0.671	0.808	-0.154	0.300	6.08E-01	-0.743	0.435
random factors	***variance by batch***	*0.292*	*0.193*	-	*0.080*	*1.069*	*0.538*	*0.155*	-	*0.305*	*0.947*
	residual	*0.671*	*0.083*	-	*0.527*	*0.855*	*0.839*	*0.038*	-	*0.767*	*0.917*

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 *apoa* , *apobb.2* and *ldlrb* . Associations and interactions were examined in larvae with two mutated alleles that were highly likely to affect protein function vs. zero CRISPR-mutated alleles (left), as well as for each additional mutated allele, weighted by its predicted effect on protein function, i.e. using an additive model (right). Associations were adjusted for time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 26 - The effect of gene x gene interactions on whole-body lipid and glucose levels

		2 vs. 0 mutated alleles (n=50)					Additive model (n=284)				
		LDL cholesterol levels									
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.282	0.596	6.36E-01	-0.886	1.450	0.158	0.175	3.68E-01	-0.186	0.501
	apobb.1	0.814	0.817	3.19E-01	-0.787	2.416	0.123	0.197	5.32E-01	-0.263	0.510
	ldlra	0.201	0.395	6.10E-01	-0.573	0.975	-0.045	0.128	7.26E-01	-0.295	0.205
	apoea* x *apobb.1	0.115	1.326	9.31E-01	-2.483	2.714	-0.067	0.155	6.63E-01	-0.371	0.236
	apoea* x *ldlra	-0.144	0.830	8.63E-01	-1.770	1.483	0.106	0.108	3.30E-01	-0.107	0.318
	apobb.1* x *ldlra	-1.005	1.019	3.24E-01	-3.003	0.992	-0.023	0.117	8.43E-01	-0.252	0.206
	time of day (in hours since 9AM)	-0.080	0.114	4.83E-01	-0.304	0.144	0.007	0.044	8.66E-01	-0.079	0.094
	intercept	-0.091	0.447	8.38E-01	-0.967	0.784	-0.275	0.226	2.22E-01	-0.717	0.167
random factors	***variance by batch***	*0.000*	*0.000*	-	*0.000*	*0.000*	*0.000*	*0.000*	-	*0.000*	*0.034*
	residual	*1.089*	*0.109*	-	*0.895*	*1.324*	*0.968*	*0.041*	-	*0.891*	*1.051*

		HDL cholesterol levels									
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.564	0.484	2.44E-01	-0.385	1.513	0.023	0.151	8.79E-01	-0.273	0.319
	apobb.1	-0.507	0.660	4.42E-01	-1.801	0.787	-0.027	0.169	8.73E-01	-0.359	0.304
	ldlra	0.032	0.319	9.20E-01	-0.594	0.658	-0.137	0.109	2.08E-01	-0.350	0.076
	apoea* x *apobb.1	-0.812	1.073	4.49E-01	-2.914	1.291	-0.033	0.133	8.04E-01	-0.293	0.227
	apoea* x *ldlra	0.194	0.668	7.72E-01	-1.116	1.503	0.071	0.094	4.53E-01	-0.114	0.255
	apobb.1* x *ldlra	0.595	0.820	4.68E-01	-1.013	2.203	0.014	0.100	8.87E-01	-0.182	0.210
	time of day (in hours since 9AM)	-0.092	0.093	3.22E-01	-0.275	0.090	-0.026	0.044	5.62E-01	-0.112	0.061
	intercept	0.385	0.368	2.95E-01	-0.336	1.106	0.192	0.298	5.20E-01	-0.393	0.777
random factors	***variance by batch***	*0.136*	*0.685*	-	*0.000*	*2665*	*0.612*	*0.168*	-	*0.357*	*1.049*
	residual	*0.872*	*0.125*	-	*0.658*	*1.156*	*0.818*	*0.035*	-	*0.752*	*0.889*

		Triglyceride levels									
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.653	0.338	5.33E-02	-1.315	0.009	-0.117	0.122	3.39E-01	-0.356	0.122
	apobb.1	-0.314	0.430	4.65E-01	-1.156	0.528	-0.116	0.136	3.93E-01	-0.384	0.151
	ldlra	0.045	0.214	8.33E-01	-0.374	0.464	0.030	0.088	7.33E-01	-0.142	0.202
	apoea* x *apobb.1	0.444	0.745	5.51E-01	-1.016	1.903	0.152	0.107	1.56E-01	-0.058	0.362
	apoea* x *ldlra	0.938	0.436	3.15E-02	0.083	1.792	0.004	0.076	9.62E-01	-0.145	0.153
	apobb.1* x *ldlra	0.116	0.530	8.27E-01	-0.923	1.155	0.001	0.081	9.89E-01	-0.157	0.159
	time of day (in hours since 9AM)	0.044	0.069	5.23E-01	-0.091	0.180	-0.093	0.036	9.64E-03	-0.164	-0.023
	intercept	-0.351	0.348	3.13E-01	-1.033	0.331	0.140	0.319	6.61E-01	-0.485	0.765
random factors	***variance by batch***	*0.632*	*0.193*	-	*0.347*	*1.149*	*0.769*	*0.198*	-	*0.465*	*1.273*
	residual	*0.547*	*0.060*	-	*0.442*	*0.679*	*0.659*	*0.028*	-	*0.606*	*0.717*

		Total cholesterol levels									
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	-0.308	0.472	5.13E-01	-1.232	0.616	-0.022	0.152	8.85E-01	-0.320	0.276
	apobb.1	-0.475	0.646	4.63E-01	-1.742	0.792	-0.128	0.170	4.51E-01	-0.462	0.205
	ldlra	-0.407	0.312	1.92E-01	-1.020	0.205	-0.250	0.109	2.21E-02	-0.465	-0.036
	apoea* x *apobb.1	-0.935	1.049	3.73E-01	-2.991	1.121	-0.046	0.134	7.31E-01	-0.308	0.216
	apoea* x *ldlra	1.508	0.657	2.17E-02	0.221	2.796	0.157	0.095	9.69E-02	-0.028	0.343
	apobb.1* x *ldlra	0.283	0.806	7.26E-01	-1.298	1.863	0.099	0.101	3.26E-01	-0.098	0.296
	time of day (in hours since 9AM)	0.047	0.090	6.01E-01	-0.130	0.225	0.085	0.044	5.54E-02	-0.002	0.172
	intercept	-0.218	0.354	5.38E-01	-0.911	0.475	-0.054	0.297	8.57E-01	-0.635	0.528
random factors	***variance by batch***	*0.000*	*0.000*	-	*0.000*	*0.000*	*0.601*	*0.181*	-	*0.333*	*1.084*
	residual	*0.861*	*0.086*	-	*0.708*	*1.048*	*0.823*	*0.035*	-	*0.757*	*0.895*

		Glucose levels									
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
fixed factors	***apoea***	0.132	0.427	7.57E-01	-0.704	0.969	0.030	0.171	8.59E-01	-0.305	0.366
	apobb.1	-1.549	0.585	8.09E-03	-2.696	-0.403	-0.256	0.191	1.81E-01	-0.631	0.119
	ldlra	-0.595	0.283	3.53E-02	-1.149	-0.041	-0.113	0.123	3.57E-01	-0.355	0.128
	apoea* x *apobb.1	-1.323	0.949	1.63E-01	-3.183	0.538	0.000	0.150	9.98E-01	-0.294	0.295
	apoea* x *ldlra	0.381	0.594	5.21E-01	-0.784	1.546	-0.061	0.106	5.67E-01	-0.270	0.148
	apobb.1* x *ldlra	1.905	0.730	9.03E-03	0.475	3.336	0.173	0.113	1.27E-01	-0.049	0.395
	time of day (in hours since 9AM)	0.145	0.082	7.70E-02	-0.016	0.305	0.022	0.049	6.50E-01	-0.074	0.118
	intercept	-0.402	0.320	2.09E-01	-1.029	0.225	0.093	0.277	7.37E-01	-0.450	0.637
random factors	***variance by batch***	*0.000*	*0.000*	-	*0.000*	*0.000*	*0.433*	*0.139*	-	*0.230*	*0.814*
	residual	*0.779*	*0.078*	-	*0.641*	*0.948*	*0.927*	*0.040*	-	*0.852*	*1.008*

