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

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Abstract

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

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

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

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

Introduction

Coronary artery disease (CAD) is the main cause of death worldwide, and results from the progression of atherosclerosis in the coronary arteries¹. 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 susceptibility²⁻⁴. Some of these loci harbor genes with well-known roles in cholesterol metabolism – e.g. *APOE*⁵, *APOB*⁶ and *LDLR*⁷ – and some encode the targets of lipid-lowering drugs, i.e. *HMGCR* (statins)⁸, *NPC1L1* (ezetimibe)⁹ and *PCSK9* (evolocumab)^{10,11}. It thus seems plausible that identifying and characterizing causal genes in the remaining loci would further increase our understanding of cholesterol metabolism, atherosclerosis and CAD pathophysiology, and yield new targets for prevention and treatment of CAD^{11,12}.

Murine model systems have traditionally been used to characterize genes that play a role in familial hypercholesterolemia and atherosclerosis^{13,14}. 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*¹⁵, 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^{16,17}.

Proof-of-principle experiments on using zebrafish larvae as a model system for early-stage atherosclerosis have so far provided promising results¹⁸⁻²³, but were based on observations in fewer than 25 larvae per condition. This was at least in part because mounting larvae in low melting agarose for imaging is time-consuming. In addition, whole-body cholesterol and triglyceride levels were usually quantified in samples of 20-100 pooled larvae^{24,25}. While suitable

1 and efficient for dietary and drug treatment interventions, pooling larvae for phenotypic
2 characterization is not optimal in CRISPR-based genetic interventions, where – depending on the
3 approach - sequencing of individual larvae may be required. Hence, confirmation of initial
4 findings, an improved resolution of quantitative readouts, and a higher throughput are desirable
5 before zebrafish larvae can be used as a model system for large-scale characterization of
6 candidate genes for dyslipidemia, atherosclerosis and CAD. To this end, we performed a large-
7 scale dietary intervention, a treatment intervention with lipid lowering drugs, and a multiplexed,
8 CRISPR-Cas9-based genetic intervention for proof-of-concept genes, followed by the
9 characterization of three candidate genes in a GWAS-identified, pleiotropic locus on chr
10 19p13.11²⁶.

Results

Overfeeding and cholesterol supplementation have independent pro-atherogenic effects

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

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

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

As described in earlier studies^{18,19,25}, we supplemented regular dry food with extra cholesterol using diethyl ether, which may itself affect endogenous cholesterol levels²⁷. Our results show that diethyl ether per se indeed resulted in: 1) higher triglyceride (trend) and total cholesterol levels (**Supplementary Table 4**); 2) less vascular co-localization of lipids with neutrophils; 3) a lower endothelial thickness (**Supplementary Table 5**); and 5) a lower food intake (**Supplementary Fig. 4**). Hence, absence of a control group fed on diethyl ether-treated food without cholesterol supplementation would have resulted in biased estimates for the effect of cholesterol supplementation.

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

Combined treatment with atorvastatin and ezetimibe has an atheroprotective effect

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

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

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

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

Next, 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 *ldlr*) (**Supplementary Tables 11 and 12**). Across the seven CRISPR-Cas9-targeted orthologues, we observed a median of 15 unique amplicons per targeted site in the 384 sequenced F₁ larvae (**Supplementary Table 13**). Compared with the reference genome, the 384 sequenced F₁ larvae together contained 55 frameshift variants, nine variants that introduced a premature stop codon, 34 missense variants, 13 in frame deletions, two in frame insertions, four synonymous variants, and 18 upstream variants within ± 30 bp of the targeted sites (**Supplementary Table 14**). The mutant allele frequency was typically high across the seven targeted sites (i.e. median 0.883, **Supplementary Table 15**).

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

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

macrophages with neutrophils, without affecting whole-body lipoprotein or glucose levels (Supplementary Fig. 6b, Supplementary Tables 20 and 21). On average, larvae with two functionally knocked *apobb.1* alleles were shorter than larvae with two unmodified alleles (Fig. 2e-i, Supplementary Table 19), and had higher triglyceride (trend) and lower total cholesterol and glucose levels (Fig. 2e-iii, Supplementary Table 20). They were also characterized by more vascular accumulation of lipids, and by more vascular co-localization of lipids with macrophages and with neutrophils, independently of whole-body lipoprotein or glucose levels (Fig. 2e-ii, Supplementary Table 21). While less than half of the larvae free from mutated *apobb.1* alleles showed any vascular co-localization of lipids with macrophages (44%) and neutrophils (15%), more than two out of three larvae carrying two functionally knocked *apobb.1* alleles showed such vascular co-localization. Finally, larvae with two functionally knocked *ldlra* alleles were similar on all accounts to larvae free from CRISPR-induced mutations in the gene, except for having less vascular co-localization of macrophages with neutrophils (Supplementary Fig. 6d, Supplementary Tables 19-21).

Across the four zebrafish orthologues (*apoec1a*, *apoec1b*, *apobb.1* and *ldlra*), results were similar when data were analyzed using an additive model in which the number of mutated alleles was weighted by their predicted effect on protein function (Supplementary Tables 22-24). Additional analyses showed that suboptimal image quality or image quantification in a small subset of larvae is unlikely to have influenced the results (Supplementary Table 25). Since *APOE*, *APOB* and *LDLR* interact to process triglyceride-rich LDLc in humans, we next examined two-way gene x gene interactions for *apoec1a*, *apobb.1* and *ldlra*; i.e. the genes that showed the most promising results individually. Focusing on interactions that were observed under an additive model and that were confirmed when comparing larvae with two vs. zero functionally knocked alleles only shows cautious evidence of a positive interaction between mutations in

apoea and *ldlra* for vascular accumulation of lipids and co-localization of lipids with macrophages (**Supplementary Tables 26-28**).

Vascular atherogenic traits are associated with whole-body triglyceride levels

Data from the dietary, drug treatment and genetic interventions combined showed that LDLc, HDLc and triglyceride levels together explained 47% of the variance in directly assessed total cholesterol levels (n=1,867). Interestingly, the Friedewald equation (i.e. LDLc + HDLc + triglycerides/5)²⁸ did not perform much worse, explaining 43% of the variance in total cholesterol levels (**Supplementary Fig. 7**). We next explored the mutually adjusted association of vascular atherogenic traits with whole-body LDLc, HDLc, triglyceride and glucose levels in data from the dietary, drug treatment and proof of concept genetic intervention studies combined. Vascular accumulation of lipids, co-localization of lipids with macrophages and neutrophils, and co-localization of oxLDL with macrophages were all positively associated with whole-body triglyceride levels, independently of LDLc, HDLc and glucose levels. Furthermore, vascular accumulation of oxLDL and co-localization of lipids with neutrophils showed some evidence of a positive association with whole-body HDLc levels, in line with the absence of effects on primary clinical endpoint events observed in large clinical trials that therapeutically elevated HDLc levels and reduced triglyceride and/or LDLc levels²⁹⁻³². Interestingly, vascular co-localization of lipids with neutrophils showed independent positive associations with LDLc, HDLc and triglyceride levels. Finally, we observed negative associations of whole-body glucose levels with vascular accumulation of lipids, co-localization of lipids with macrophages, and co-localization of macrophages with oxLDL, suggesting that hyperglycemia per se is perhaps not responsible for the elevated risk of CAD in diabetes patients, at least not by increasing early stage atherosclerosis (**Supplementary Fig. 8, Supplementary Table 29**).

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

Based on the positive association of vascular atherogenic traits with triglyceride levels in our combined analysis, in combination with the known causal effect of high triglyceride levels on CAD incidence³³, we used DEPICT³⁴ to prioritize candidate genes in 23 triglyceride-associated loci²⁶. In one of these loci, represented by the intronic rs10401969 in *SUGPI* on chr 19p13.11, DEPICT prioritized *LPAR2*, *GMIP*, *GATAD2A* and *TM6SF2*. The four prioritized genes together have six orthologues in zebrafish (**Supplementary Table 30**), which we targeted simultaneously (**Supplementary Table 31**).

Across the six CRISPR-Cas9-targeted orthologues (*lpar2a*, *lpar2b*, *gmip*, *gatad2ab*, *tm6sf2* and *zgc:85843*), we observed a median of 2.5 unique amplicons per targeted site (**Supplementary Table 32**). Compared with the reference genome, the 547 sequenced F₁ larvae together contained four frameshift variants, three missense variants, and four in-frame deletions that were located within ± 30 bp of the CRISPR targeted sites (**Supplementary Table 33**). In spite of having pre-tested the CRISPR gRNAs for efficiency, all F₁ larvae carried two unmodified alleles for the zebrafish orthologues of *TM6SF2* (*tm6sf2* and *zgc:85843*) and *GMIP* (*gmip*), and mutant allele frequencies were low for *gatad2ab* (0.029), *lpar2a* (0.010), and *lpar2b* (0.005) (**Supplementary Table 34**).

In spite of the low statistical power to find associations, we observed evidence for lower LDLc, triglyceride and total cholesterol levels in the 11 larvae with a mutated *lpar2a* allele, when compared with larvae with two unmodified alleles. Counterintuitively, these larvae also showed some evidence for having more vascular co-localization of lipids with macrophages and with neutrophils. (**Fig. 3a, Supplementary Tables 35-37**). In addition to the effects observed for *lpar2a*, the six larvae with a mutated *lpar2b* allele were longer and tended to have lower HDLc

1 levels compared with larvae free from CRISPR-induced *lpar2b* mutations (**Fig. 3b**,
2 **Supplementary Tables 35-37**). Finally, the 32 larvae with a mutated *gatad2ab* allele were larger
3 and tended to have lower HDL and higher triglyceride levels when compared with larvae with
4 two unmodified alleles (**Fig. 3c, Supplementary Table 36**). Exclusion of larvae with suboptimal
5 image quality or image quantification is unlikely to have influenced the results (**Supplementary**
6 **Table 38**).

Discussion

We developed and validated a largely image-based experimental pipeline in zebrafish larvae that is suitable to systematically characterize candidate genes and drugs for a role in dyslipidemia and early-stage atherosclerosis and inflammation. Our dietary intervention showed that five days of overfeeding is 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* and *APOB* trigger a pro-dyslipidemia, pro-atherogenic and pro-inflammatory phenotype that is in line with the known role of these genes. Finally, we illustrated the merit of our pipeline by attributing a role in cholesterol metabolism and atherosclerosis to *LPAR2* and *GATAD2A*; two genes in a pleiotropic locus on chr 19p13.11²⁶.

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. At the vascular level, overfeeding resulted in an overall more pro-atherogenic profile; cholesterol supplementation only resulted in more vascular co-localization of lipids with neutrophils. These results suggest that primary accumulation of lipids in the vessel wall was likely mostly driven by elevated triglyceride levels. In line with this, data from the dietary, drug treatment and genetic interventions combined showed a positive association for triglyceride levels – but not LDLc – with vascular lipid deposition. Furthermore, mutations in

apobb.1 resulted in higher whole-body triglyceride levels as well as in more vascular accumulation of lipids – albeit independently of triglyceride levels – while mutations in *apoec* resulted in higher whole-body LDLc levels but did not influence vascular lipid deposition.

Treating larvae with atorvastatin and ezetimibe resulted in lower whole-body LDLc and total cholesterol levels; and in less vascular co-localization of lipids with macrophages; yet – paradoxically – in more vascular co-localization of oxLDL with macrophages. A directionally consistent (i.e. lowering) effect was observed for dietary cholesterol supplementation on vascular co-localization of oxLDL with macrophages. Moreover, cholesterol supplementation or drug treatment did not affect accumulation of oxLDL or macrophages per se. Taken together, these observations suggest that ezetimibe's exogenous cholesterol lowering effect may be responsible for improved: 1) recruitment of macrophages to oxLDL; 2) engulfing of oxLDL by macrophages; 3) survival of macrophages that successfully engulfed oxLDL; and/or 4) 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^{35,36} and genetic association studies^{37,38} 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 should be sufficiently sensitive to provide valuable new insights.

Of the three *APOB* orthologues in zebrafish (*apoba*, *apobb.1* and *apobb.2*), *apobb.1*, accounts for 95% of apob protein²¹. *Apobb.1* is mainly expressed in intestine and liver²¹, where it facilitates the assembly and secretion of triglyceride-rich chylomicrons and VLDL, respectively³⁹. Unlike mice⁴⁰, but similar to humans⁴¹, zebrafish larvae with two loss of function

mutations in *apobb.1* alongside similar mutations in *apoba* and *apobb.2* were viable, at least until 10dpf. Viability during early development despite absence of functional apob protein suggests that Apo B is more essential for processing fetal nutrition in mice than in humans and zebrafish. However, homozygous mutations described in humans⁴² and observed here in zebrafish result in a truncated protein, while those described in mice inhibit protein synthesis completely⁴⁰. Hence, alternatively, complete absence of Apo B protein may induce a more severe phenotype than presence of a truncated protein. The CRISPR-induced mutations in *apobb.1* may result in a truncated apobb.1 protein that cannot act as a ligand for lipoprotein lipase; the enzyme that catalyzes the conversion of triglyceride-rich- chylomicrons and VLDL to cholesterol-rich- IDL and LDL. This would result in higher triglyceride and lower total cholesterol levels, as we observed in this study. In line with results in humans⁴³, we also observed a more severe pro-atherogenic and pro-inflammatory profile in *apobb.1* mutant zebrafish larvae. These findings together suggest that *apobb.1*^{-/-} zebrafish are likely a promising model to examine candidate genes and drugs for a role in dyslipidemia and atherosclerosis. The lower glucose levels in *apobb.1* mutants are in line with results in humans^{44,45}, and may result from impaired insulin clearance in the presence of hypobetalipoproteinemia⁴⁶.