All outcomes were normalized for protein level using residuals and 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 in larvae with two mutated alleles that were highly likely to affect protein function vs. zero CRISPR-mutated alleles (left), as well as for each additional mutated allele, weighted by its predicted effect on protein function, i.e. using an additive model (right). 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 image-based vascular atherogenic traits

		Vascular lipid deposition									
		2 vs. 0 mutated alleles (n=35)					Additive model (n=202)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	0.214	0.849	8.01E-01	-1.450	1.879	-0.531	0.304	8.00E-02	-1.126	0.064
	apobb.1	0.057	0.943	9.52E-01	-1.791	1.904	0.282	0.355	4.27E-01	-0.414	0.977
	ldlra	-0.204	0.646	7.52E-01	-1.470	1.062	0.138	0.232	5.53E-01	-0.318	0.593
	apoea* x *apobb.1	-4.929	1.374	3.33E-04	-7.621	-2.236	0.008	0.282	9.77E-01	-0.544	0.561
	apoea* x *ldlra	4.947	1.312	1.63E-04	2.375	7.519	0.502	0.189	7.88E-03	0.132	0.873
	apobb.1* x *ldlra	1.810	1.163	1.20E-01	-0.470	4.090	-0.191	0.206	3.54E-01	-0.596	0.213
	time of day (in hours since 9AM)	-0.403	0.280	1.51E-01	-0.952	0.147	-0.049	0.135	7.18E-01	-0.314	0.217
	body length (in SD)	1.057	0.624	9.05E-02	-0.167	2.280	-0.461	0.150	2.13E-03	-0.755	-0.167
	dorsal body surface area (in SD)	1.089	0.971	2.62E-01	-0.815	2.993	0.141	0.152	3.52E-01	-0.156	0.439
	batch 1						4.952	1.055	2.66E-06	2.885	7.019
	batch 2	4.089	1.164	4.45E-04	1.807	6.371	2.827	1.051	7.14E-03	0.767	4.887
	batch 3	5.416	0.871	5.11E-10	3.708	7.124	3.775	1.067	4.02E-04	1.684	5.866
	batch 4	6.063	1.589	1.35E-04	2.949	9.176	3.285	1.109	3.06E-03	1.111	5.459
	batch 5	6.217	1.070	6.34E-09	4.119	8.315	4.411	1.081	4.53E-05	2.291	6.531
	batch 6	5.528	1.869	3.10E-03	1.864	9.192	4.963	1.087	4.99E-06	2.832	7.094
	batch 7						4.078	1.141	3.53E-04	1.841	6.315
	intercept	-0.175	1.396	9.00E-01	-2.910	2.560	0.406	1.085	7.08E-01	-1.720	2.532

		Vascular infiltration by macrophages									
		2 vs. 0 mutated alleles (n=43)					Additive model (n=248)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	0.086	0.472	8.56E-01	-0.840	1.011	0.152	0.175	3.86E-01	-0.192	0.495
	apobb.1	0.064	0.641	9.20E-01	-1.193	1.321	-0.122	0.202	5.45E-01	-0.519	0.274
	ldlra	0.086	0.333	7.97E-01	-0.566	0.737	-0.004	0.130	9.73E-01	-0.260	0.251
	apoea* x *apobb.1	-0.462	1.023	6.51E-01	-2.467	1.543	0.010	0.155	9.47E-01	-0.293	0.314
	apoea* x *ldlra	0.778	0.658	2.37E-01	-0.511	2.068	-0.092	0.111	4.05E-01	-0.309	0.125
	apobb.1* x *ldlra	0.057	0.783	9.42E-01	-1.478	1.591	0.061	0.116	6.01E-01	-0.167	0.288
	time of day (in hours since 9AM)	0.118	0.094	2.10E-01	-0.066	0.303	0.035	0.055	5.27E-01	-0.072	0.142
	body length (in SD)	-0.327	0.162	4.39E-02	-0.646	-0.009	0.061	0.083	4.62E-01	-0.101	0.223
	dorsal body surface area (in SD)	-0.173	0.156	2.68E-01	-0.478	0.133	-0.030	0.070	6.68E-01	-0.167	0.107
	intercept	-0.297	0.365	4.16E-01	-1.013	0.419	-0.088	0.305	7.73E-01	-0.685	0.509
random factors	***variance by batch***	*0.000*	*0.000*	-	*0.000*	*0.002*	*0.509*	*0.151*	-	*0.285*	*0.910*
	residual	*0.811*	*0.087*	-	*0.656*	*1.001*	*0.900*	*0.041*	-	*0.823*	*0.984*

		Vascular co-localization of lipids with macrophages									
		2 vs. 0 mutated alleles (n=34)					Additive model (n=200)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***apoea***	0.509	1.274	6.90E-01	-1.989	3.006	-0.476	0.374	2.03E-01	-1.209	0.257
	apobb.1	0.233	1.022	8.19E-01	-1.769	2.236	0.803	0.499	1.07E-01	-0.174	1.780
	ldlra	1.794	1.257	1.54E-01	-0.671	4.258	0.858	0.330	9.34E-03	0.211	1.504
	apoea* x *apobb.1	12.960	1.742	1.02E-13	9.545	16.374	0.085	0.330	7.97E-01	-0.562	0.731
	apoea* x *ldlra	2.306	2.580	3.72E-01	-2.751	7.363	0.186	0.227	4.13E-01	-0.259	0.630
	apobb.1* x *ldlra	-1.172	1.385	3.97E-01	-3.886	1.542	-0.807	0.278	3.77E-03	-1.353	-0.261
	time of day (in hours since 9AM)	0.297	0.322	3.56E-01	-0.334	0.928	0.165	0.144	2.50E-01	-0.116	0.447
	body length (in SD)	-1.444	0.492	3.34E-03	-2.409	-0.480	-0.630	0.202	1.79E-03	-1.025	-0.235
	dorsal body surface area (in SD)	0.331	0.833	6.91E-01	-1.303	1.964	0.404	0.153	8.15E-03	0.105	0.703
	batch 1	18.516	1.493	2.57E-35	15.590	21.443	2.137	1.115	5.52E-02	-0.048	4.322
	batch 2	0.979	1.866	6.00E-01	-2.679	4.637	1.410	1.317	2.84E-01	-1.170	3.991
	batch 3	19.534	2.131	4.89E-20	15.357	23.711	1.330	1.135	2.41E-01	-0.894	3.554
	batch 4	18.511	2.072	4.12E-19	14.450	22.572	1.725	1.194	1.49E-01	-0.616	4.065
	batch 5	20.806	1.813	1.78E-30	17.252	24.360	1.808	1.209	1.35E-01	-0.561	4.177
	batch 6	21.979	1.892	3.46E-31	18.270	25.687	1.834	1.187	1.22E-01	-0.493	4.161
	batch 7	-	-	-	-	-	-0.256	1.338	8.48E-01	-2.878	2.367
	intercept	-20.310	1.536	6.12E-40	-23.320	-17.301	-0.682	1.152	5.54E-01	-2.939	1.576

		Vascular infiltration by neutrophils									
		2 vs. 0 mutated alleles (n=45)					Additive model (n=250)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***apoea***	0.166	0.494	7.37E-01	-0.803	1.134	-0.088	0.166	5.97E-01	-0.413	0.238
	apobb.1	1.102	0.672	1.01E-01	-0.214	2.418	0.331	0.192	8.43E-02	-0.045	0.706
	ldlra	-0.234	0.336	4.87E-01	-0.893	0.426	0.038	0.123	7.58E-01	-0.202	0.278
	apoea* x *apobb.1	-0.580	1.075	5.89E-01	-2.688	1.527	0.017	0.147	9.08E-01	-0.271	0.305
	apoea* x *ldlra	-0.125	0.687	8.56E-01	-1.471	1.222	0.020	0.104	8.50E-01	-0.185	0.224
	apobb.1* x *ldlra	-0.851	0.822	3.00E-01	-2.463	0.760	-0.104	0.110	3.46E-01	-0.321	0.112
	time of day (in hours since 9AM)	-0.152	0.098	1.21E-01	-0.345	0.040	-0.002	0.050	9.60E-01	-0.101	0.096
	body length (in SD)	-0.229	0.166	1.68E-01	-0.555	0.096	-0.125	0.076	9.96E-02	-0.274	0.024
	dorsal body surface area (in SD)	0.200	0.156	1.99E-01	-0.105	0.505	0.062	0.064	3.37E-01	-0.064	0.188
	intercept	0.631	0.379	9.64E-02	-0.113	1.374	-0.073	0.255	7.73E-01	-0.572	0.426
random factors	***variance by batch***	*0.000*	*0.000*	-	*0.000*	*0.000*	*0.307*	*0.099*	-	*0.163*	*0.577*
	residual	*0.853*	*0.090*	-	*0.694*	*1.049*	*0.863*	*0.039*	-	*0.789*	*0.943*

continued **Supplementary Table 27**

		Vascular co-localization of lipids with neutrophils									
		2 vs. 0 mutated alleles (n=26)					Additive model (n=194)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	***apoea***	6.728	3.162	3.34E-02	0.530	12.926	0.254	0.506	6.15E-01	-0.738	1.247
	apobb.1	8.510	1.672	3.58E-07	5.233	11.787	0.917	0.460	4.59E-02	0.017	1.818
	ldlra	0.486	1.094	6.57E-01	-1.659	2.631	0.139	0.385	7.18E-01	-0.616	0.894
	apoea* x *apobb.1	-	-	-	-	-	-0.155	0.453	7.33E-01	-1.043	0.733
	apoea* x *ldlra	-4.739	3.277	1.48E-01	-11.162	1.683	-0.018	0.333	9.57E-01	-0.672	0.635
	apobb.1* x *ldlra	-1.985	1.670	2.35E-01	-5.257	1.288	0.377	0.333	2.58E-01	-0.276	1.030
	time of day (in hours since 9AM)	3.499	0.741	2.37E-06	2.046	4.952	0.288	0.228	2.06E-01	-0.159	0.734
	body length (in SD)	-2.791	1.005	5.51E-03	-4.761	-0.820	-1.400	0.272	2.68E-07	-1.933	-0.867
	dorsal body surface area (in SD)	-0.332	3.344	9.21E-01	-6.885	6.222	0.204	0.271	4.52E-01	-0.328	0.736
	batch 1	-	-	-	-	-	-	-	-	-	-
	batch 2	-	-	-	-	-	-1.480	1.256	2.39E-01	-3.943	0.982
	batch 3	9.253	2.871	1.27E-03	3.625	14.881	-2.140	0.820	9.02E-03	-3.747	-0.534
	batch 4	8.490	3.820	2.63E-02	1.002	15.977	-1.176	0.720	1.03E-01	-2.587	0.236
	batch 5	7.815	5.223	1.35E-01	-2.423	18.052	-0.321	0.617	6.03E-01	-1.531	0.889
	batch 6	-	-	-	-	-	0.636	0.800	4.27E-01	-0.932	2.204
	batch 7	-	-	-	-	-	-0.081	1.180	9.46E-01	-2.394	2.233
	intercept	-26.446	2.750	6.79E-22	-31.835	-21.056	-1.166	1.054	2.69E-01	-3.233	0.900

		Vascular co-localization of macrophages and neutrophils									
		2 vs. 0 mutated alleles (n=43)					Additive model (n=248)				
		Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
negative binomial terms	***apoea***	0.191	1.433	8.94E-01	-2.618	3.001	-0.460	0.287	1.09E-01	-1.023	0.103
	apobb.1	1.231	1.022	2.28E-01	-0.772	3.235	0.381	0.273	1.62E-01	-0.153	0.916
	ldlra	-1.103	0.658	9.36E-02	-2.392	0.186	-0.546	0.207	8.47E-03	-0.952	-0.140
	apoea* x *apobb.1	-2.767	1.315	3.53E-02	-5.344	-0.191	-0.256	0.209	2.19E-01	-0.665	0.153
	apoea* x *ldlra	-0.084	1.350	9.50E-01	-2.730	2.562	0.392	0.183	3.22E-02	0.033	0.751
	apobb.1* x *ldlra	0.068	1.048	9.48E-01	-1.985	2.122	0.094	0.151	5.35E-01	-0.202	0.389
	time of day (in hours since 9AM)	0.024	0.190	9.00E-01	-0.348	0.396	0.156	0.083	6.15E-02	-0.007	0.319
	body length (in SD)	0.182	0.411	6.58E-01	-0.624	0.988	0.165	0.128	1.97E-01	-0.086	0.417
	dorsal body surface area (in SD)	-0.088	0.690	8.99E-01	-1.440	1.264	0.258	0.122	3.42E-02	0.019	0.497
	batch 1	-1.849	0.698	8.09E-03	-3.217	-0.480	0.562	0.657	3.93E-01	-0.726	1.850
	batch 2	-0.694	1.129	5.39E-01	-2.906	1.518	0.466	0.727	5.22E-01	-0.960	1.891
	batch 3	-2.781	1.190	1.94E-02	-5.113	-0.450	-0.766	0.712	2.82E-01	-2.160	0.629
	batch 4	-1.190	0.672	7.64E-02	-2.506	0.126	1.235	0.709	8.17E-02	-0.155	2.626
	batch 5	-1.737	1.383	2.09E-01	-4.447	0.974	-0.065	0.688	9.25E-01	-1.413	1.283
	batch 6	-20.211	2.017	1.26E-23	-24.165	-16.257	-1.809	0.700	9.72E-03	-3.180	-0.438
	batch 7	-2.999	2.066	1.47E-01	-7.048	1.050	-0.683	0.800	3.93E-01	-2.252	0.885
	intercept	6.106	1.157	1.32E-07	3.837	8.374	3.891	0.697	2.35E-08	2.525	5.256

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 infiltration by macrophages and neutrophils) in larvae carrying two mutated alleles in *apoba* , *apobb.2* and *ldlrb* . Associations and interactions were examined in larvae with two mutated alleles that were highly likely to affect protein function vs. zero CRISPR-mutated alleles (left), as well as for each additional mutated allele, weighted by its predicted effect on protein function, i.e. using an additive model (right). 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 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 28**

		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 29 - 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, CILP2*
		zgc:85843	ENSDARG00000105208	2	43.86	39.79		ENSDARP00000130339	45.67	*HOMER3, GMIP, SCL25A42, ARMC6*

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

Human gene	Zebrafish orthologue	CRISPR gRNA target sequence	Genomic location (dabRer11/GRCz11)		Exon	Strand	GC (%)	Self-complementarity	Off-targets				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
			Chr	Pos					0	1	2	3						
LPAR2	*lpar2a*	GATGCCAGCGAAGAGGTCAG	3	53,091,511	2 of 3	+	60	0	0	0	0	6	0.65	-	NA	ATTGTCAACCGAAAGTTCCACT	TGAGGCTCATGTTAATCAATGC	175
		GgGCACTCATGACTTTGTGG	**3**	**53,091,654**	**2 of 3**	**-**	**55**	**1**	**0**	**0**	**0**	**1**	**0.63**	**53**	**high**	**TTAACAGCTGTGAGGCTTTTGA**	**AGTGGAACTTTCGGTTGACAAT**	**186**
	lpar2b	**GGGGACTAAAGCGAAGGCGG**	**1**	**59,206,929**	**2 of 7**	**-**	**65**	**1**	**0**	**0**	**0**	**0**	**0.76**	**76**	**very high**	**TTTTCTTCTACAGCATCAGCCA**	**CCAGCAGGTAATAAATGGGGTA**	**174**
		GGTCAAACACAAGGAGACGG	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*	**GgTCCACGCCATCCTCGCAG**	**3**	**52,763,869**	**5 of 20**	**-**	**70**	**1**	**0**	**0**	**0**	**0**	**0.68**	**-**	**moderate**	**GTTGATGCTGATGTGTTCGTTT**	**TCCAGCCTAATACAATGTGTCG**	**243**
		gGTGAAGATCTGCCGTGAAG	3	52,753,647	4 of 20	+	50	0	0	0	0	1	0.62	-	moderate	TGCCACTGGGAATATTAAAAGC	ACGAGTTCTCATCCCAAATCTC	205
GATAD2A	*gatad2ab*	GAGAAGATGTCAGAAGACGC	22	18,353,216	2 of 11	+	50	0	0	0	0	3	0.70	51	NA	GGTCAGACCACTTGTATGTCCA	TCTACAGCTCCAGGTTCTCCTC	207
		GGTGAAGGCCACCATCAAGG	**22**	**18,353,404**	**2 of 11**	**+**	**60**	**1**	**0**	**0**	**1**	**1**	**0.63**	**51**	**moderate/high**	**GAGGAGAACCTGGAGCTGTAGA**	**ATGATCGACCCTAGTTAGCAGC**	**194**
TM6SF2	*tm6sf2*	GGTTATTCTTGAAATTGGCG	22	17,790,559	3 of 11	+	40	0	0	0	0	7	0.60	10	no	ACAACCTCAGCATCCTATTTCC	GGATCCTTAGGAGGATTGAAGC	239
		GAGGTCAATGACACACGTGA	22	17,792,919	4 of 11	-	50	1	0	0	0	0	0.63	62	NA	ACACCACAACACTGAAAGCAAT	ACGCTAACCGTTTTCTGGTAGA	186
		GgGTAGCGAGGTAGACCAGG	**22**	**17,790,601**	**3 of 11**	**-**	**65**	**1**	**0**	**0**	**0**	**0**	**0.67**	**69**	**very high**	**ttctatcccacagcaagctaaa**	**aggatgaaatgcagaatgtgg**	**229**
		GAGGATTGAAGCGCGTAGCG	22	17,790,613	3 of 11	-	60	1	0	0	0	0	0.63	58	very high	ttctatcccacagcaagctaaa	aggatgaaatgcagaatgtgg	229
	zgc:85843	GATGCTGACAACAGACGTGA	2	56,897,287	3 of 10	-	50	0	0	0	4	2	0.63	54	moderate	GATGGGGAGGAGAGAGGGAG*	AAAGTCCATGAAGCCTTTGATG*	231
		gGGTCTTACCGTAGAACAGA	2	56,896,546	2 of 10	-	45	1	0	0	0	1	0.57	46	NA	TGGATGTGTTGTGTGAAATGATG	GCCTAATTATCCTAACCTGCCCA	241
		GgGATGATGAGCTACTGGGA	2	56,904,057	4 of 10	+	50	0	0	0	0	6	0.68	70	very high	CTTGTGCTGTTGTTGTAGGCAG	cacaggagggcgaatagtttag	244
		ggACACTGAGGTTTGCCAGG	**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 31 - Unique CRISPR-Cas9-induced mutations for 19p13.11 candidate genes