Mutations in *ldlra* were not associated with dyslipidemia, early-stage atherosclerosis or vascular inflammation in our study. This contrast with established results in humans and mouse models likely reflects the presence of a second – albeit downregulated - *LDLR* orthologue in zebrafish (*ldlrb*); the possibility of *cetp*-mediated reverse cholesterol transport to remove excess cholesterol from the body in zebrafish; or the early stage of development at which we performed our screen. Two studies previously implicated *ldlra* in dyslipidemia and early-stage atherosclerosis in zebrafish larvae^{25,47}. While differences in age, food intake, microbial environment, enzymatic assays, normalization for protein content⁴⁸, genetic manipulation⁴⁹ and

adjustment for co-variables across studies may have influenced the results, the difference in sample size between studies is most noteworthy. O'Hare et al. compared combined LDLc and VLDLc levels using repeated measures on a sample of 100 pooled morpholino-injected and a sample of 100 pooled control-injected larvae²⁵, while Liu et al. compared triglyceride and total cholesterol levels in four wildtype larvae and four larvae that were homozygous for mutations in *ldlra*⁴⁷. In contrast, we compared cholesterol levels in 181 and 120 individual larvae with two and zero functionally knocked alleles, respectively, and included data from 381 larvae in our additive analyses. While mutations in *ldlra* and *apoea* alone did not trigger early-stage atherosclerosis, mutations in these genes showed a positive interaction for vascular accumulation of lipids and co-localization of lipids with macrophages. It appears that absence of both *ldlra* and *apoea* cannot be compensated in zebrafish larvae.

Like humans, zebrafish are genetically heterogeneous, and we observed a normal or negative binomial distribution for the examined outcomes, with substantial variance by transgenic background and batch in the dietary, drug treatment and genetic interventions. These findings stress the importance of including data from a large number of larvae to acquire meaningful results. We show it is now feasible to objectively quantify relevant traits in a large number of larvae with relative ease. Hence, adequately powered, *in vivo*, systematic gene and drug screens are now possible for these complex outcomes.

Characterizing zebrafish orthologues of candidate genes in a pleiotropic locus on chr 19p13.11 highlighted a role for *LPAR2* in cholesterol metabolism and early-stage atherosclerosis, and for *GATAD2A* in cholesterol metabolism. *LPAR2* belongs to family I of the G-protein coupled receptors and functions to mobilize calcium in response to lysophosphatidic acid (LPA), while *GATAD2A* encodes a transcriptional repressor. Unfortunately, all larvae in our screen were wildtype for the two CRISPR-targeted orthologues of *TM6SF2*. Knockdown and knockout of

Tm6sf2 in mice was previously shown to result in lower circulating triglyceride, LDLc, HDLc and total cholesterol levels; as well as in higher hepatic triglyceride and cholesteryl esters; more and larger neutral lipid droplets in the liver; a higher risk of hepatic steatosis; and less atherosclerosis⁵⁰⁻⁵². Like *Tm6sf2* deficient mice, *lpar2a* mutant zebrafish larvae had lower triglyceride, LDLc and total cholesterol levels. However, in contrast with *Tm6sf2* mutant mice, *lpar2a* mutant zebrafish larvae had more early-stage atherosclerosis, possibly driven by higher lysophosphatidic acid levels. Lysophosphatidic acid has been shown to increase NFκB, IL-8 and MCP-1 secretion from endothelial cells, which attract neutrophils and macrophages^{53,54}; and induces barrier dysfunction and elevated monocyte adhesion to the minimally modified LDL within the vascular intima⁵⁵. The bi-directional effects of mutations in putative causal genes in this pleiotropic locus on cardiovascular risk factors likely explains why the C allele of the regulatory rs10401969 is only associated with a trend towards a lower risk of CAD in humans (OR=0.95, P=2.8•10⁻³, n=268,744)².

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

Online Methods

1 Transgenic backgrounds and atherogenic traits

We used three combinations of fluorescent transgenes (backgrounds) with a lipid-staining dye⁵⁶ (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*⁵⁷) and neutrophils (*Tg:mpo-EGFP*⁵⁸) were crossed to yield a stable line in which we can visualize and quantify vascular accumulation and co-localization of lipids⁵⁶, macrophages⁵⁷ and neutrophils⁵⁸ (**Fig. 1b**). Secondly, we in-crossed zebrafish that express a fluorescently labelled antibody (IK17) against oxLDL (*Tg:hsp70:IK17-EGFP*)²⁰ to allow visualization and quantification of vascular accumulation of lipids⁵⁶ and oxLDL²⁰, and we crossed *Tg:hsp70:IK17-EGFP*²⁰ carriers with *Tg:mpeg1-mCherry* carriers to yield a stable line in which we can visualize and quantify vascular accumulation and co-localization of lipids⁵⁶, oxLDL²⁰ and macrophages⁵⁷ (**Fig. 1b-c**). Thirdly, carriers of the *flk:EGFP* transgene (*Tg:flk-EGFP*⁵⁹) 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)⁵⁶.

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)¹⁸; 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^{60–62}. 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^{24,25}. In addition, evidence suggests that treatment with atorvastatin and ezetimibe may reduce vascular lipid deposition^{25,63}.

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 food⁶³ 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 previously⁶⁴. Briefly, 75µl of yellow-green 2.0 µm polystyrene 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 CAD⁵⁻⁷. 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.⁶⁵.

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 Genomicus⁶⁶, and a literature search²¹ (**Supplementary Table 10**). We then designed CRISPR guide RNAs (gRNAs) to target these zebrafish orthologues – aiming for an early exon – using chopchop⁶⁷ and CRISPRscan⁶⁸, 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 F₁ 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 (F₁) 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 DEPICT³⁴-identified candidate genes in triglyceride-associated loci²⁶, 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)^{69,70}, 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

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

7 **7.2.1 Quantification of morphological features in zebrafish larvae**

8 Whole-body images of larvae acquired by the bright field camera of the VAST BioImager were
 9 used to quantify body length, dorsal and lateral body surface area, and body volume. To
 10 distinguish the larva from the capillary in which it was positioned, the capillary was assumed to
 11 be horizontal and the position of the capillary was obtained by projecting all pixel intensity
 12 values to the y-axis. That is, for each y-level, the sum of all pixels on that level in x was
 13 computed (**Fig. 1a**). The edges of the capillary appeared as minima of the projection, and the
 14 position of the inner walls were defined as the inner slopes of those minima with the steepest
 15 angle, i.e. the highest absolute derivative. Once the region inside the capillary was defined, larvae
 16 were segmented from the image background using grey-level thresholding based on optimized
 17 precision with regards to a given size interval⁷¹. This method efficiently tries all possible
 18 threshold levels and selects the threshold level that maximizes the per-threshold-precision (true
 19 positive / (true positive + false positive), where true positive is defined as the number of pixels in
 20 objects within the size interval and false positive is defined as the number of pixels in objects
 21 outside the size interval. This pre-processing was performed in ImageJ. Holes within the binary
 22 mask were filled automatically using CellProfiler⁷², and the largest connected component was
 23 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 ilastik⁷³. 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 ImageJ⁷⁴, 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 Abbott Laboratories (Abbott 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)⁷⁵ to merge the trimmed paired-end reads; FastX version 0.0.14⁷⁶ to remove reads containing bases with a quality score below 20 (-q 20, -p 100); and Spliced Transcripts Alignment to a Reference (STAR) version 2.4.1c⁷⁷ to map the reads to the reference genome (Danio_rerio.GRCz11.dna.toplevel.fa as downloaded from Ensembl). SAMtools version 0.1.19⁷⁸ 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**).

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 F₁ 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 $\pm 5 \times$ 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, TK and MdH optimized the CRISPR-Cas9 multiplex pipeline; EM, OD and MDH generated the post NGS QC and variant calling pipeline; AL assessed whole-body lipid and glucose levels; HLB and MdH performed the statistical analysis; MKB and MdH wrote the manuscript; all authors provided critical feedback to the manuscript.

1 Competing Financial Interests statement

- 2 None of the authors have a competing financial interest to declare. Funding bodies did not
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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 and cholesterol supplementation ($n > 2000$); treatment with atorvastatin and ezetimibe ($n > 1000$); and mutations in *apoEa* and *apoBb.1* ($n = 384$) on body size (i), vascular atherogenic traits (ii) and whole-body lipid and glucose levels (iii). Across a-e, dorsal and lateral body surface area and body volume were normalized for body length before the analysis; whole-body lipid and glucose levels were normalized for protein levels; and endothelial thickness was normalized for surface area of the circulation. For normally distributed traits, associations were examined using hierarchical linear models on inverse-normally transformed outcomes. For these traits effect sizes and 95% confidence intervals are expressed in standard deviation units (SD). The remaining vascular atherogenic traits (shown in italics) showed a negative binomial distribution and data were analyzed accordingly. For these traits, effect sizes and 95% confidence intervals are expressed in μm^2 . In d and e, open circles and the dotted lines represent the effect of two functionally knocked-out alleles vs. two unmodified alleles, and full circles and filled lines represent the additive per mutated allele effect. Associations were adjusted for time of day; use of diethyl ether (for overfeeding and cholesterol supplementation); cholesterol supplementation (for overfeeding); the amount fed (for cholesterol supplementation); body length and dorsal body surface area (for vascular outcomes); batch; and transgenic background.

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

SUPPLEMENTARY FIGURES

Supplementary Figure 1 - The effect of overfeeding, cholesterol supplementation and treatment with atorvastatin and ezetimibe on body size (p53)

Supplementary Figure 2 - The effect of overfeeding, cholesterol supplementation and treatment with atorvastatin and ezetimibe on whole-body lipid and glucose levels (p54)

Supplementary Figure 3 - The effect of overfeeding, cholesterol supplementation and treatment with atorvastatin and ezetimibe on vascular atherogenic traits (p55-56)

Supplementary Figure 4 - Food intake as a function of dietary or drug treatment intervention (p57)

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 (p58)

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 (p59-60)

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 (p61)

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 (p62-63)

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

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

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

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

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

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

Supplementary Figure 6. The effect of mutations in *apoea*, *apoeb*, *apobb.1* and *Idlra* 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.

SUPPLEMENTARY TABLES

Supplementary Table 1 - Descriptive information for larvae at 10 days post-fertilization in the dietary, drug treatment and genetic interventions (p67)

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

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

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

Rationale for exclusion	Traits for which exclusion is relevant	Dietary Intervention			Drug treatment intervention			Genetic intervention						
		Available (n)	Excluded (n)	Excluded (%)	Available (n)	Excluded (n)	Excluded (%)	Proof-of-concept			Discovery (19p13.11 locus)			
								Available (n)	Excluded (n)	Excluded (%)	Available (n)	Excluded (n)	Excluded (%)	
<i>Monodansylpentane cadaverase</i>														
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	
<i>Tg(IK17:EGFP)</i>														
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		
<i>Tg(mpeg1:mCherry)</i>														
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	
<i>Tg(mpo:EGFP)</i>														
<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	
<i>Bright field</i>														
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 $\pm$ 5xSD that are free from the image quality-based annotation of interest plus the number of larvae that were excluded due to the quality-based annotation of interest for vascular infiltration by lipids (monodansylpentane cadaverase), oxidized LDL (Tg(IK17:EGFP)), macrophages (Tg(mpeg1:mCherry)), neutrophils (Tg(mpo:EGFP)), and body size (Bright field). For Tg(IK17:EGFP), larvae with many false positive or negative deposits were not excluded from further analysis. For all other traits, larvae with suboptimal image or quantification quality were excluded from further analyses.

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

		Body length (n=2193)				
		Effect	SE	P	lci	uci
fixed factors	overfeeding	0.350	0.040	9.15E-23	0.280	0.420
	cholesterol supplementation	-0.220	0.040	2.32E-07	-0.300	-0.140
	diethyl ether treatment	-0.070	0.040	9.57E-02	-0.160	0.010
	time of day (in hours since 9AM)	0.010	0.010	1.28E-01	0.000	0.030
	intercept	-0.150	0.210	4.80E-01	-0.550	0.260
random factors	<i>variation by transgenic background</i>	0.380	0.150	-	0.170	0.830
	<i>variation by batch</i>	0.350	0.060	-	0.250	0.480
	<i>residual</i>	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	<i>variation by transgenic background</i>	0.360	0.160	-	0.150	0.870
	<i>variation by batch</i>	0.420	0.070	-	0.310	0.580
	<i>residual</i>	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	<i>variation by transgenic background</i>	-	-	-	-	-
	<i>variation by batch</i>	0.390	0.120	-	0.220	0.720
	<i>residual</i>	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	<i>variation by transgenic background</i>	-	-	-	-	-
	<i>variation by batch</i>	0.460	0.140	-	0.260	0.830
	<i>residual</i>	0.860	0.030	-	0.810	0.910

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

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

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

		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	<i>variation by batch</i>	<i>0.480</i>	<i>0.146</i>	-	<i>0.264</i>	<i>0.871</i>
	<i>residual</i>	<i>0.903</i>	<i>0.027</i>	-	<i>0.850</i>	<i>0.958</i>

		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	<i>variation by transgenic background</i>	<i>0.253</i>	<i>0.178</i>	-	<i>0.064</i>	<i>1.005</i>
	<i>variation by batch</i>	<i>0.574</i>	<i>0.096</i>	-	<i>0.414</i>	<i>0.795</i>
	<i>residual</i>	<i>0.750</i>	<i>0.012</i>	-	<i>0.727</i>	<i>0.773</i>

		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	<i>variation by transgenic background</i>	<i>0.505</i>	<i>0.208</i>	-	<i>0.226</i>	<i>1.133</i>
	<i>variation by batch</i>	<i>0.459</i>	<i>0.077</i>	-	<i>0.331</i>	<i>0.637</i>
	<i>residual</i>	<i>0.706</i>	<i>0.011</i>	-	<i>0.685</i>	<i>0.727</i>

		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	<i>variation by transgenic background</i>	<i>0.512</i>	<i>0.212</i>	-	<i>0.227</i>	<i>1.154</i>
	<i>variation by batch</i>	<i>0.487</i>	<i>0.082</i>	-	<i>0.351</i>	<i>0.677</i>
	<i>residual</i>	<i>0.744</i>	<i>0.011</i>	-	<i>0.722</i>	<i>0.767</i>

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

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

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

continued Supplementary Table 5

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

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

continued Supplementary Table 5

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

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

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

continued Supplementary Table 5

		Vascular co-localization of oxLDL with macrophages														
		Model 1 (n=433)					Model 2 (n=433)					Model 3 (n=430)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
	batch 19	0.869	0.236	2.26E-04	0.407	1.331	0.892	0.259	5.72E-04	0.385	1.400	0.805	0.273	3.16E-03	0.270	1.340
	intercept	2.076	0.278	7.97E-14	1.531	2.620	2.082	0.303	6.85E-12	1.487	2.677	2.052	0.313	5.92E-11	1.438	2.666
		Vascular infiltration by neutrophils														
		Model 1 (n=494)					Model 2 (n=494)					Model 3 (n=395)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	overfeeding	0.199	0.054	2.59E-04	0.092	0.306	0.131	0.063	3.80E-02	0.007	0.255	0.196	0.069	4.64E-03	0.060	0.332
	cholesterol supplementation	0.046	0.069	5.07E-01	-0.090	0.181	0.045	0.069	5.13E-01	-0.091	0.181	0.183	0.074	1.39E-02	0.037	0.329
	diethyl ether treatment	-0.033	0.066	6.15E-01	-0.164	0.097	0.001	0.066	9.87E-01	-0.128	0.130	0.018	0.070	8.00E-01	-0.120	0.156
	time of day (in hours since 9AM)	0.033	0.011	2.07E-03	0.012	0.053	0.023	0.011	4.32E-02	0.001	0.045	0.026	0.013	4.46E-02	0.001	0.051
	body length (in SD)	-	-	-	-	-	0.054	0.030	7.75E-02	-0.006	0.113	0.059	0.035	9.34E-02	-0.010	0.129
	dorsal body surface area (in SD)	-	-	-	-	-	0.071	0.038	6.56E-02	-0.005	0.146	0.032	0.042	4.49E-01	-0.051	0.115
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.077	0.056	1.70E-01	-0.187	0.033
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.053	0.036	1.41E-01	-0.124	0.018
	batch 1	-0.209	0.086	1.56E-02	-0.378	-0.040	-0.263	0.088	2.74E-03	-0.435	-0.091	-0.260	0.088	3.21E-03	-0.434	-0.087
	batch 2	-0.245	0.086	4.45E-03	-0.414	-0.076	-0.330	0.087	1.46E-04	-0.500	-0.159	-0.343	0.092	1.98E-04	-0.524	-0.163
	batch 3	-1.742	0.109	2.22E-57	-1.956	-1.528	-1.816	0.116	1.85E-55	-2.043	-1.589	-	-	-	-	-
	batch 6	-0.071	0.118	5.47E-01	-0.301	0.160	-0.114	0.116	3.25E-01	-0.342	0.113	-0.072	0.137	5.97E-01	-0.341	0.196
	batch 7	-2.087	0.105	2.93E-88	-2.293	-1.882	-2.121	0.107	5.84E-87	-2.331	-1.910	-2.310	0.167	1.11E-43	-2.636	-1.983
	intercept	7.658	0.105	0.00E+00	7.451	7.864	7.760	0.115	0.00E+00	7.534	7.985	7.776	0.152	0.00E+00	7.479	8.074
		Vascular co-localization of lipids with neutrophils														
		Model 1 (n=380)					Model 2 (n=380)					Model 3 (n=286)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	overfeeding	0.727	0.246	3.07E-03	0.246	1.209	0.826	0.251	1.02E-03	0.333	1.319	0.901	0.255	4.01E-04	0.402	1.401
	cholesterol supplementation	0.845	0.284	2.89E-03	0.289	1.401	0.830	0.280	2.98E-03	0.282	1.378	0.882	0.306	3.95E-03	0.282	1.482
	diethyl ether treatment	-0.659	0.319	3.91E-02	-1.285	-0.033	-0.744	0.325	2.21E-02	-1.381	-0.107	-0.258	0.286	3.66E-01	-0.819	0.302
	time of day (in hours since 9AM)	0.017	0.050	7.40E-01	-0.082	0.115	0.039	0.054	4.64E-01	-0.066	0.144	0.049	0.053	3.58E-01	-0.055	0.152
	body length (in SD)	-	-	-	-	-	-0.151	0.140	2.82E-01	-0.425	0.124	-0.059	0.129	6.46E-01	-0.312	0.194
	dorsal body surface area (in SD)	-	-	-	-	-	-0.088	0.162	5.88E-01	-0.405	0.230	-0.082	0.175	6.38E-01	-0.426	0.261
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.102	0.208	6.23E-01	-0.305	0.509
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.132	0.127	2.98E-01	-0.117	0.381
	batch 1	-0.804	0.340	1.79E-02	-1.469	-0.138	-0.701	0.378	6.37E-02	-1.441	0.040	-0.804	0.353	2.27E-02	-1.497	-0.112
	batch 2	0.117	0.356	7.41E-01	-0.580	0.815	0.289	0.402	4.73E-01	-0.500	1.077	0.391	0.414	3.45E-01	-0.421	1.203
	batch 3	-2.749	0.523	1.44E-07	-3.774	-1.725	-2.714	0.572	2.05E-06	-3.834	-1.594	-	-	-	-	-
	batch 6	-0.652	0.441	1.40E-01	-1.517	0.213	-0.557	0.462	2.28E-01	-1.462	0.349	-0.510	0.464	2.71E-01	-1.420	0.399
	intercept	2.288	0.576	7.12E-05	1.159	3.416	2.105	0.602	4.69E-04	0.925	3.284	1.409	0.679	3.79E-02	0.079	2.740

continued Supplementary Table 5

		Vascular co-localization of macrophages with neutrophils														
		Model 1 (n=488)					Model 2 (n=488)					Model 3 (n=392)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	overfeeding	0.096	0.104	3.55E-01	-0.107	0.299	-0.019	0.115	8.67E-01	-0.244	0.205	0.060	0.113	5.99E-01	-0.162	0.281
	cholesterol supplementation	0.153	0.133	2.50E-01	-0.108	0.413	0.119	0.136	3.81E-01	-0.147	0.385	0.299	0.127	1.90E-02	0.049	0.549
	diethyl ether treatment	-0.240	0.136	7.75E-02	-0.506	0.026	-0.164	0.136	2.27E-01	-0.430	0.102	-0.164	0.133	2.18E-01	-0.426	0.097
	time of day (in hours since 9AM)	-0.007	0.021	7.39E-01	-0.048	0.034	-0.027	0.023	2.42E-01	-0.072	0.018	-0.009	0.026	7.23E-01	-0.059	0.041
	body length (in SD)	-	-	-	-	-	0.034	0.054	5.27E-01	-0.071	0.139	-0.022	0.054	6.84E-01	-0.127	0.083
	dorsal body surface area (in SD)	-	-	-	-	-	0.170	0.067	1.08E-02	0.039	0.302	0.097	0.068	1.55E-01	-0.037	0.231
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.231	0.089	9.49E-03	0.056	0.405
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.153	0.066	1.96E-02	-0.282	-0.025
	batch 1	0.223	0.131	8.87E-02	-0.034	0.479	0.090	0.146	5.34E-01	-0.195	0.376	0.225	0.145	1.21E-01	-0.059	0.509
	batch 2	-0.355	0.150	1.79E-02	-0.650	-0.061	-0.523	0.166	1.59E-03	-0.848	-0.198	-0.336	0.175	5.57E-02	-0.679	0.008
	batch 3	-2.971	0.240	4.01E-35	-3.441	-2.500	-3.183	0.279	3.32E-30	-3.729	-2.637	-	-	-	-	-
	batch 6	0.175	0.191	3.60E-01	-0.199	0.549	0.059	0.199	7.67E-01	-0.331	0.448	0.426	0.232	6.61E-02	-0.028	0.880
	batch 7	-4.803	0.258	1.43E-77	-5.308	-4.298	-4.918	0.274	3.21E-72	-5.454	-4.382	-4.433	0.338	2.72E-39	-5.096	-3.771
	intercept	5.839	0.218	1.63E-158	5.412	6.266	6.054	0.250	5.85E-130	5.565	6.543	5.617	0.302	2.18E-77	5.026	6.208
		Endothelial thickness														
		Model 1 (n=467)					Model 2 (n=467)					Model 3 (n=411)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	overfeeding	0.252	0.073	5.34E-04	0.109	0.395	0.176	0.079	2.69E-02	0.020	0.331	0.171	0.089	5.47E-02	-0.003	0.346
	cholesterol supplementation	0.091	0.082	2.65E-01	-0.069	0.252	0.115	0.082	1.60E-01	-0.045	0.276	0.119	0.090	1.89E-01	-0.058	0.296
	diethyl ether treatment	-0.320	0.087	2.40E-04	-0.490	-0.149	-0.330	0.087	1.42E-04	-0.500	-0.160	-0.337	0.096	4.13E-04	-0.525	-0.150
	time of day (in hours since 9AM)	0.065	0.014	1.43E-06	0.039	0.092	0.066	0.013	8.20E-07	0.040	0.093	0.076	0.015	2.11E-07	0.048	0.105
	body length (in SD)	-	-	-	-	-	0.063	0.043	1.39E-01	-0.020	0.147	0.033	0.049	5.06E-01	-0.064	0.129
	dorsal body surface area (in SD)	-	-	-	-	-	0.073	0.040	6.63E-02	-0.005	0.150	0.076	0.043	7.67E-02	-0.008	0.161
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.023	0.041	5.73E-01	-0.057	0.104
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.045	0.043	3.00E-01	-0.040	0.129
	intercept	-0.445	0.259	8.56E-02	-0.953	0.062	-0.378	0.262	1.49E-01	-0.890	0.135	-0.366	0.288	2.04E-01	-0.930	0.198
random factors	variation by batch	0.672	0.173	-	0.405	1.113	0.676	0.174	-	0.408	1.120	0.693	0.192	-	0.402	1.192
	residual	0.703	0.023	-	0.659	0.750	0.698	0.023	-	0.655	0.745	0.716	0.025	-	0.669	0.767

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

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

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

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

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

continued Supplementary Table 6

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

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

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

continued Supplementary Table 6

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

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

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

		Body length (n=1004)				
		Effect	SE	P	lci	uci
fixed factors	atorvastatin and ezetimibe	-0.025	0.053	6.29E-01	-0.128	0.078
	time of day (in hours since 9AM)	0.000	0.012	9.78E-01	-0.023	0.024
	intercept	0.012	0.162	9.41E-01	-0.305	0.330
random factors	<i>variation by transgenic background</i>	0.000	-	-	-	-
	<i>variation by batch</i>	0.495	0.147	-	0.276	0.886
	<i>residual</i>	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	<i>variation by transgenic background</i>	0.561	0.239	-	0.244	1.291
	<i>variation by batch</i>	0.176	0.057	-	0.093	0.330
	<i>residual</i>	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	<i>variation by transgenic background</i>	0.221	0.122	-	0.075	0.654
	<i>variation by batch</i>	0.066	0.079	-	0.006	0.678
	<i>residual</i>	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	<i>variation by transgenic background</i>	0.458	0.249	-	0.158	1.332
	<i>variation by batch</i>	0.209	0.101	-	0.082	0.538
	<i>residual</i>	0.922	0.029	-	0.867	0.981