Zebrafish orthologue	Sequence	Annotation	Number of alleles	mean ± SD number of reads
gatad2ab	**TGGACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCACCATCAAGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA**	**150M (wildtype reference)**	**746**	**989 ± 504**
	TGGACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	64M12D74M	13	466 ± 283
	TGGACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCACCATCAGGTGGTGCAGACCAGCGGTGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	77M1S1M12I1M1S2M1S66M	2	424 ± 98
	TGAACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCAAGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	2M1S66M6D75M	2	323 ± 48
	TGGACTCAAGACCAAAAGCGAACAGGCCAACAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	70M8D72M	1	436
gmip	TCAGCCCAGGATGCCGACCTGAGCCTCTGCCACTGCGAGGATGGCGTGGAGCTTGCCCTGCAGTACGCCAAAATGTGGTGCCGCTACGCCAAAGACCTGCTCACCTGGATGGACAAGAGAATCAGCCTAGGTGAGTGCTTCTGATTTCTGTGTAAGATCACACACTTTTACTGTCA GAAATTAGATGTGTTTAATGTTC	14M1S127M1S56M	385	635 ± 488
	TCAGCCCAGGATGCTGACCTGAGCCTCTGCCACTGCGAGGATGGCGTGGAGCTTGCCCTGCAGTACGCCAAAATGTGGTGCCGCTACGCCAAAGACCTGCTCACCTGGATGGACAAGAGAATCAGCCTAGGTGAGTGCTTCTAATTTCTGTGTAAGATCACACACTTTTACTGTCA GAAATTAGATGTGTTTAATGTTC	**199M (wildtype reference)**	**381**	**671 ± 519**
lipcb	GTAGATGTCGCTGATCTTGCAGCCGGGCTGGAAGGTTCCGCCGTTGGGGTAGAAGTCCACATGAGCCACGCTCTGCTTGATGCCCACCCCCGGCAGCAGAGGAGACTTGGTGAAGGTGTGTATGGCGTCCACAAACTGAGCGTCGTCTGGAGACAGCCTGTCCAGCGCCG	150M1S2M1S16M	518	375 ± 270
	GTAGATGTCGCTGATCTTGCAGCCGGGCTGGAAGGTTCCGCCGTTGGGGTAGAAGTCCACATGAGCCACGCTCTGCTTGATGCCCACCCCCGGCAGCAGAGGAGACTTGGTGAAGGTGTGTATGGCGTCCACAAACTGAGCGTCGTCTGGAGAGAGCCTGTCCAGCGCCG	150M1S19M	238	241 ± 170
	GTAGATGTCGCTGATCTTGCAGCCGGGCTGGAAGGTTCCGCCGTTGGGGTAGAAGTCCACATGAGCCACGCTCTGCTTGATGCCCACCCCCGGCAGCAGAGGAGACTTGGTGAAGGTGTGTATGGCGTCCACAAACTGAGCGTCGTCTGGTGAGAGCCTGTCCAGCGCCG	**170M (wildtype reference)**	**0**	**-**
lpar2a	**TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACCACAAAGTCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG**	**142M (wildtype reference)**	**755**	**935 ± 522**
	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACCACAAAGTCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	69M2D71M	8	512 ± 569
	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	69M8D65M	2	327 ± 65
	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCAAAGTCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	66M5D71M	1	673
lpar2b	**GTGAAAGCGGCGGTTCATGAAGATGGCCGCCATCACCAGGATGTTGGTGAAGATGACAAAAACACTGACCAGCAGCCCCATACCCACCACCGCCTTCGCTTTAGTCCCCCACGTATCGCTGATGTTCTTA**	**130M (wildtype reference)**	**756**	**368 ± 172**
	GTGAAAGCGGCGGTTCATGAAGATGGCCGCCATCACCAGGATGTTGGTGAAGATGACAAAAACACTGACCAGCAGCCCCATACCCACCACCTTCGCTTTAGTCCCCCACGTATCGCTGATGTTCTTA	89M3D38M	6	278 ± 91
tm6sf2	**TTTGCTCTAATATTTACTATTGATTATTGTTTTGTATTTTCAGGCCAGTGGTTATTCTTGAAATTGGCGTGGCTGTTCTTGTGGCAGTTTTCCTCCTGGTCTACCTCGCTACGCGCTTCAATCCTCCTAAGGATCCTTTGTTCTATGGTATGATTTGATTGGTTGATTCTTAAAAA CACTGAATTTAT**	**188M (wildtype reference)**	**441**	**100 ± 86**
	TTTGCTCTAATATTTACTATTGATTATTGTTTTGTATTTTCAGGCCAGTGGTTATTCTTGAAATTGGCGTGGCTGTTCTTGTGGCAGTTTTCCTCCTGGTCTACCTCGCTACGCGCTTCAATCCTCCTAAGGATCCTTTGTTCTATGGTATGATTTGATTGGTTGATTCTAAAAAA CACTGAATTTAT	170M1S17M	261	78 ± 66

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 32 - 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	13
		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 384 sequenced larvae in which the variant was observed (possible range 0 to 768)

Supplementary Table 33 - 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	365	11	0	0	376	376	0.015	0.99
lpar2b	370	6	0	0	376	376	0.008	0.99
gatad2ab	358	18	0	0	376	376	0.024	0.99

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. Of 384 sequenced larvae, four were wildtype controls used to exclude variants that are inherently present from influencing the results, and four more larvae were excluded for having more than two missing calls across the seven successfully sequenced orthologues. 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 34 - The effect of a mutated allele in *lpar2a* , *lpar2b* and *gatad2ab* on body size

		Body length (n=373)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.023	0.243	9.26E-01	-0.499	0.453
	lpar2b	1.081	0.489	2.70E-02	0.123	2.040
	gatad2ab	-0.260	0.281	3.55E-01	-0.811	0.291
	age (11dpf vs. 10dpf)	0.312	0.102	2.21E-03	0.112	0.513
	time of day (in hours since 9AM)	-0.002	0.021	9.25E-01	-0.044	0.040
	intercept	0.170	0.391	6.64E-01	-0.596	0.936
random factors	***variance by batch***	*0.778*	*0.029*		*0.724*	*0.836*
	residual	*0.753*	*0.272*		*0.371*	*1.530*