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

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

		LDL cholesterol levels (n=567)				
		Effect	SE	P	lci	uci
fixed factors	atorvastatin and ezetimibe	-0.544	0.079	5.22E-12	-0.699	-0.390
	time of day (in hours since 9AM)	0.017	0.017	3.28E-01	-0.017	0.050
	intercept	0.173	0.343	6.13E-01	-0.499	0.846
random factors	<i>variation by transgenic background</i>	<i>0.461</i>	<i>0.242</i>	-	<i>0.165</i>	<i>1.288</i>
	<i>variation by batch</i>	<i>0.147</i>	<i>0.071</i>	-	<i>0.057</i>	<i>0.378</i>
	<i>residual</i>	<i>0.861</i>	<i>0.026</i>	-	<i>0.812</i>	<i>0.913</i>
		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	<i>variation by transgenic background</i>	<i>0.516</i>	<i>0.278</i>	-	<i>0.180</i>	<i>1.483</i>
	<i>variation by batch</i>	<i>0.228</i>	<i>0.094</i>	-	<i>0.101</i>	<i>0.512</i>
	<i>residual</i>	<i>0.837</i>	<i>0.025</i>	-	<i>0.789</i>	<i>0.888</i>
		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	<i>variation by transgenic background</i>	<i>0.174</i>	<i>0.351</i>	-	<i>0.003</i>	<i>9.122</i>
	<i>variation by batch</i>	<i>0.521</i>	<i>0.145</i>	-	<i>0.302</i>	<i>0.899</i>
	<i>residual</i>	<i>0.832</i>	<i>0.019</i>	-	<i>0.796</i>	<i>0.869</i>
		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	<i>variation by transgenic background</i>	<i>0.443</i>	<i>0.221</i>	-	<i>0.166</i>	<i>1.178</i>
	<i>variation by batch</i>	<i>0.344</i>	<i>0.092</i>	-	<i>0.203</i>	<i>0.581</i>
	<i>residual</i>	<i>0.768</i>	<i>0.017</i>	-	<i>0.735</i>	<i>0.803</i>
		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	<i>variation by transgenic background</i>	<i>0.520</i>	<i>0.223</i>	-	<i>0.224</i>	<i>1.206</i>
	<i>variation by batch</i>	<i>0.204</i>	<i>0.059</i>	-	<i>0.115</i>	<i>0.360</i>
	<i>residual</i>	<i>0.810</i>	<i>0.018</i>	-	<i>0.775</i>	<i>0.847</i>

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

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

		Vascular lipid deposition																			
		Model 1 (n=776)					Model 2 (n=776)					Model 3 (n=728)					Model 4 (n=344)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	atorvastatin and ezetimibe	-1.523	0.176	4.75E-18	-1.868	-1.178	-1.496	0.177	2.32E-17	-1.842	-1.150	-1.423	0.180	3.04E-15	-1.776	-1.069	-2.001	0.299	2.18E-11	-2.587	-1.415
	time of day (in hours since 9AM)	0.155	0.038	4.83E-05	0.080	0.229	0.145	0.037	1.07E-04	0.072	0.219	0.151	0.040	1.53E-04	0.073	0.229	0.327	0.054	1.88E-09	0.221	0.434
	body length (in SD)	-	-	-	-	-	-0.222	0.119	6.27E-02	-0.456	0.012	-0.221	0.120	6.43E-02	-0.455	0.013	0.352	0.243	1.48E-01	-0.125	0.829
	dorsal body surface area (in SD)	-	-	-	-	-	0.183	0.102	7.15E-02	-0.016	0.383	0.118	0.120	3.28E-01	-0.118	0.354	0.179	0.193	3.51E-01	-0.198	0.557
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.231	0.149	1.21E-01	-0.524	0.061
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.216	0.133	1.06E-01	-0.477	0.046
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.178	0.119	1.36E-01	-0.056	0.412	0.426	0.216	4.87E-02	0.002	0.849
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.125	0.103	2.27E-01	-0.327	0.078	-0.159	0.231	4.91E-01	-0.611	0.293
	Tg(flk:EGFP) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-0.915	0.335	6.37E-03	-1.572	-0.257	-0.823	0.360	2.22E-02	-1.527	-0.118	-0.808	0.383	3.50E-02	-1.560	-0.057	-	-	-	-	-
	Tg(hsp70:IK17:EGFP; mpeg1:mCherry) carriers vs. Tg(mpo:EGFP; mpeg1:mCherry) carriers	-0.477	0.245	5.17E-02	-0.958	0.003	0.103	0.353	7.72E-01	-0.590	0.795	-0.020	0.403	9.60E-01	-0.810	0.770	0.562	0.606	3.54E-01	-0.626	1.751
	batch 1	-0.727	0.456	1.11E-01	-1.621	0.167	-0.600	0.453	1.85E-01	-1.488	0.288	-0.263	0.497	5.97E-01	-1.237	0.711	-	-	-	-	-
	batch 2	-0.480	0.330	1.47E-01	-1.127	0.168	-0.240	0.349	4.92E-01	-0.924	0.444	0.182	0.376	6.28E-01	-0.555	0.920	-	-	-	-	-
	batch 3	-1.264	0.319	7.40E-05	-1.889	-0.639	-1.204	0.311	1.08E-04	-1.814	-0.595	-0.895	0.361	1.32E-02	-1.603	-0.187	-	-	-	-	-
	batch 4	-0.678	0.325	3.70E-02	-1.316	-0.041	-0.611	0.331	6.52E-02	-1.260	0.039	-0.322	0.381	3.97E-01	-1.069	0.424	-	-	-	-	-
	batch 5	-0.385	0.377	3.07E-01	-1.125	0.355	-0.504	0.388	1.94E-01	-1.265	0.257	-0.427	0.384	2.66E-01	-1.179	0.325	-	-	-	-	-
	batch 6	-0.252	0.384	5.11E-01	-1.005	0.500	-0.509	0.392	1.93E-01	-1.277	0.258	-0.492	0.397	2.16E-01	-1.271	0.287	0.269	0.458	5.57E-01	-0.629	1.167
	batch 7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.124	0.454	7.85E-01	-0.766	1.014
	batch 8	-2.432	0.386	3.12E-10	-3.189	-1.674	-2.576	0.374	5.73E-12	-3.309	-1.843	-2.513	0.374	1.85E-11	-3.246	-1.780	-2.101	0.479	1.14E-05	-3.040	-1.163
	intercept	3.849	0.268	1.31E-46	3.322	4.375	3.740	0.274	2.47E-42	3.202	4.277	3.570	0.298	4.95E-33	2.986	4.155	1.707	0.455	1.75E-04	0.815	2.598
		Vascular accumulation of oxLDL																			
		Model 1 (n=236)					Model 2 (n=236)					Model 3 (n=233)					Model 4 (n=229)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	atorvastatin and ezetimibe	0.019	0.126	8.78E-01	-0.228	0.267	0.100	0.126	4.29E-01	-0.147	0.347	0.099	0.127	4.35E-01	-0.150	0.349	0.130	0.130	3.19E-01	-0.126	0.385
	time of day (in hours since 9AM)	-0.017	0.024	4.94E-01	-0.064	0.031	-0.018	0.024	4.45E-01	-0.064	0.028	-0.028	0.024	2.44E-01	-0.075	0.019	-0.031	0.024	1.96E-01	-0.079	0.016
	body length (in SD)	-	-	-	-	-	0.111	0.085	1.90E-01	-0.055	0.278	0.143	0.094	1.30E-01	-0.042	0.328	0.157	0.096	1.01E-01	-0.031	0.344
	dorsal body surface area (in SD)	-	-	-	-	-	0.189	0.063	2.46E-03	0.067	0.312	0.206	0.081	1.14E-02	0.046	0.365	0.220	0.081	6.84E-03	0.060	0.379
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.007	0.066	9.16E-01	-0.122	0.135
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.127	0.067	5.80E-02	-0.004	0.258
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.010	0.087	9.06E-01	-0.181	0.160	0.014	0.092	8.76E-01	-0.166	0.195
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.152	0.096	1.13E-01	-0.036	0.341	0.096	0.108	3.76E-01	-0.116	0.308
	intercept	0.169	0.256	5.09E-01	-0.333	0.672	0.261	0.256	3.10E-01	-0.242	0.763	0.433	0.280	1.22E-01	-0.116	0.981	0.323	0.299	2.81E-01	-0.264	0.909
random factors	variation by batch	0.378	0.169	-	0.157	0.907	0.373	0.173	-	0.151	0.924	0.382	0.177	-	0.154	0.948	0.400	0.185	-	0.162	0.988
	residual	0.839	0.039	-	0.767	0.919	0.820	0.038	-	0.749	0.898	0.818	0.038	-	0.746	0.896	0.811	0.038	-	0.739	0.889
		Vascular infiltration by macrophages																			
		Model 1 (n=633)					Model 2 (n=633)					Model 3 (n=585)					Model 4 (n=224)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	atorvastatin and ezetimibe	-0.001	0.049	9.80E-01	-0.097	0.094	0.005	0.049	9.17E-01	-0.090	0.101	0.010	0.051	8.50E-01	-0.090	0.109	-0.003	0.072	9.64E-01	-0.144	0.138
	time of day (in hours since 9AM)	0.036	0.011	9.87E-04	0.015	0.058	0.033	0.011	3.11E-03	0.011	0.054	0.029	0.011	1.00E-02	0.007	0.052	0.009	0.013	4.96E-01	-0.017	0.035
	body length (in SD)	-	-	-	-	-	0.001	0.031	9.81E-01	-0.060	0.061	0.011	0.032	7.36E-01	-0.051	0.073	0.065	0.053	2.20E-01	-0.039	0.169
	dorsal body surface area (in SD)	-	-	-	-	-	0.059	0.029	4.03E-02	0.003	0.116	0.043	0.032	1.82E-01	-0.020	0.105	0.022	0.044	6.14E-01	-0.065	0.109
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.040	0.036	2.71E-01	-0.110	0.031
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.031	0.037	4.08E-01	-0.042	0.104
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.027	0.030	3.68E-01	-0.032	0.087	0.091	0.051	7.67E-02	-0.010	0.191
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.011	0.025	6.76E-01	-0.039	0.060	-0.007	0.059	9.10E-01	-0.122	0.109
	intercept	-0.285	0.505	5.73E-01	-1.275	0.706	-0.252	0.486	6.04E-01	-1.204	0.701	-0.238	0.483	6.22E-01	-1.186	0.709	-0.877	0.196	7.53E-06	-1.261	-0.493
random factors	variation by transgenic background	0.699	0.361	-	0.253	1.925	0.670	0.348	-	0.242	1.857	0.666	0.347	-	0.240	1.849	0.000	0.000	-	0.000	-
	variation by batch	0.241	0.075	-	0.131	0.442	0.247	0.077	-	0.134	0.457	0.246	0.077	-	0.133	0.456	0.289	0.126	-	0.123	0.680
	residuals	0.583	0.017	-	0.552	0.617	0.581	0.016	-	0.550	0.614	0.567	0.017	-	0.536	0.601	0.438	0.021	-	0.399	0.481

continued Supplementary Table 9

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

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

		Vascular infiltration by neutrophils																			
		Model 1 (n=404)					Model 2 (n=404)					Model 3 (n=359)									
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci					
fixed factors	atorvastatin and ezetimibe	0.088	0.083	2.87E-01	-0.074	0.251	0.080	0.083	3.36E-01	-0.083	0.242	0.052	0.089	5.60E-01	-0.123	0.227	no observations				
	time of day (in hours since 9AM)	0.023	0.021	2.76E-01	-0.018	0.063	0.020	0.021	3.49E-01	-0.022	0.062	0.003	0.023	8.83E-01	-0.041	0.048					
	body length (in SD)	-	-	-	-	-	0.100	0.055	6.61E-02	-0.007	0.207	0.111	0.057	5.06E-02	0.000	0.223					
	dorsal body surface area (in SD)	-	-	-	-	-	-0.005	0.057	9.28E-01	-0.117	0.106	-0.015	0.062	8.13E-01	-0.137	0.107					
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.020	0.051	7.02E-01	-0.081	0.120					
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.034	0.040	3.92E-01	-0.044	0.112					
random factors	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					
	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					

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

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

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

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

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

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

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

Human gene	ENSG	Zebrafish orthologue	ENSDARG	Target %identity	Query %identity	Main human protein	Top hit BLAST	%identity (protein)	Conserved genes in locus
<i>APOE</i>	ENSG00000130203	<i>apoea</i>	ENSDARG00000102004	25.65	21.77	ENSP00000252486	ENSDARP00000137865	27.78	<i>TOMM40</i>
		<i>apoeb</i>	ENSDARG00000040295	28.11	24.92		ENSDARP00000119141	32.04	<i>BCAM, NECTIN2</i>
<i>APOB</i>	ENSG00000084674	<i>apoba</i>	ENSDARG00000042780	33.70	32.63	ENSP00000233242	ENSDARP00000062792	34.51	<i>C2orf43, GDF7, ITS2, PFN4</i>
		<i>apobb.1</i>	ENSDARG00000022767	29.68	24.26		ENSDARP00000119179	30.33	NA
		<i>apobb.2</i>	ENSDARG00000075016	29.64	16.46		ENSDARP00000144532	37.37	NA
<i>LDLR</i>	ENSG00000130164	<i>ldlra</i>	ENSDARG00000029476	52.80	55.93	ENSP00000252444	ENSDARP00000115492	58.69	<i>SMARCA4, KR11, SPC24</i>
		<i>ldlrbb</i>	ENSDARG00000026759	54.06	49.53		ENSDARP00000141207	58.57	<i>SMARCA4, AP1M2, CDKN2D</i>

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

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

Human gene	Zebrafish orthologue	CRISPR gRNA target sequence	Genomic location (danRer11/GRCz11)		Exon	Strand	GC (%)	Self-complementarity	Off-targets				Predicted efficiency	CRISPRscan score	Canonical (yes/no)	Target activity (NA ^a , no ^b , low; moderate ^c , high ^d or very high ^e)	Forward primer	Reverse primer	Product size
			Chr	Pos					0	1	2	3							
APOE	apoec	GGCTCTCTCTCGCGCGTAAG	19	10,856,063	3 of 4	-	65	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	0.52	37	yes	moderate	TCCGTTTTGACTTTGACGGC	GAGCTGAGTGGCCTTGATGT	155	
		GgGGGGCATCAGCCTGGAAC	16	23,961,545	2 of 4	-	65	1	0	0	0	1	0.61	59	no	very high	TGCCTGACTTGCTAATTGTGAT	CCGTGAGTTTGTGTGTTGAGTT	178
		GgTGACGTGAAGAACCCTGT	16	23,962,014	3 of 4	+	50	0	0	0	0	2	0.62	68	no	very high	AGTGAAAATCTCCAAACCAGA	TGAAGGAGCATCCCAACTTACT	269
		GAGGGGCATCAGCCTGGAAC	16	23,961,545	2 of 4	-	65	1	0	0	0	1	0.61	59	no	high	CTGTAAATTGCTCTGACTTGCTAA	GCCCTTGATGTTTTCACCA	208
	apoeb	GgTGACGTGAAGAACCCTGT	16	23,962,014	3 of 4	+	50	0	0	0	0	2	0.62	68	no	high	CTGCTGGTCAGCTCAGTAAAG	TGAAGGAGCATCCCAACTTACT	226
		GgGGATCTTCTGGGAGTAGG	16	23,962,897	4 of 4	-	60	0	0	0	0	0	0.59	85	no	moderate	AGGAGAAGCTGGAGGAGACAG	CTCTTAAGCCTGAGTGGGAAGA	170
		GgCATACATGAGCCAGGCC	16	23,962,700	4 of 4	+	65	1	0	0	0	0	0.58	59	no	moderate	GCAACCTACATGAGTGAGATGC	GTAGGTTCTCGGCTGTCTCTCT	220
		GAACCTAACACACAAACTGA	16	23,961,615	2 of 4	+	40	0	0	0	0	8	0.70	25	no	no	CTCCAAACCAGGATGACCCC	CAGTTTGCCTGTGTAGGTGC	201
		APOB	apoba	gGGGAGGGCTCTATCTTAGG	17	30,717,989	24 of 29	+	55	0	0	0	0	0.69	100	no	high	CGCACTTTGGAATTCTCCTTAC	TCAATTTTGTATGACAGGGGTG
gGATGAGGCAGACAGAGAGG	17			30,708,635	9 of 29	+	60	0	0	0	0	12	0.74	61	no	high	CTCACATGGCAGACACTCTTTC	GGGCATACACTCAGCATATCTCT	172
GGACACATTCTGTGTGTCGG	17			30,705,707	4 of 29	-	60	1	0	0	0	5	0.64	48	yes	no	ATGTCAACAACCTCTGCAGCTAA	ACTTCTCCATAGCTGCCTGAAA	944
GGAAGCACTGAGGTTGCTG	17			30,704,770	2 of 29	+	55	1	0	0	0	7	0.60	35	no	no	AGGCCGCTATTAATTCAGTTT	ATGTACACAACCTCTGCAGCTAA	173
GgAGTATGGTATCTCCTCAG	17			30,708,080	8 of 29	+	50	0	0	0	0	0	0.59	74	no	no	ATTTTGTGAAGGGTGGGAACA	AAAAAGCAACAACCCATTTCAT	224
apobb.1	GgTGCTTTTTGCACAGGCAG		17	30,709,180	11 of 29	-	57	1	0	0	0	0	0.71	44	no	no	TCATTGGTGTGATGGGAAAATA	CACCTAGAATGCAGAAAATCCCC	260
	GgAGCTGACAAGTACCAAG		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	AACCTGCTCGTGACATGGTATG	TTGAGACCACCTCTCGTGGTAGA	227
	GAGCCAGTTTCAGTGGGCTG		20	31,273,334	11 of 27	-	60	2	0	0	0	22	0.47	38	no	moderate	GCAGAGAGGTGCTAATGAAGGT	TGTATACTCACTCCCCGGTCTC	222
	GgGTTTATCCAGATTTCGAG		20	31,277,737	24 of 27	-	45	0	0	0	0	8	0.73	47	no	moderate	TTGACACTTTGTTTGGAAATCG	CCATTGAAATTGTTCTGCAGTG	217
apobb.2	GAAATCAAGCAGCAAGATGG	20	31,277,192	24 of 27	+	45	0	0	0	1	5	0.70	-	no	moderate	TGTTTAGGATCAACCTTCCTGG	ATTCAAAGGACCGCCTTGATA	279	
	GGCTCTATTTCTCCATTG	20	31,272,363	8 of 27	-	40	0	0	0	0	8	0.32	21	yes	no	CAGTCCATCCAATTCAAGACAA	TACAGAGGAACGGTCAAAGGTT	275	
	gGATTAGCTGAGCAAGAGGA	20	53,444,329	5 of 22	-	45	1	0	0	0	7	0.61	49	no	moderate	GTGGACCCAGCATAGACATTT	AACAAAATAGCAGGGATGCAT	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	AAAAACATGTTCTCGTGCACCT	216	
LDLR	ldlr	gGACAAGTTCAGACCCATCG	20	53,443,193	4 of 22	+	50	1	0	0	0	2	0.59	38	no	no	CCCAGCATCTATGGTCTGTGTA	TTTAATGGAATTGCACCAAGTT	234
		GATCCCCCTCTTAATGTTG	20	53,442,015	3 of 22	-	45	0	0	0	0	2	0.53	34	no	no	AAATCCTCTGAAATTCACCGT	TGGTTGAAGTGAAGGACAAA	238
		gGTGAAGGAAATGTTGGCGA	20	53,445,098	7 of 22	+	45	0	0	0	0	4	0.77	62	no	NA	GAGGTGGATGCTGCTGTATATG	AATCTAACCCAATACCTTGGCA	201
		GATTACGGCAGTATCAGTG	3	19,304,761	2 of 18	+	50	1	0	0	0	25	0.50	50	no	high	TAGCGCATATATCACACGGAC	CCATCACCACAGTCATCAGTTT	228
		GGAAGTGGGAATGCATACA	3	19,308,392	4 of 18	+	50	0	0	0	0	3	0.46	75	yes	moderate	GACAATTGAGATGAGTTGGCTG	ATACCATCCAGTGATAATCGGC	274
	ldlr	GGAGCGGATTCTGCGAGCGG	6	102,541	1 of 5	-	70	0	0	0	0	0	0.79	66	yes	high	CCCTGGCCCTCAACACTACAG	ACCCAGAAGAGCAGCAGAAC	215
		gGCGCTGAGGAGTTCCGCTG	6	103,574	3 of 5	+	65	1	0	0	0	1	0.67	80	no	high	CGAGCAGAACTGCGGTAAT	TGCACTGGAATGCTGTGG	249
		gGGGCACACACTCTCCGCTG	6	103,852	3 of 5	-	70	2	0	0	0	2	0.68	78	no	no	GTGTCCCAACACACACACAC	gtACTCACTGCAGTTGTCTCTCG	271
		GgGTCACGTTAGAGCTCTGA	6	102,589	1 of 5	-	55	0	0	0	0	0	0.52	61	no	no	TTCTGCTCAGAGAGGGAGAATC	GATCAGTGAAACTCACCGGTTT	182
		GgGGATTCTGCGAGCGGTGG	6	102,538	1 of 5	-	70	0	0	0	1	0	0.56	94	no	no	TAACATCACACCCTGCTGGAG	GATCAGTGAAACTCACCGGTTT	270

CRISPR gRNA target sequences were preferentially 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 capillary electrophoresis while estimating the length of the targeted region of an exon; No: 8 of 8 larvae test-injected with the gRNA only showed wildtype sequences; Low: 8 of 8 larvae showed wildtype sequence and fewer than 4 of 8 also contained indel sequence; Moderate: 8 of 8 larvae showed wildtype sequence and >4 of 8 also contained indel sequence; High: 8 of 8 larvae showed wildtype as well as indel sequence; Very high: Fewer than 4 of 8 larvae showed wildtype sequence and all larvae showed indel sequence. Target sequences highlighted in bold were selected and used to generate multiplexed mutant zebrafish. Of note: after completion of the study a new version of the zebrafish genome was released. Data shown for gRNA target sequences are from the new version of the genome (built GRCz11).

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

Sehbrafish ortholog	Sequence	Annotation	Number of alleles	mean $\pm$ SD number of reads	
apoea	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCCTTACGCGCAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	119M	430	1079 $\pm$ 766	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCGCGAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	41M1D167M	91	861 $\pm$ 515	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCCTTGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M8D60M	67	873 $\pm$ 498	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCGCGCGAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	48M5D66M	50	726 $\pm$ 397	
	ATGATGGACAGCATGTAGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCGAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	2M4847M1D67M	30	735 $\pm$ 344	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCCTTCAACGCGCAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M1S3167M	29	698 $\pm$ 293	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCGCGCGAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	50M281M1S11163M	15	782 $\pm$ 366	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCCTTCTCGCGCAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	49M41ZM2S66M	14	636 $\pm$ 204	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCGAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	48M9D62M	12	577 $\pm$ 355	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCCTTGAGAGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M281M1S64M	7	824 $\pm$ 601	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCGAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	45M1D163M	7	695 $\pm$ 234	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCCTTGAGAGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	52M4D1M1S61M	5	862 $\pm$ 430	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	35M2ZD62M	2	828 $\pm$ 729	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCCTTGATCGCGCAGGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	51M3I68M	2	664 $\pm$ 109	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCCTTGAGAGAGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	47M6D66M	1	2374	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCGCGCGAGGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	50M2D67M	1	552	
	ATGATGGAGCTGCACAAATGTACAGAGATGATCTGCACATCCAAATGGCCGAGGAGAGCCAGAAAGTTCAACGAAGATCTGCAGTTGTTGGTCACCAAGCTCCGCACACA	45M9D65M	1	21	
	apoeb	TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTTGATGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA	31M1S44M1I2M3S1M2S81M	157	664 $\pm$ 416
		TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGGTCAGTACAGCTGATGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA	31M1S43M1S51I1S98M	116	683 $\pm$ 500
		TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA	31M1S39M3S1M4D86M	100	708 $\pm$ 413
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S131M	91	677 $\pm$ 465	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S39M1D084M	75	619 $\pm$ 399	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S38M6D89M	46	455 $\pm$ 273	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		76M91I2S0M1S9M81S3M1S4M	31	47 $\pm$ 26	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S44M91I2S0M1S9M81S5M	29	32 $\pm$ 19	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S43M1D080M	22	475 $\pm$ 380	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S41M5D5M1S1S3M1S67M	16	357 $\pm$ 294	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S40M1D308M	11	596 $\pm$ 279	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		75M7D4M1I79M	9	409 $\pm$ 291	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S38M6D7M2S1M1I79M	8	660 $\pm$ 346	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S26M1D809M	8	658 $\pm$ 158	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTT		69M1I7D79M	7	576 $\pm$ 469	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S40M2D1S2M2S86M	6	676 $\pm$ 235	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S65M1S62M1S4M	3	213 $\pm$ 81	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		31M1S26M4D062M1S4M	3	205 $\pm$ 157	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		76M91I2S0M1S9M81S5M	2	27 $\pm$ 10	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA		71M5D89M	1	2044	
TTGTGATTAACCTAGTTGGTAAAGTTACAGCTCTTCTCAACCTCTTGAGGCTGCGAGGCTGTAGCTGTGTGCCCTCAGCCAGATGGGAGAGATGTTGGACCGTTTCTGGCAGTATGTGTCTGAACCTCAACACAAACTGACGGCA	69M1I1D85M	1	1032		
apoba	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGCTCTATCTCTATGTAATGGGAGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	69M1I13S43M1S25M	122	666 $\pm$ 434	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	58M1S5D42M1S25M	119	782 $\pm$ 474	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	64M5D46M1S25M	91	742 $\pm$ 433	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	58M1D469M	90	655 $\pm$ 474	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	69M4D1M1S40M1S25M	86	752 $\pm$ 426	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	68M1D46M1S25M	76	758 $\pm$ 458	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	64M5D10M3136M1S25M	56	795 $\pm$ 540	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	58M14D43M1S25M	29	588 $\pm$ 284	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	69M8I2M1S2169M	18	627 $\pm$ 372	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	69M1I1D35M1S25M	16	805 $\pm$ 385	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	69M1S8I45M1S25M	12	612 $\pm$ 275	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	69M1I46M1S25M	8	641 $\pm$ 302	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	58M1S5D68M	7	698 $\pm$ 295	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	67M1I7D57M	6	498 $\pm$ 295	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	68M14I1S1M1S70M	5	497 $\pm$ 382	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	69M7I46M1S25M	4	666 $\pm$ 97	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	69M9I1M1S4M1S25M	3	590 $\pm$ 32	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	69M9D37M1S25M	3	517 $\pm$ 460	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	57M13D45M1S25M	2	816 $\pm$ 240	
	CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	65M1D6D0M	2	681 $\pm$ 57	
CCATGTTGGGTTAGCAGAGCTGTCAGCTAAAGTGAACAGCAACTTTTGAATGGGAGGGGCTCTATCTCTATGTCAGAGTGGGCAACAACACTGTTGATGTTCCCAATTACATTGCTAAAGTACAAAATAATGGCCAGCTGCCCTTAA	68M13I1M2S70M	1	1120		