		Dorsal body surface area (n=373)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.001	0.253	9.97E-01	-0.497	0.495
	lpar2b	-0.929	0.509	6.79E-02	-1.927	0.068
	gatad2ab	0.444	0.293	1.29E-01	-0.130	1.017
	age (11dpf vs. 10dpf)	0.174	0.106	1.00E-01	-0.033	0.382
	time of day (in hours since 9AM)	0.021	0.022	3.50E-01	-0.023	0.064
	intercept	0.027	0.317	9.32E-01	-0.594	0.648
random factors	***variance by batch***	*0.810*	*0.030*		*0.753*	*0.870*
	residual	*0.595*	*0.217*		*0.292*	*1.215*

		Lateral body surface area (n=371)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	0.306	0.277	2.69E-01	-0.237	0.850
	lpar2b	0.057	0.558	9.19E-01	-1.038	1.151
	gatad2ab	0.302	0.321	3.47E-01	-0.327	0.930
	age (11dpf vs. 10dpf)	0.247	0.116	3.29E-02	0.020	0.474
	time of day (in hours since 9AM)	-0.055	0.024	2.53E-02	-0.102	-0.007
	intercept	0.310	0.265	2.41E-01	-0.208	0.829
random factors	***variance by batch***	*0.888*	*0.033*		*0.826*	*0.954*
	residual	*0.473*	*0.177*		*0.227*	*0.985*

		Body volume (n=364)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	0.210	0.272	4.41E-01	-0.324	0.744
	lpar2b	0.129	0.598	8.29E-01	-1.043	1.302
	gatad2ab	0.482	0.315	1.26E-01	-0.135	1.100
	age (11dpf vs. 10dpf)	0.270	0.115	1.88E-02	0.045	0.496
	time of day (in hours since 9AM)	-0.004	0.024	8.60E-01	-0.052	0.043
	intercept	0.113	0.290	6.96E-01	-0.455	0.681
random factors	***variance by batch***	*0.871*	*0.032*		*0.810*	*0.938*
	residual	*0.530*	*0.197*		*0.256*	*1.098*

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 35 - The effect of a mutated allele in *lpar2a, lpar2b* and *gatad2ab* on whole-body lipid and glucose levels

		LDL cholesterol levels (n=374)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.528	0.294	7.29E-02	-1.105	0.049
	lpar2b	-0.566	0.647	3.82E-01	-1.835	0.702
	gatad2ab	-0.311	0.340	3.61E-01	-0.978	0.356
	age (11dpf vs. 10dpf)	-0.302	0.121	1.25E-02	-0.539	-0.065
	time of day (in hours since 9AM)	0.017	0.026	5.11E-01	-0.033	0.067
	intercept	0.133	0.183	4.69E-01	-0.227	0.493
random factors	***variation by batch***	*0.943*	*0.035*	-	*0.878*	*1.014*
	residual	*0.270*	*0.120*	-	*0.113*	*0.647*

		HDL cholesterol levels (n=374)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.347	0.295	2.40E-01	-0.925	0.231
	lpar2b	-1.662	0.648	1.03E-02	-2.933	-0.392
	gatad2ab	-0.228	0.341	5.03E-01	-0.897	0.440
	age (11dpf vs. 10dpf)	-0.057	0.121	6.38E-01	-0.294	0.180
	time of day (in hours since 9AM)	-0.046	0.026	7.41E-02	-0.096	0.004
	intercept	0.211	0.182	2.46E-01	-0.145	0.567
random factors	***variation by batch***	*0.945*	*0.035*	-	*0.879*	*1.016*
	residual	*0.265*	*0.113*	-	*0.115*	*0.610*

		Triglyceride levels (n=374)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.480	0.250	5.55E-02	-0.970	0.011
	lpar2b	-0.068	0.550	9.01E-01	-1.147	1.010
	gatad2ab	-0.297	0.290	3.05E-01	-0.865	0.271
	age (11dpf vs. 10dpf)	0.047	0.105	6.55E-01	-0.159	0.253
	time of day (in hours since 9AM)	-0.041	0.022	5.95E-02	-0.084	0.002
	intercept	0.376	0.348	2.79E-01	-0.305	1.058
random factors	***variation by batch***	*0.802*	*0.029*	-	*0.746*	*0.862*
	residual	*0.662*	*0.241*	-	*0.325*	*1.349*

		Total cholesterol levels (n=374)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.564	0.283	4.61E-02	-1.118	-0.010
	lpar2b	0.563	0.621	3.65E-01	-0.655	1.780
	gatad2ab	-0.373	0.327	2.54E-01	-1.013	0.268
	age (11dpf vs. 10dpf)	-0.588	0.117	5.22E-07	-0.818	-0.358
	time of day (in hours since 9AM)	0.013	0.025	6.04E-01	-0.035	0.061
	intercept	0.205	0.205	3.19E-01	-0.198	0.607
random factors	***variation by batch***	*0.905*	*0.033*	-	*0.842*	*0.973*
	residual	*0.334*	*0.134*	-	*0.152*	*0.731*

		Glucose levels (n=374)				
		Effect	**SE**	***P***	**lci**	**uci**
fixed factors	***lpar2a***	-0.119	0.286	6.78E-01	-0.680	0.442
	lpar2b	-0.313	0.629	6.19E-01	-1.546	0.920
	gatad2ab	-0.586	0.331	7.63E-02	-1.235	0.062
	age (11dpf vs. 10dpf)	0.154	0.119	1.95E-01	-0.079	0.386
	time of day (in hours since 9AM)	-0.069	0.025	5.55E-03	-0.118	-0.020
	intercept	0.178	0.203	3.80E-01	-0.219	0.575
random factors	***variation by batch***	*0.917*	*0.034*	-	*0.853*	*0.985*
	residual	*0.325*	*0.132*	-	*0.146*	*0.722*

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

		Vascular lipid deposition														
		Model 1 (n=183)					Model 2 (n=180)					Model 3 (n=178)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***lpar2a***	1.898	1.007	5.95E-02	-0.076	3.872	1.832	1.051	8.13E-02	-0.228	3.892	1.737	1.052	9.87E-02	-0.325	3.799
	lpar2b	0.978	1.215	4.21E-01	-1.403	3.359	0.872	1.192	4.64E-01	-1.464	3.207	0.786	1.330	5.55E-01	-1.821	3.393
	gatad2ab	-0.050	0.424	9.07E-01	-0.881	0.782	-0.071	0.402	8.60E-01	-0.859	0.717	-0.198	0.399	6.20E-01	-0.979	0.584
	body length (in SD)	-	-	-	-	-	0.109	0.180	5.42E-01	-0.243	0.461	0.134	0.178	4.51E-01	-0.215	0.484
	dorsal body surface area (in SD)	-	-	-	-	-	0.028	0.188	8.84E-01	-0.342	0.397	0.111	0.182	5.42E-01	-0.245	0.467
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.068	0.090	4.48E-01	-0.108	0.244
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.148	0.134	2.69E-01	-0.410	0.114
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.033	0.126	7.96E-01	-0.215	0.280
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.013	0.131	9.21E-01	-0.244	0.270
	age (11dpf vs. 10dpf)	0.215	0.510	6.73E-01	-0.785	1.215	0.249	0.499	6.18E-01	-0.729	1.226	0.210	0.477	6.60E-01	-0.724	1.144
	time of day (in hours since 9AM)	-0.071	0.051	1.65E-01	-0.171	0.029	-0.065	0.052	2.13E-01	-0.168	0.038	-0.070	0.053	1.87E-01	-0.175	0.034
	batch 1	3.244	0.636	3.36E-07	1.998	4.490	3.296	0.618	9.85E-08	2.084	4.508	3.222	0.598	7.13E-08	2.050	4.394
	batch 2	4.917	0.743	3.55E-11	3.462	6.372	4.819	0.802	1.92E-09	3.246	6.391	4.607	0.789	5.21E-09	3.061	6.153
	batch 3	4.623	0.722	1.53E-10	3.208	6.038	4.554	0.777	4.51E-09	3.032	6.076	4.369	0.743	4.10E-09	2.913	5.825
	intercept	0.785	0.724	2.79E-01	-0.635	2.204	0.728	0.702	3.00E-01	-0.648	2.104	0.810	0.652	2.14E-01	-0.467	2.088