apobb.1 CTTCCGTGACACCATG

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

Ortholog	Chr	Start	End	RefSeq	Position	Variant	Impact	n _{affected}
<i>apoea</i>	19	10,856,052	10,856,073	CTCCAACTGGCCCTTACGCG/-	-22	frameshift variant	high	2
		10,856,058	10,856,068	ACTGGCCCTT/-	-11	frameshift variant	high	116
		10,856,062	10,856,070	GCCCTTAC/-	-9	inframe deletion	moderate	1
		10,856,062	10,856,072	GCCCTTACGCG/-	-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
		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
<i>apoeb</i>	16	23,961,533	23,961,550	CCAGGCTCGTAGCCTGTT/-	-18	inframe deletion	moderate	7
		23,961,533	23,961,572	CCAGGCTCGTAGCCTGTTCCAGGCTGATGCCCTCAGCCC/-	-40	frameshift variant	high	3
		23,961,544	23,961,554	GCCTGTTCAG/-	-11	frameshift variant	high	1
		23,961,544	23,961,560	GCCTGTTCAGGCTGAT/-	-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	GTTC/-	-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
		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/CT	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
<i>apoba</i>	17	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	ATCTTAGGGGCAACA/-	-16	frameshift variant	high	2
		30,718,003	30,718,019	CTTAGGGGCAACAACA/-	-17	frameshift variant	high	6
		30,718,004	30,718,003	-/AGCAACTTTTATGA	14	frameshift variant	high	5
		30,718,004	30,718,003	-/TATCTTTATGAA	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
		30,718,005	30,718,004	-/CCATTCA	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
<i>apobb.1</i>	20	31,273,922	31,273,942	TGACAAAGTACCAAGGGCAA/-	-21	inframe deletion	moderate	1
		31,273,923	31,273,936	GACAAAGTACCAAG/-	-14	frameshift variant	high	2
		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

Zebrafish orthologue	Chr	Start	End	Variant	VEP	Impact	n _{affected} alleles
<i>apobb.1</i>	20	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
		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
<i>apobb.2</i>	20	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
		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
<i>ldra</i>	3	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
		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
<i>ldrb</i>	6	102,538	102,546	CCGCCACCG/-	-9	upstream gene variant	modifier 7
		102,543	102,543	A/T	0	upstream gene variant	modifier 1
		102,543	102,543	A/-	-1	upstream gene variant	modifier 7
		102,544	102,544	C/T	0	upstream gene variant	modifier 7
		102,544	102,546	CCG/-	-3	upstream gene variant	modifier 75
		102,544	102,550	CCGCTCG/-	-7	upstream gene variant	modifier 15
		102,544	102,556	CCGCTCGCAGAAT/-	-13	upstream gene variant	modifier 7
		102,545	102,544	-/A	1	upstream gene variant	modifier 120
		102,545	102,546	CG/-	-2	upstream gene variant	modifier 3
		102,545	102,546	CG/TT	0	upstream gene variant	modifier 120
		102,545	102,548	CGCT/-	-4	upstream gene variant	modifier 140
		102,546	102,546	G/T	0	upstream gene variant	modifier 7
		102,546	102,612	GCTCGCAGAATCCGCTCCCGGTA CAGAACAGCATCTCTATCCGCC TCAGAGCTCTAACGTGACGCT/-	-67	upstream gene variant	modifier 5
		102,547	102,546	-/AAGAATCGCAGAATCCGAGA	20	upstream gene variant	modifier 9
		102,547	102,546	-/CAGGGAGAATCTCT	14	upstream gene variant	modifier 9
		102,547	102,547	C/A	0	upstream gene variant	modifier 9
		102,548	102,547	-/CA	2	upstream gene variant	modifier 40
		102,548	102,547	-/ATTCTGT	7	upstream gene variant	modifier 1

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

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

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

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

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

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

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

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

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

A genetic burden score was calculated by summing the dosage scores for *apoea*, *apoeb*, *apobb.1* and *ldlra*. Dorsal and lateral body surface area and body volume were normalized for body length using residuals. All outcomes were inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models and were adjusted for mutations in *apoba*, *apobb.2* and *ldlr*, 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 1 - The effect of a genetic burden score on whole-body lipid and glucose levels

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

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

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

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

continued Supplementary Table 1/7

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

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

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

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

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

continued Supplementary Table 18

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=301)					Model 2 (n=269)					Model 3 (n=269)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	genetic burden score	0.066	0.092	4.71E-01	-0.114	0.247	0.029	0.095	7.59E-01	-0.158	0.216	0.010	0.103	9.25E-01	-0.192	0.211
	<i>apoba</i>	0.259	0.869	7.65E-01	-1.443	1.962	0.072	0.832	9.31E-01	-1.559	1.703	0.481	0.875	5.82E-01	-1.233	2.196
	<i>apobb.2</i>	-0.765	0.587	1.92E-01	-1.917	0.386	-0.754	0.557	1.76E-01	-1.846	0.338	-0.360	0.493	4.65E-01	-1.327	0.607
	<i>ldlr</i>	15.180	3.761	5.43E-05	7.809	22.551	17.068	3.698	3.93E-06	9.819	24.316	15.483	3.640	2.10E-05	8.350	22.616
	time of day (in hours since 9AM)	0.022	0.101	8.24E-01	-0.175	0.219	-0.041	0.113	7.16E-01	-0.262	0.180	0.042	0.123	7.36E-01	-0.200	0.283
	body length (in SD)	-	-	-	-	-	-0.397	0.204	5.16E-02	-0.796	0.003	-0.338	0.230	1.42E-01	-0.789	0.113
	dorsal body surface area (in SD)	-	-	-	-	-	0.067	0.148	6.52E-01	-0.223	0.357	0.061	0.149	6.81E-01	-0.231	0.354
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.119	0.150	4.29E-01	-0.414	0.176
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.182	0.153	2.35E-01	-0.118	0.482
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.482	0.241	4.59E-02	0.009	0.955
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.128	0.139	3.56E-01	-0.400	0.144
	batch 1	1.324	0.750	7.74E-02	-0.146	2.793	1.525	0.835	6.76E-02	-0.110	3.161	1.415	0.877	1.07E-01	-0.303	3.133
	batch 2	0.132	0.926	8.87E-01	-1.683	1.946	0.012	0.969	9.90E-01	-1.887	1.912	0.018	0.994	9.86E-01	-1.931	1.967
	batch 3	0.273	0.753	7.17E-01	-1.203	1.748	0.252	0.781	7.46E-01	-1.278	1.782	0.152	0.771	8.44E-01	-1.360	1.663
	batch 4	1.378	0.834	9.84E-02	-0.256	3.011	0.986	0.849	2.46E-01	-0.679	2.650	0.851	0.818	2.98E-01	-0.752	2.454
	batch 5	1.816	0.868	3.65E-02	0.114	3.517	1.766	0.917	5.43E-02	-0.033	3.564	1.203	0.969	2.14E-01	-0.696	3.102
	batch 6	0.740	0.789	3.48E-01	-0.806	2.286	1.264	0.933	1.76E-01	-0.565	3.094	0.589	1.029	5.67E-01	-1.427	2.606
	batch 7	-0.383	0.915	6.76E-01	-2.176	1.411	-0.144	1.066	8.92E-01	-2.234	1.945	-0.449	1.121	6.89E-01	-2.645	1.748
	intercept	-4.162	2.165	5.46E-02	-8.406	0.082	-4.308	2.087	3.90E-02	-8.399	-0.217	-4.870	2.132	2.23E-02	-9.049	-0.692
		Vascular infiltration by neutrophils														
		Model 1 (n=371)					Model 2 (n=330)					Model 3 (n=330)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	genetic burden score	-0.018	0.033	5.78E-01	-0.082	0.046	-0.026	0.035	4.57E-01	-0.094	0.042	-0.029	0.035	4.10E-01	-0.098	0.040
	<i>apoba</i>	0.096	0.272	7.24E-01	-0.436	0.628	0.144	0.284	6.11E-01	-0.412	0.701	0.140	0.283	6.20E-01	-0.414	0.695
	<i>apobb.2</i>	-0.084	0.198	6.71E-01	-0.472	0.304	0.016	0.211	9.40E-01	-0.397	0.429	0.003	0.213	9.90E-01	-0.414	0.420
	<i>ldlr</i>	-2.023	2.259	3.71E-01	-6.451	2.405	-1.483	2.282	5.16E-01	-5.955	2.990	-1.459	2.286	5.23E-01	-5.940	3.021
	time of day (in hours since 9AM)	0.012	0.041	7.65E-01	-0.067	0.092	-0.020	0.045	6.55E-01	-0.107	0.067	-0.022	0.045	6.20E-01	-0.110	0.065
	body length (in SD)	-	-	-	-	-	-0.122	0.070	7.94E-02	-0.258	0.014	-0.114	0.070	1.04E-01	-0.252	0.023
	dorsal body surface area (in SD)	-	-	-	-	-	0.060	0.059	3.12E-01	-0.056	0.176	0.075	0.060	2.11E-01	-0.043	0.193
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.002	0.053	9.65E-01	-0.103	0.107
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.081	0.060	1.79E-01	-0.037	0.200
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.042	0.071	5.50E-01	-0.181	0.097
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.060	0.054	2.71E-01	-0.046	0.166
	intercept	0.845	1.091	4.38E-01	-1.293	2.983	0.536	1.116	6.31E-01	-1.651	2.723	0.570	1.117	6.10E-01	-1.619	2.759
random factors	<i>variance by batch</i>	0.356	0.101	-	0.204	0.622	0.323	0.097	-	0.179	0.582	0.297	0.092	-	0.162	0.545
	<i>residual</i>	0.885	0.033	-	0.823	0.952	0.890	0.035	-	0.824	0.962	0.888	0.035	-	0.822	0.959

continued Supplementary Table 18

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

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

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

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

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

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

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

continued Supplementary Table 19

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

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

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

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

		HDL cholesterol levels														
		<i>apoea</i>					<i>apoeb</i>					<i>apobb.1</i>				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	2 vs. 0 mutated alleles	0.123	0.190	5.15E-01	-0.248	0.495	0.223	0.180	2.16E-01	-0.130	0.577	0.253	0.189	1.79E-01	-0.116	0.623
	<i>apoea</i>	-	-	-	-	-	0.035	0.086	6.80E-01	-0.132	0.203	-0.040	0.109	7.12E-01	-0.254	0.174
	<i>apoeb</i>	-0.058	0.132	6.59E-01	-0.317	0.200	-	-	-	-	-	0.148	0.102	1.47E-01	-0.052	0.347
	<i>apobb.1</i>	0.011	0.124	9.29E-01	-0.233	0.255	0.037	0.095	6.93E-01	-0.148	0.223	-	-	-	-	-
	<i>ldlra</i>	0.130	0.101	1.99E-01	-0.068	0.328	0.104	0.073	1.56E-01	-0.040	0.248	0.090	0.098	3.60E-01	-0.103	0.283
	time of day (in hours since 9AM)	-0.077	0.066	2.42E-01	-0.206	0.052	-0.065	0.047	1.66E-01	-0.157	0.027	-0.109	0.056	5.18E-02	-0.219	0.001
	intercept	79.225	73.332	2.80E-01	-64.504	222.954	-2.809	57.043	9.61E-01	-114.611	108.993	-22.711	77.230	7.69E-01	-174.080	128.657
	<i>apoba</i>	0.053	0.489	9.13E-01	-0.905	1.012	-0.412	0.333	2.16E-01	-1.065	0.240	0.014	0.404	9.73E-01	-0.777	0.805
	<i>apobb.2</i>	0.444	0.324	1.70E-01	-0.191	1.078	0.196	0.214	3.60E-01	-0.223	0.614	0.210	0.243	3.88E-01	-0.266	0.686
	<i>ldlr</i>	-199.333	183.370	2.77E-01	-558.731	160.065	7.909	142.733	9.56E-01	-271.843	287.661	55.951	193.319	7.72E-01	-322.947	434.849
random factors	variance by batch	0.570	0.172	-	0.316	1.029	0.579	0.160	-	0.336	0.997	0.528	0.161	-	0.290	0.958
	residual	0.901	0.052	-	0.804	1.008	0.847	0.036	-	0.779	0.921	0.822	0.045	-	0.739	0.914
		0.869	0.036	-	0.801	0.942										