		Vascular infiltration by macrophages														
		Model 1 (n=221)					Model 2 (n=218)					Model 3 (n=216)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***lpar2a***	0.236	0.349	4.99E-01	-0.448	0.920	0.214	0.353	5.43E-01	-0.477	0.906	0.266	0.356	4.55E-01	-0.431	0.963
	lpar2b	0.433	0.484	3.71E-01	-0.516	1.382	0.464	0.491	3.45E-01	-0.499	1.427	0.418	0.547	4.45E-01	-0.655	1.491
	gatad2ab	-0.087	0.323	7.88E-01	-0.721	0.547	-0.075	0.326	8.19E-01	-0.713	0.564	-0.085	0.327	7.95E-01	-0.726	0.556
	body length (in SD)	-	-	-	-	-	0.034	0.075	6.46E-01	-0.113	0.182	0.022	0.076	7.75E-01	-0.128	0.171
	dorsal body surface area (in SD)	-	-	-	-	-	0.054	0.070	4.45E-01	-0.084	0.192	0.048	0.071	5.03E-01	-0.091	0.186
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.017	0.053	7.48E-01	-0.120	0.086
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.030	0.055	5.91E-01	-0.078	0.138
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.115	0.063	7.02E-02	-0.010	0.239
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.035	0.058	5.49E-01	-0.147	0.078
	age (11dpf vs. 10dpf)	-0.193	0.143	1.78E-01	-0.474	0.088	-0.202	0.144	1.61E-01	-0.485	0.080	-0.200	0.144	1.65E-01	-0.482	0.082
	time of day (in hours since 9AM)	0.057	0.026	3.07E-02	0.005	0.108	0.058	0.027	3.05E-02	0.005	0.110	0.055	0.027	4.25E-02	0.002	0.107
	intercept	-0.068	0.210	7.47E-01	-0.479	0.344	-0.101	0.206	6.25E-01	-0.505	0.303	-0.102	0.191	5.93E-01	-0.476	0.272
random factors	**variation by batch**	*0.322*	*0.134*	-	*0.143*	*0.727*	*0.301*	*0.128*	-	*0.131*	*0.694*	*0.258*	*0.115*	-	*0.107*	*0.619*
	intercept	*0.765*	*0.037*	-	*0.696*	*0.840*	*0.769*	*0.037*	-	*0.699*	*0.845*	*0.766*	*0.037*	-	*0.696*	*0.842*

continued **Supplementary Table 36**

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=172)					Model 2 (n=169)					Model 3 (n=167)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***lpar2a***	3.491	1.201	3.64E-03	1.138	5.845	3.980	1.232	1.23E-03	1.566	6.394	3.491	1.232	4.60E-03	1.077	5.906
	lpar2b	0.731	1.027	4.77E-01	-1.282	2.744	0.697	1.067	5.14E-01	-1.394	2.788	0.449	1.424	7.52E-01	-2.341	3.240
	gatad2ab	0.029	0.511	9.55E-01	-0.972	1.030	0.066	0.552	9.05E-01	-1.017	1.148	0.395	0.723	5.85E-01	-1.022	1.813
	body length (in SD)	-	-	-	-	-	-0.122	0.216	5.72E-01	-0.546	0.302	-0.037	0.188	8.43E-01	-0.406	0.331
	dorsal body surface area (in SD)	-	-	-	-	-	-0.255	0.201	2.05E-01	-0.649	0.140	-0.181	0.219	4.09E-01	-0.610	0.248
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.101	0.098	3.01E-01	-0.293	0.091
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.075	0.148	6.12E-01	-0.215	0.366
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.253	0.142	7.46E-02	-0.531	0.025
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.201	0.147	1.70E-01	-0.489	0.086
	age (11dpf vs. 10dpf)	0.299	0.644	6.42E-01	-0.963	1.561	0.112	0.610	8.55E-01	-1.084	1.308	0.079	0.657	9.04E-01	-1.208	1.367
	time of day (in hours since 9AM)	-0.191	0.065	3.40E-03	-0.319	-0.063	-0.201	0.068	3.16E-03	-0.334	-0.068	-0.218	0.065	8.01E-04	-0.346	-0.091
	batch 1	4.452	0.809	3.69E-08	2.867	6.038	4.444	0.776	1.02E-08	2.923	5.964	4.653	0.807	8.12E-09	3.071	6.234
	batch 2	6.112	0.952	1.36E-10	4.246	7.978	6.307	0.968	7.16E-11	4.410	8.204	6.522	1.071	1.15E-09	4.422	8.621
	batch 3	5.736	0.900	1.86E-10	3.972	7.501	6.046	0.910	3.01E-11	4.263	7.829	5.970	1.005	2.83E-09	4.001	7.939
	intercept	-1.169	0.934	2.11E-01	-3.000	0.661	-1.113	0.862	1.97E-01	-2.802	0.577	-1.170	0.963	2.24E-01	-3.059	0.718

		Vascular infiltration by neutrophils														
		Model 1 (n=232)					Model 2 (n=229)					Model 3 (n=227)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
fixed factors	***lpar2a***	0.743	0.395	5.99E-02	-0.031	1.517	0.659	0.394	9.43E-02	-0.113	1.431	0.614	0.394	1.19E-01	-0.158	1.386
	lpar2b	0.096	0.548	8.61E-01	-0.978	1.169	0.068	0.549	9.02E-01	-1.007	1.143	0.230	0.605	7.03E-01	-0.956	1.417
	gatad2ab	0.099	0.365	7.86E-01	-0.617	0.815	0.098	0.363	7.86E-01	-0.614	0.810	0.124	0.362	7.33E-01	-0.586	0.834
	body length (in SD)	-	-	-	-	-	0.152	0.075	4.40E-02	0.004	0.300	0.138	0.078	7.79E-02	-0.015	0.291
	dorsal body surface area (in SD)	-	-	-	-	-	0.117	0.072	1.07E-01	-0.025	0.259	0.093	0.075	2.13E-01	-0.053	0.239
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.065	0.057	2.60E-01	-0.177	0.048
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.023	0.060	6.97E-01	-0.140	0.094
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.046	0.068	5.01E-01	-0.087	0.178
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.043	0.063	4.97E-01	-0.081	0.166
	age (11dpf vs. 10dpf)	-0.198	0.151	1.89E-01	-0.493	0.098	-0.192	0.148	1.96E-01	-0.482	0.099	-0.239	0.151	1.14E-01	-0.535	0.057
	time of day (in hours since 9AM)	0.052	0.028	6.65E-02	-0.004	0.108	0.043	0.028	1.31E-01	-0.013	0.099	0.050	0.029	8.02E-02	-0.006	0.107
	intercept	-0.010	0.185	9.57E-01	-0.373	0.353	-0.049	0.178	7.82E-01	-0.398	0.300	-0.047	0.185	8.01E-01	-0.410	0.316
random factors	**variation by batch**	*0.225*	*0.100*	-	*0.094*	*0.538*	*0.192*	*0.099*	-	*0.069*	*0.530*	*0.217*	*0.109*	-	*0.081*	*0.581*
	intercept	*0.867*	*0.041*	-	*0.791*	*0.950*	*0.860*	*0.041*	-	*0.784*	*0.944*	*0.850*	*0.040*	-	*0.775*	*0.933*

continued **Supplementary Table 36**

		Vascular co-localization of lipids with neutrophils														
		Model 1 (n=176)					Model 2 (n=173)					Model 3 (n=171)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***lpar2a***	2.693	1.323	4.18E-02	0.100	5.287	2.505	1.340	6.17E-02	-0.122	5.132	2.972	1.402	3.41E-02	0.223	5.720
	lpar2b	-0.100	1.075	9.26E-01	-2.208	2.008	-0.728	1.092	5.05E-01	-2.867	1.411	-0.877	1.259	4.86E-01	-3.345	1.590
	gatad2ab	-1.545	1.448	2.86E-01	-4.383	1.292	-2.143	1.291	9.69E-02	-4.673	0.387	-2.900	1.211	1.66E-02	-5.273	-0.527
	body length (in SD)	-	-	-	-	-	0.532	0.244	2.96E-02	0.053	1.010	0.476	0.265	7.26E-02	-0.044	0.995
	dorsal body surface area (in SD)	-	-	-	-	-	0.089	0.265	7.37E-01	-0.430	0.608	0.128	0.265	6.28E-01	-0.391	0.648
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.167	0.163	3.06E-01	-0.153	0.487
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.241	0.192	2.09E-01	-0.617	0.135
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.200	0.197	3.09E-01	-0.185	0.586
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.104	0.222	6.38E-01	-0.330	0.539
	age (11dpf vs. 10dpf)	0.829	0.618	1.80E-01	-0.382	2.040	0.886	0.595	1.37E-01	-0.281	2.052	0.783	0.609	1.98E-01	-0.410	1.975
	time of day (in hours since 9AM)	-0.101	0.085	2.35E-01	-0.269	0.066	-0.080	0.081	3.20E-01	-0.239	0.078	-0.114	0.083	1.72E-01	-0.277	0.049
	batch 1	3.050	1.019	2.77E-03	1.052	5.048	3.227	0.935	5.58E-04	1.395	5.060	3.178	0.807	8.30E-05	1.595	4.760
	batch 2	4.083	1.204	6.97E-04	1.723	6.443	3.458	1.200	3.95E-03	1.107	5.810	3.344	1.164	4.05E-03	1.064	5.625
	batch 3	3.432	1.157	3.01E-03	1.165	5.699	3.100	1.139	6.51E-03	0.867	5.333	3.126	1.086	4.00E-03	0.997	5.254
	intercept	-1.445	1.165	2.15E-01	-3.729	0.839	-1.665	1.046	1.12E-01	-3.715	0.386	-1.533	0.950	1.07E-01	-3.395	0.329

		Vascular co-localization of macrophages with neutrophils														
		Model 1 (n=218)					Model 2 (n=215)					Model 3 (n=213)				
		Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
negative binomial terms	***lpar2a***	0.179	0.300	5.50E-01	-0.408	0.767	0.145	0.312	6.42E-01	-0.467	0.757	0.096	0.337	7.75E-01	-0.564	0.756
	lpar2b	-0.031	0.512	9.51E-01	-1.035	0.973	0.026	0.479	9.56E-01	-0.912	0.965	0.108	0.566	8.49E-01	-1.001	1.217
	gatad2ab	-0.507	0.543	3.51E-01	-1.571	0.558	-0.489	0.562	3.84E-01	-1.591	0.612	-0.628	0.528	2.35E-01	-1.663	0.407
	body length (in SD)	-	-	-	-	-	-0.034	0.094	7.22E-01	-0.219	0.151	-0.038	0.098	7.02E-01	-0.230	0.155
	dorsal body surface area (in SD)	-	-	-	-	-	0.108	0.085	2.06E-01	-0.059	0.275	0.089	0.084	2.87E-01	-0.075	0.254
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.102	0.073	1.61E-01	-0.246	0.041
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.022	0.063	7.21E-01	-0.146	0.101
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.134	0.072	6.41E-02	-0.008	0.276
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.022	0.063	7.27E-01	-0.102	0.147
	age (11dpf vs. 10dpf)	-0.246	0.166	1.37E-01	-0.571	0.079	-0.236	0.168	1.60E-01	-0.566	0.093	-0.286	0.167	8.67E-02	-0.613	0.041
	time of day (in hours since 9AM)	0.051	0.035	1.41E-01	-0.017	0.119	0.052	0.035	1.38E-01	-0.017	0.120	0.058	0.034	8.68E-02	-0.008	0.123
	batch 1	0.004	0.178	9.83E-01	-0.345	0.352	0.057	0.181	7.51E-01	-0.298	0.413	-0.050	0.199	8.04E-01	-0.440	0.341
	batch 2	0.425	0.258	9.96E-02	-0.081	0.931	0.389	0.350	2.66E-01	-0.296	1.075	0.238	0.379	5.30E-01	-0.505	0.981
	batch 3	1.085	0.241	6.76E-06	0.612	1.557	1.029	0.291	4.03E-04	0.459	1.598	0.932	0.314	3.01E-03	0.316	1.549
	intercept	3.950	0.216	1.22E-74	3.527	4.374	3.937	0.218	4.87E-73	3.510	4.363	4.001	0.233	6.77E-66	3.544	4.459

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 37 - 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=195)					Model 2 (n=195)					Model 3 (n=194)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	1.057	1.230	9.62E-01	0.108	10.336	5.497	7.312	2.00E-01	0.405	74.535	6.792	9.958	1.91E-01	0.384	120.216
lpar2b	all 30 larvae with an undetected vessel are wildtype for mutations in *lpar2b* ; 1.04 mutant larvae were expected.														
gatad2ab	all 30 larvae with an undetected vessel are wildtype for mutations in *gatad2ab* ; 1.40 mutant larvae were expected.														
age (11dpf vs. 10dpf)	3.824	1.592	1.27E-03	1.691	8.648	1.679	0.831	2.95E-01	0.636	4.430	1.252	0.665	6.72E-01	0.442	3.544
time of day (in hours since 9AM)	0.911	0.090	3.46E-01	0.751	1.106	1.019	0.121	8.77E-01	0.806	1.286	1.101	0.143	4.57E-01	0.854	1.420
body length (in SD)	-	-	-	-	-	0.172	0.064	1.95E-06	0.083	0.355	0.132	0.059	6.47E-06	0.055	0.318
dorsal body surface area (in SD)	-	-	-	-	-	0.324	0.103	3.71E-04	0.175	0.603	0.279	0.104	5.81E-04	0.135	0.578
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.035	0.345	9.19E-01	0.538	1.989
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.687	0.500	7.78E-02	0.943	3.016
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.414	0.155	1.89E-02	0.198	0.864
glucose levels	-	-	-	-	-	-	-	-	-	-	1.123	0.349	7.09E-01	0.610	2.066
intercept	0.148	0.079	3.75E-04	0.052	0.424	0.080	0.052	1.01E-04	0.022	0.285	0.037	0.030	3.30E-05	0.008	0.177

	Many false positive lipid deposits														
	Model 1 (n=205)					Model 2 (n=205)					Model 3 (n=204)				
	Effect	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**	**Effect**	**SE**	***P***	**lci**	**uci**
lpar2a	all 37 larvae with many false positive lipid deposits were wildtype for mutations in *lpar2a* ; 1.06 mutant larvae were expected.														
lpar2b	all 37 larvae with many false positive lipid deposits were wildtype for mutations in *lpar2b* ; 1.28 mutant larvae were expected.														
gatad2ab	2.625	2.496	3.10E-01	0.407	16.924	2.534	2.420	3.30E-01	0.390	16.474	2.784	2.705	2.92E-01	0.414	18.700
age (11dpf vs. 10dpf)	1.239	0.486	5.86E-01	0.574	2.673	1.128	0.482	7.78E-01	0.488	2.608	1.024	0.449	9.58E-01	0.434	2.416
time of day (in hours since 9AM)	0.843	0.078	6.43E-02	0.704	1.010	0.847	0.080	7.81E-02	0.704	1.019	0.863	0.083	1.24E-01	0.714	1.041
body length (in SD)	-	-	-	-	-	0.986	0.213	9.49E-01	0.646	1.505	1.070	0.250	7.72E-01	0.677	1.690
dorsal body surface area (in SD)	-	-	-	-	-	0.882	0.178	5.34E-01	0.593	1.311	0.915	0.192	6.73E-01	0.607	1.381
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.946	0.175	7.63E-01	0.658	1.358
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.032	0.200	8.72E-01	0.706	1.508
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.847	0.184	4.43E-01	0.554	1.295
glucose levels	-	-	-	-	-	-	-	-	-	-	1.121	0.227	5.75E-01	0.753	1.668
intercept	0.405	0.185	4.84E-02	0.165	0.994	0.421	0.196	6.30E-02	0.169	1.048	0.405	0.190	5.36E-02	0.162	1.014

continued **Supplementary Table 37**

	Many false negative lipid deposits														
	Model 1 (n=187)					Model 2 (n=187)					Model 3 (n=186)				
	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* ; 0.55 mutant larvae were expected.														
lpar2b	all 19 larvae with many false negative lipid deposits were wildtype for mutations in *lpar2b* ; 0.66 mutant larvae were expected.														
gatad2ab	0.882	1.417	9.38E-01	0.038	20.579	0.462	0.848	6.74E-01	0.013	16.818	0.998	1.890	9.99E-01	0.024	40.849
age (11dpf vs. 10dpf)	1.076	0.566	8.89E-01	0.384	3.017	0.489	0.283	2.16E-01	0.157	1.519	0.442	0.269	1.79E-01	0.134	1.454
time of day (in hours since 9AM)	0.879	0.104	2.75E-01	0.698	1.108	0.969	0.130	8.15E-01	0.745	1.261	1.048	0.146	7.35E-01	0.798	1.377
body length (in SD)	-	-	-	-	-	0.401	0.136	7.17E-03	0.206	0.780	0.420	0.161	2.36E-02	0.198	0.890
dorsal body surface area (in SD)	-	-	-	-	-	0.385	0.124	3.14E-03	0.204	0.725	0.411	0.141	9.69E-03	0.209	0.806
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.939	0.281	8.33E-01	0.523	1.687
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.373	0.374	2.44E-01	0.805	2.342
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.608	0.206	1.42E-01	0.313	1.182
glucose levels	-	-	-	-	-	-	-	-	-	-	1.367	0.380	2.61E-01	0.792	2.359
intercept	0.195	0.114	5.23E-03	0.062	0.615	0.176	0.112	6.29E-03	0.050	0.612	0.108	0.075	1.49E-03	0.027	0.426