		Triglyceride levels														
		<i>apoea</i>					<i>apoeb</i>					<i>apobb.1</i>				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	2 vs. 0 mutated alleles	-0.265	0.141	6.00E-02	-0.541	0.011	-0.052	0.145	7.21E-01	-0.336	0.233	0.251	0.139	7.06E-02	-0.021	0.522
	<i>apoea</i>	-	-	-	-	-	-0.075	0.069	2.77E-01	-0.210	0.060	-0.093	0.081	2.51E-01	-0.251	0.066
	<i>apoeb</i>	-0.021	0.097	8.26E-01	-0.210	0.168	-	-	-	-	-	-0.057	0.075	4.44E-01	-0.204	0.089
	<i>apobb.1</i>	0.012	0.091	8.93E-01	-0.166	0.190	0.115	0.076	1.30E-01	-0.034	0.265	-	-	-	-	-
	<i>ldlra</i>	0.034	0.074	6.46E-01	-0.111	0.179	0.022	0.059	7.15E-01	-0.094	0.138	0.045	0.073	5.33E-01	-0.097	0.188
	time of day (in hours since 9AM)	-0.146	0.050	3.27E-03	-0.244	-0.049	-0.126	0.038	9.97E-04	-0.201	-0.051	-0.145	0.042	5.90E-04	-0.228	-0.062
	intercept	43.986	53.653	4.12E-01	-61.173	149.145	21.252	46.003	6.44E-01	-68.911	111.415	36.478	56.734	5.20E-01	-74.719	147.675
	<i>apoba</i>	0.079	0.358	8.25E-01	-0.622	0.780	-0.091	0.268	7.35E-01	-0.616	0.435	0.025	0.298	9.32E-01	-0.558	0.609
	<i>apobb.2</i>	-0.401	0.236	8.97E-02	-0.865	0.062	-0.402	0.172	1.96E-02	-0.739	-0.064	-0.538	0.179	2.59E-03	-0.889	-0.188
	<i>ldlr</i>	-108.252	134.160	4.20E-01	-371.202	154.697	-50.755	115.105	6.59E-01	-276.357	174.846	-88.498	142.009	5.33E-01	-366.830	189.835
random factors	variance by batch	0.789	0.209	-	0.470	1.326	0.810	0.209	-	0.489	1.342	0.720	0.188	-	0.431	1.203
	residual	0.657	0.038	-	0.587	0.736	0.681	0.029	-	0.626	0.741	0.603	0.033	-	0.543	0.671
		0.682	0.028	-	0.629	0.740										

continued Supplementary Table 20

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

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

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

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

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

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

continued Supplementary Table 21

		Vascular co-localization of lipids with macrophages														
		31 vs. 80 larvae with 2 vs. 0 mutated alleles (n=111)					30 vs. 65 larvae with 2 vs. 0 mutated alleles (n=95)					30 vs. 65 larvae with 2 vs. 0 mutated alleles (n=95)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	-0.387	0.699	5.80E-01	-1.758	0.984	-0.748	0.875	3.93E-01	-2.463	0.967	-0.531	0.976	5.86E-01	-2.444	1.381
	<i>apoeb</i>	0.021	0.295	9.43E-01	-0.558	0.600	0.251	0.314	4.24E-01	-0.365	0.868	0.337	0.345	3.29E-01	-0.339	1.014
	<i>apobb.1</i>	1.362	0.326	2.93E-05	0.723	2.001	1.142	0.513	2.61E-02	0.136	2.148	0.694	0.859	4.19E-01	-0.990	2.378
	<i>ldlra</i>	0.166	0.351	6.35E-01	-0.521	0.854	0.195	0.454	6.68E-01	-0.696	1.086	-0.096	0.468	8.37E-01	-1.014	0.821
	body length (in SD)	-	-	-	-	-	0.078	0.479	8.70E-01	-0.860	1.016	0.023	0.611	9.71E-01	-1.174	1.219
	dorsal body surface area (in SD)	-	-	-	-	-	0.481	0.297	1.05E-01	-0.101	1.062	0.426	0.645	5.09E-01	-0.838	1.689
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.081	0.327	8.03E-01	-0.722	0.559
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.016	0.498	9.74E-01	-0.993	0.960
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	1.035	0.501	3.89E-02	0.053	2.018
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.228	0.522	6.62E-01	-1.250	0.794
	time of day (in hours since 9AM)	0.215	0.140	1.25E-01	-0.060	0.489	0.183	0.237	4.39E-01	-0.281	0.648	0.327	0.361	3.65E-01	-0.380	1.034
	batch 2	1.037	1.056	3.26E-01	-1.033	3.107	0.982	1.145	3.91E-01	-1.263	3.227	0.438	1.648	7.90E-01	-2.792	3.668
	batch 3	-1.382	0.712	5.22E-02	-2.777	0.013	-1.267	0.862	1.42E-01	-2.956	0.423	-1.449	1.537	3.46E-01	-4.460	1.563
	batch 4	-0.418	0.699	5.50E-01	-1.789	0.952	-0.393	0.911	6.66E-01	-2.179	1.393	-0.693	1.405	6.22E-01	-3.447	2.061
	batch 5	0.438	0.619	4.80E-01	-0.776	1.651	0.017	0.789	9.83E-01	-1.529	1.563	-1.515	1.427	2.89E-01	-4.312	1.283
	batch 6	-0.877	0.644	1.73E-01	-2.139	0.386	-1.652	0.760	2.98E-02	-3.142	-0.162	-3.576	1.802	4.72E-02	-7.107	-0.044
	batch 7	-2.995	0.769	9.76E-05	-4.501	-1.488	-3.887	0.920	2.40E-05	-5.691	-2.084	-4.793	2.075	2.09E-02	-8.859	-0.726
	intercept	-233.734	227.970	3.05E-01	-680.548	213.080	-196.479	316.933	5.35E-01	-817.657	424.699	-194.514	380.442	6.09E-01	-940.167	551.139
	<i>apoba</i>	-1.350	1.667	4.18E-01	-4.617	1.916	-1.213	1.698	4.75E-01	-4.540	2.115	-0.244	2.329	9.16E-01	-4.809	4.320
	<i>apobb.2</i>	-0.885	0.700	2.06E-01	-2.256	0.486	-0.837	0.713	2.41E-01	-2.235	0.561	-0.087	1.485	9.53E-01	-2.997	2.824
	<i>ldlr</i>	596.038	572.764	2.98E-01	-526.558	1718.634	502.398	792.141	5.26E-01	-1100.000	2054.967	492.382	952.213	6.05E-01	-1400.000	2358.685
		Vascular infiltration by neutrophils														
		47 vs. 106 larvae with 2 vs. 0 mutated alleles (n=153)					44 vs. 91 larvae with 2 vs. 0 mutated alleles (n=135)					44 vs. 91 larvae with 2 vs. 0 mutated alleles (n=135)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	2 vs. 0 mutated alleles	-0.064	0.179	7.20E-01	-0.416	0.287	-0.080	0.176	6.48E-01	-0.426	0.265	-0.138	0.179	4.40E-01	-0.489	0.213
	<i>apoeb</i>	-0.108	0.128	3.98E-01	-0.359	0.142	-0.086	0.131	5.12E-01	-0.344	0.171	-0.083	0.131	5.30E-01	-0.340	0.175
	<i>apobb.1</i>	0.140	0.125	2.65E-01	-0.106	0.386	-0.113	0.131	3.89E-01	-0.369	0.144	-0.112	0.132	3.95E-01	-0.370	0.146
	<i>ldlra</i>	-0.008	0.099	9.33E-01	-0.202	0.185	0.069	0.098	4.84E-01	-0.124	0.261	0.063	0.098	5.19E-01	-0.129	0.256
	body length (in SD)	-	-	-	-	-	-0.315	0.103	2.28E-03	-0.517	-0.113	-0.325	0.103	1.59E-03	-0.527	-0.123
	dorsal body surface area (in SD)	-	-	-	-	-	0.191	0.094	4.25E-02	0.006	0.376	0.216	0.096	2.41E-02	0.028	0.404
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.130	0.077	9.08E-02	-0.021	0.282
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.091	0.085	2.85E-01	-0.076	0.257
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.047	0.103	6.48E-01	-0.155	0.249
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.008	0.080	9.18E-01	-0.149	0.165
	time of day (in hours since 9AM)	0.006	0.062	9.22E-01	-0.115	0.128	-0.030	0.065	6.45E-01	-0.158	0.098	-0.017	0.064	7.90E-01	-0.142	0.108
	intercept_random	-120.289	71.401	9.20E-02	-260.231	19.654	-125.307	73.902	9.00E-02	-270.152	19.539	-134.596	73.421	6.68E-02	-278.498	9.306
	<i>apoba</i>	0.345	0.471	4.63E-01	-0.577	1.268	0.182	0.456	6.89E-01	-0.711	1.076	0.087	0.455	8.49E-01	-0.805	0.978
	<i>apobb.2</i>	-0.028	0.310	9.29E-01	-0.636	0.580	0.174	0.306	5.71E-01	-0.426	0.773	0.103	0.315	7.45E-01	-0.515	0.721
	<i>ldlr</i>	299.596	178.573	9.34E-02	-50.401	649.593	312.556	184.759	9.07E-02	-49.565	674.677	336.427	183.574	6.69E-02	-23.371	696.226
random factors	variance by batch	0.375	0.121	-	0.199	0.706	0.334	0.121	-	0.164	0.681	0.271	0.117	-	0.116	0.632
	residual	0.861	0.051	-	0.768	0.967	0.812	0.051	-	0.717	0.919	0.807	0.051	-	0.713	0.913

continued Supplementary Table 21

		Vascular co-localization of lipids with neutrophils														
		31 vs. 75 larvae with 2 vs. 0 mutated alleles (n=106)					30 vs. 60 larvae with 2 vs. 0 mutated alleles (n=90)					30 vs. 60 larvae with 2 vs. 0 mutated alleles (n=90)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	-0.823	0.679	2.25E-01	-2.154	0.507	-0.243	0.568	6.69E-01	-1.355	0.870	-0.523	0.644	4.17E-01	-1.786	0.740
	<i>apoeb</i>	0.219	0.437	6.17E-01	-0.638	1.075	0.780	0.294	7.90E-03	0.204	1.355	0.770	0.322	1.67E-02	0.140	1.401
	<i>apobb.1</i>	1.968	0.327	1.80E-09	1.327	2.610	2.615	0.502	1.90E-07	1.631	3.599	2.243	0.549	4.37E-05	1.167	3.319
	<i>ldlra</i>	0.702	0.327	3.20E-02	0.061	1.343	0.724	0.372	5.17E-02	-0.005	1.452	0.562	0.354	1.13E-01	-0.132	1.256
	body length (in SD)	-	-	-	-	-	0.073	0.477	8.79E-01	-0.862	1.008	0.181	0.533	7.34E-01	-0.863	1.225
	dorsal body surface area (in SD)	-	-	-	-	-	-0.512	0.503	3.08E-01	-1.497	0.473	-0.284	0.538	5.98E-01	-1.338	0.770
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.033	0.332	9.22E-01	-0.617	0.683
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.646	0.379	8.87E-02	-0.098	1.389
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.655	0.340	5.43E-02	-0.012	1.322
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.106	0.262	6.85E-01	-0.407	0.620
	time of day (in hours since 9AM)	0.469	0.179	9.00E-03	0.117	0.821	0.784	0.279	4.96E-03	0.237	1.331	0.642	0.305	3.50E-02	0.045	1.239
	batch 2	0.551	1.161	6.35E-01	-1.725	2.827	1.792	1.096	1.02E-01	-0.356	3.940	2.003	1.165	8.55E-02	-0.280	4.286
	batch 3	-1.322	1.155	2.52E-01	-3.586	0.941	-0.854	1.017	4.01E-01	-2.847	1.139	-0.100	1.270	9.38E-01	-2.589	2.390
	batch 4	-0.266	0.953	7.80E-01	-2.134	1.603	0.286	0.971	7.68E-01	-1.616	2.189	0.975	1.147	3.95E-01	-1.273	3.223
	batch 5	-0.247	0.830	7.66E-01	-1.874	1.380	0.722	0.745	3.32E-01	-0.738	2.182	0.661	1.019	5.16E-01	-1.336	2.659
	batch 6	-2.620	0.959	6.28E-03	-4.499	-0.741	-1.984	0.865	2.19E-02	-3.680	-0.288	-2.230	1.129	4.83E-02	-4.443	-0.017
	intercept	-791.606	250.244	1.56E-03	-1300.000	-301.137	-918.003	298.459	2.10E-03	-1500.000	-333.034	-853.180	303.486	4.93E-03	-1400.000	-258.358
	<i>apoba</i>	-3.117	1.464	3.32E-02	-5.987	-0.248	-2.355	1.211	5.17E-02	-4.728	0.017	-2.021	1.458	6.85E-01	-4.879	0.837
	<i>apobb.2</i>	1.520	0.907	9.38E-02	-0.258	3.298	-0.202	0.809	8.02E-01	-1.787	1.383	0.105	0.976	9.14E-01	-1.808	2.018
	<i>ldlr</i>	1982.551	626.570	1.56E-03	754.497	3210.604	2291.772	746.022	2.13E-03	829.596	3753.949	2128.907	756.916	4.91E-03	645.379	3612.435
		Vascular co-localization of macrophages with neutrophils														
		47 vs. 104 larvae with 2 vs. 0 mutated alleles (n=151)					44 vs. 89 larvae with 2 vs. 0 mutated alleles (n=133)					44 vs. 89 larvae with 2 vs. 0 mutated alleles (n=133)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	-0.335	0.255	1.88E-01	-0.834	0.164	-0.252	0.247	3.07E-01	-0.735	0.231	-0.218	0.245	3.75E-01	-0.699	0.263
	<i>apoeb</i>	-0.434	0.195	2.61E-02	-0.816	-0.052	-0.336	0.200	9.26E-02	-0.728	0.056	-0.367	0.197	6.30E-02	-0.754	0.020
	<i>apobb.1</i>	-0.105	0.162	5.18E-01	-0.422	0.213	-0.416	0.205	4.26E-02	-0.818	-0.014	-0.427	0.201	3.36E-02	-0.821	-0.033
	<i>ldlra</i>	0.198	0.138	1.50E-01	-0.071	0.468	0.203	0.143	1.57E-01	-0.078	0.483	0.177	0.145	2.22E-01	-0.107	0.462
	body length (in SD)	-	-	-	-	-	0.009	0.192	9.61E-01	-0.366	0.385	-0.019	0.190	9.18E-01	-0.391	0.352
	dorsal body surface area (in SD)	-	-	-	-	-	0.741	0.289	1.04E-02	0.174	1.308	0.701	0.287	1.47E-02	0.138	1.264
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.229	0.114	4.45E-02	0.006	0.451
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.176	0.146	2.29E-01	-0.110	0.461
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.293	0.146	4.49E-02	0.007	0.580
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.173	0.141	2.20E-01	-0.104	0.449
	time of day (in hours since 9AM)	0.062	0.109	5.65E-01	-0.150	0.275	-0.112	0.142	4.27E-01	-0.390	0.165	-0.104	0.135	4.43E-01	-0.368	0.161
	batch 1	-0.433	0.383	2.58E-01	-1.183	0.317	-0.120	0.550	8.28E-01	-1.199	0.959	0.085	0.667	8.99E-01	-1.223	1.393
	batch 2	-0.964	0.392	1.38E-02	-1.732	-0.197	-0.997	0.445	2.52E-02	-1.870	-0.124	-0.329	0.542	5.43E-01	-1.391	0.732
	batch 3	-1.324	0.485	6.36E-03	-2.276	-0.373	-1.012	0.547	6.45E-02	-2.085	0.061	-0.777	0.552	1.59E-01	-1.858	0.304
	batch 4	-0.112	0.466	8.09E-01	-1.025	0.800	0.237	0.546	6.63E-01	-0.832	1.307	0.430	0.558	4.40E-01	-0.663	1.524
	batch 5	0.030	0.469	9.48E-01	-0.890	0.951	0.003	0.489	9.95E-01	-0.956	0.962	0.060	0.535	9.10E-01	-0.989	1.109
	batch 6	-2.377	0.454	1.66E-07	-3.267	-1.487	-3.075	0.624	8.32E-07	-4.298	-1.852	-3.125	0.630	7.01E-07	-4.359	-1.890
	batch 7	-1.110	0.731	1.29E-01	-2.542	0.323	-1.873	0.731	1.04E-02	-3.306	-0.440	-1.714	0.733	1.93E-02	-3.151	-0.278
	intercept	-55.609	120.106	6.43E-01	-291.013	179.796	-196.032	143.724	1.73E-01	-477.726	85.662	-287.996	137.895	3.68E-02	-558.265	-17.727
	<i>apoba</i>	1.159	0.625	6.37E-02	-0.066	2.384	1.815	0.750	1.56E-02	0.344	3.286	1.848	0.744	1.30E-02	0.389	3.307
	<i>apobb.2</i>	-0.200	0.324	5.38E-01	-0.835	0.436	-0.270	0.373	4.69E-01	-1.002	0.461	-0.283	0.404	4.84E-01	-1.075	0.510
	<i>ldlr</i>	146.298	300.491	6.26E-01	-442.654	735.250	495.866	359.236	1.67E-01	-208.223	1199.955	725.424	344.591	3.53E-02	50.039	1400.809