	Many false positive macrophages														
	Model 1 (n=271)					Model 2 (n=271)					Model 3 (n=270)				
	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
lpar2a	all 11 larvae with many false positive macrophages were wildtype for mutations in *lpar2a* ; 0.38 mutant larvae were expected.														
lpar2b	all 11 larvae with many false positive macrophages were wildtype for mutations in *lpar2b* ; 0.19 mutant larvae were expected.														
gatad2ab	all 11 larvae with many false positive macrophages were wildtype for mutations in *gatad2ab* ; 0.72 mutant larvae were expected.														
age (11dpf vs. 10dpf)	0.824	0.569	7.79E-01	0.213	3.190	0.812	0.593	7.75E-01	0.194	3.396	1.137	0.884	8.69E-01	0.248	5.216
time of day (in hours since 9AM)	1.046	0.155	7.61E-01	0.783	1.397	1.032	0.154	8.34E-01	0.770	1.383	0.956	0.156	7.82E-01	0.694	1.316
body length (in SD)	-	-	-	-	-	0.748	0.246	3.77E-01	0.393	1.424	0.619	0.225	1.88E-01	0.304	1.263
dorsal body surface area (in SD)	-	-	-	-	-	1.370	0.436	3.23E-01	0.734	2.555	1.272	0.423	4.70E-01	0.663	2.440
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	2.352	0.859	1.93E-02	1.149	4.813
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.763	0.287	4.72E-01	0.365	1.595
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.009	0.417	9.83E-01	0.448	2.269
glucose levels	-	-	-	-	-	-	-	-	-	-	0.919	0.326	8.11E-01	0.458	1.842
intercept	0.037	0.028	1.41E-05	0.008	0.163	0.037	0.028	9.26E-06	0.009	0.159	0.034	0.028	2.81E-05	0.007	0.166

	Clumped macrophages														
	Model 1 (n=271)					Model 2 (n=271)					Model 3 (n=270)				
	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* ; 0.39 mutant larvae were expected.														
lpar2b	14.241	26.688	1.56E-01	0.362	560.676	16.779	32.023	1.40E-01	0.398	706.875	29.333	69.590	1.54E-01	0.281	3067
gatad2ab	all 11 larvae with clumped macrophages were wildtype for mutations in *gatad2ab* ; 0.72 mutant larvae were expected.														
age (11dpf vs. 10dpf)	0.824	0.569	7.79E-01	0.213	3.190	0.812	0.593	7.75E-01	0.194	3.396	1.137	0.884	8.69E-01	0.248	5.216
time of day (in hours since 9AM)	1.046	0.155	7.61E-01	0.783	1.397	1.032	0.154	8.34E-01	0.770	1.383	0.956	0.156	7.82E-01	0.694	1.316
body length (in SD)						0.748	0.246	3.77E-01	0.393	1.424	0.619	0.225	1.88E-01	0.304	1.263
dorsal body surface area (in SD)						1.370	0.436	3.23E-01	0.734	2.555	1.272	0.423	4.70E-01	0.663	2.440
LDLc levels (in SD)						-	-	-	-	-	2.352	0.859	1.93E-02	1.149	4.813

continued **Supplementary Table 37**

	Clumped macrophages														
	Model 1 (n=271)					Model 2 (n=271)					Model 3 (n=270)				
	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
HDLc levels (in SD)						-	-	-	-	-	0.763	0.287	4.72E-01	0.365	1.595
triglyceride levels (in SD)						-	-	-	-	-	1.009	0.417	9.83E-01	0.448	2.269
glucose levels						-	-	-	-	-	0.919	0.326	8.11E-01	0.458	1.842
intercept	0.037	0.028	1.41E-05	0.008	0.163	0.037	0.028	9.26E-06	0.009	0.159	0.034	0.028	2.81E-05	0.007	0.166

	Many macrophages outside the region of interest														
	Model 1 (n=182)					Model 2 (n=182)					Model 3 (n=181)				
	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* ; 0.53 mutant larvae were expected.														
lpar2b	all 15 larvae with many macropahages outside the region of interest were wildtype for mutations in *lpar2b* ; 0.26 mutant larvae were expected.														
gatad2ab	all 15 larvae with many macropahages outside the region of interest were wildtype for mutations in *gatad2ab* ; 0.18 mutant larvae were expected.														
time of day (in hours since 9AM)	0.834	0.252	5.49E-01	0.461	1.510	0.786	0.237	4.24E-01	0.436	1.419	0.744	0.249	3.76E-01	0.387	1.432
body length (in SD)	-	-	-	-	-	0.571	0.290	2.70E-01	0.211	1.546	0.595	0.335	3.57E-01	0.197	1.795
dorsal body surface area (in SD)	-	-	-	-	-	2.732	1.751	1.17E-01	0.777	9.598	2.768	1.773	1.12E-01	0.789	9.715
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	2.530	1.920	2.21E-01	0.572	11.199
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.676	0.437	5.45E-01	0.191	2.400
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.391	0.291	2.08E-01	0.091	1.685
glucose levels	-	-	-	-	-	-	-	-	-	-	1.026	0.841	9.75E-01	0.206	5.112
intercept	0.035	0.043	7.04E-03	0.003	0.399	0.025	0.031	3.14E-03	0.002	0.290	0.024	0.032	5.71E-03	0.002	0.336

	Clumped neutrophils														
	Model 1 (n=323)					Model 2 (n=323)					Model 3 (n=322)				
	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci	Effect	SE	*P*	lci	uci
lpar2a	2.929	2.464	2.01E-01	0.563	15.229	2.975	2.502	1.95E-01	0.572	15.463	2.396	2.067	3.11E-01	0.442	12.993
lpar2b	all 34 larvae with clumped neutrophils were wildtype for mutations in *lpar2b* ; 0.71 mutant larvae were expected.														
gatad2ab	1.132	1.303	9.15E-01	0.118	10.806	1.032	1.201	9.78E-01	0.106	10.099	1.134	1.340	9.15E-01	0.112	11.493
age (11dpf vs. 10dpf)	0.548	0.247	1.81E-01	0.227	1.324	0.508	0.238	1.47E-01	0.203	1.270	0.442	0.215	9.28E-02	0.171	1.145
time of day (in hours since 9AM)	1.030	0.092	7.44E-01	0.865	1.226	1.051	0.101	6.00E-01	0.872	1.268	1.074	0.105	4.62E-01	0.888	1.300
body length (in SD)	-	-	-	-	-	0.822	0.162	3.20E-01	0.558	1.210	0.914	0.196	6.75E-01	0.601	1.390
dorsal body surface area (in SD)	-	-	-	-	-	1.034	0.200	8.64E-01	0.708	1.509	1.099	0.222	6.38E-01	0.741	1.632
LDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.944	0.186	7.70E-01	0.641	1.389
HDLc levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.013	0.189	9.44E-01	0.703	1.460
triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.796	0.176	3.04E-01	0.516	1.229
glucose levels	-	-	-	-	-	-	-	-	-	-	1.158	0.218	4.34E-01	0.801	1.674
intercept	0.115	0.051	9.67E-07	0.049	0.274	0.108	0.049	9.83E-07	0.044	0.263	0.100	0.046	6.91E-07	0.040	0.249

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 qualtification pipeline. Associations were examined using logistic regression 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). 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 LDLc, HDLc, 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. Adjusting for batch would have resulted in the exclusion of larvae. Lci and uci are lower and upper boundaries of the 95% confidence interval.