continued Supplementary Table 21

		<i>apoeb</i>														
		Vascular lipid deposition														
		Model 1					Model 2					Model 3				
		179 vs. 29 larvae with 2 vs. 0 mutated alleles (n=208)					153 vs. 26 larvae with 2 vs. 0 mutated alleles (n=179)					153 vs. 26 larvae with 2 vs. 0 mutated alleles (n=179)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	0.479	0.305	1.16E-01	-0.118	1.076	0.592	0.347	8.76E-02	-0.087	1.272	0.564	0.370	1.28E-01	-0.162	1.290
	<i>apoeb</i>	-0.238	0.188	2.06E-01	-0.606	0.131	-0.331	0.210	1.15E-01	-0.742	0.081	-0.263	0.207	2.04E-01	-0.667	0.142
	<i>apobb.1</i>	0.730	0.174	2.64E-05	0.390	1.071	0.843	0.199	2.33E-05	0.452	1.234	0.671	0.201	8.13E-04	0.278	1.064
	<i>ldlr</i>	0.250	0.130	5.34E-02	-0.004	0.504	0.267	0.149	7.25E-02	-0.024	0.558	0.276	0.143	5.38E-02	-0.004	0.556
	body length (in SD)	-	-	-	-	-	0.238	0.159	1.34E-01	-0.074	0.550	0.336	0.158	3.36E-02	0.026	0.646
	dorsal body surface area (in SD)	-	-	-	-	-	0.217	0.148	1.43E-01	-0.073	0.507	0.282	0.145	5.25E-02	-0.003	0.567
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.136	0.104	1.94E-01	-0.340	0.069
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.055	0.168	7.43E-01	-0.384	0.274
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.435	0.167	9.32E-03	0.107	0.764
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.202	0.102	4.80E-02	-0.403	-0.002
	time of day (in hours since 9AM)	-0.044	0.086	6.12E-01	-0.213	0.125	-0.103	0.105	3.28E-01	-0.310	0.104	-0.018	0.110	8.68E-01	-0.233	0.197
	batch 2	-1.404	0.457	2.14E-03	-2.300	-0.508	-1.319	0.527	1.24E-02	-2.352	-0.285	-0.923	0.528	8.03E-02	-1.957	0.111
	batch 3	-1.085	0.389	5.31E-03	-1.847	-0.322	-1.113	0.409	6.48E-03	-1.914	-0.312	-1.198	0.414	3.85E-03	-2.010	-0.386
	batch 4	-1.068	0.442	1.56E-02	-1.934	-0.203	-0.943	0.476	4.73E-02	-1.876	-0.011	-0.826	0.435	5.74E-02	-1.677	0.026
	batch 5	-0.155	0.283	5.84E-01	-0.709	0.399	-0.238	0.325	4.64E-01	-0.875	0.399	-0.903	0.466	5.29E-02	-1.817	0.011
	batch 6	-0.217	0.295	4.63E-01	-0.796	0.362	-0.543	0.372	1.44E-01	-1.273	0.186	-1.323	0.550	1.62E-02	-2.402	-0.245
	batch 7	-0.867	0.388	2.55E-02	-1.628	-0.106	-1.179	0.401	3.24E-03	-1.965	-0.394	-1.622	0.595	6.37E-03	-2.787	-0.457
	intercept	58.235	136.197	6.69E-01	-208.706	325.175	41.113	152.198	7.87E-01	-257.191	339.416	31.011	152.088	8.38E-01	-267.075	329.097
	<i>apoba</i>	-0.199	0.608	7.43E-01	-1.391	0.992	-0.357	0.650	5.83E-01	-1.632	0.918	-0.180	0.646	7.81E-01	-1.447	1.087
	<i>apobb.2</i>	0.001	0.463	9.98E-01	-0.907	0.909	-0.029	0.491	9.52E-01	-0.992	0.933	0.336	0.478	4.82E-01	-0.601	1.274
	<i>ldlr</i>	-133.537	341.561	6.96E-01	-802.985	535.911	-89.418	381.314	8.15E-01	-836.779	657.943	-66.125	381.349	8.62E-01	-813.556	681.305
		Vascular infiltration by macrophages														
		237 vs. 37 larvae with 2 vs. 0 mutated alleles (n=274)					206 vs. 34 larvae with 2 vs. 0 mutated alleles (n=240)					206 vs. 34 larvae with 2 vs. 0 mutated alleles (n=240)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	2 vs. 0 mutated alleles	-0.257	0.184	1.62E-01	-0.617	0.103	-0.218	0.203	2.83E-01	-0.616	0.180	-0.245	0.204	2.30E-01	-0.646	0.155
	<i>apoeb</i>	-0.117	0.088	1.82E-01	-0.289	0.055	-0.148	0.096	1.24E-01	-0.336	0.041	-0.160	0.097	9.97E-02	-0.350	0.030
	<i>apobb.1</i>	-0.168	0.098	8.57E-02	-0.361	0.024	-0.173	0.107	1.05E-01	-0.383	0.036	-0.172	0.108	1.13E-01	-0.385	0.040
	<i>ldlr</i>	0.013	0.075	8.67E-01	-0.135	0.160	0.018	0.085	8.35E-01	-0.149	0.184	0.002	0.085	9.81E-01	-0.165	0.169
	body length (in SD)	-	-	-	-	-	0.023	0.086	7.91E-01	-0.146	0.192	0.024	0.088	7.85E-01	-0.148	0.195
	dorsal body surface area (in SD)	-	-	-	-	-	-0.037	0.075	6.27E-01	-0.184	0.111	-0.039	0.076	6.07E-01	-0.187	0.109
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.029	0.063	6.45E-01	-0.095	0.153
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.112	0.074	1.30E-01	-0.033	0.256
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.000	0.086	1.00E+00	-0.169	0.169
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.031	0.064	6.34E-01	-0.095	0.156
	time of day (in hours since 9AM)	0.020	0.048	6.72E-01	-0.074	0.114	0.018	0.056	7.43E-01	-0.091	0.128	0.023	0.056	6.79E-01	-0.086	0.133
	intercept_random	-49.906	57.788	3.88E-01	-163.168	63.355	-42.117	65.580	5.21E-01	-170.650	86.417	-34.466	65.536	5.99E-01	-162.914	93.982
	<i>apoba</i>	-0.187	0.340	5.82E-01	-0.853	0.479	-0.318	0.374	3.96E-01	-1.051	0.416	-0.283	0.374	4.49E-01	-1.017	0.450
	<i>apobb.2</i>	-0.359	0.217	9.75E-02	-0.783	0.066	-0.391	0.238	9.97E-02	-0.857	0.075	-0.416	0.242	8.58E-02	-0.891	0.059
	<i>ldlr</i>	127.830	144.603	3.77E-01	-155.586	411.246	109.097	164.010	5.06E-01	-212.356	430.551	89.972	163.907	5.83E-01	-231.281	411.224
random factors	variance by batch	0.510	0.143	-	0.295	0.883	0.492	0.143	-	0.278	0.870	0.452	0.136	-	0.250	0.816
	residual	0.857	0.037	-	0.787	0.933	0.886	0.041	-	0.809	0.971	0.884	0.041	-	0.806	0.968

continued Supplementary Table 21

		Vascular co-localization of lipids with macrophages														
		174 vs. 29 larvae with 2 vs. 0 mutated alleles (n=203)					150 vs. 26 larvae with 2 vs. 0 mutated alleles (n=176)					150 vs. 26 larvae with 2 vs. 0 mutated alleles (n=176)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	-0.468	0.389	2.29E-01	-1.231	0.295	-0.477	0.443	2.81E-01	-1.345	0.391	-0.283	0.464	5.41E-01	-1.192	0.625
	<i>apoea</i>	-0.247	0.253	3.28E-01	-0.742	0.248	-0.429	0.292	1.42E-01	-1.000	0.143	-0.402	0.343	2.41E-01	-1.074	0.271
	<i>apobb.1</i>	0.934	0.220	2.27E-05	0.502	1.366	1.015	0.287	3.99E-04	0.453	1.576	0.692	0.352	4.91E-02	0.003	1.382
	<i>ldlra</i>	0.242	0.185	1.91E-01	-0.121	0.606	0.306	0.221	1.65E-01	-0.126	0.739	0.368	0.220	9.40E-02	-0.063	0.799
	body length (in SD)	-	-	-	-	-	0.242	0.260	3.53E-01	-0.268	0.751	0.234	0.279	4.02E-01	-0.313	0.780
	dorsal body surface area (in SD)	-	-	-	-	-	0.471	0.184	1.07E-02	0.109	0.832	0.446	0.182	1.46E-02	0.088	0.804
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.307	0.232	1.87E-01	-0.762	0.149
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.051	0.279	8.56E-01	-0.496	0.597
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.467	0.265	7.77E-02	-0.052	0.986
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.139	0.163	3.92E-01	-0.459	0.180
	time of day (in hours since 9AM)	0.097	0.098	3.24E-01	-0.095	0.289	0.200	0.124	1.05E-01	-0.042	0.443	0.338	0.138	1.47E-02	0.067	0.609
	batch 2	-0.438	0.824	5.95E-01	-2.053	1.177	-0.016	0.967	9.87E-01	-1.911	1.880	-0.594	0.914	5.16E-01	-2.384	1.197
	batch 3	-1.015	0.444	2.21E-02	-1.885	-0.146	-0.976	0.490	4.65E-02	-1.936	-0.015	-1.036	0.648	1.10E-01	-2.305	0.234
	batch 4	-0.450	0.471	3.40E-01	-1.373	0.474	-0.505	0.568	3.74E-01	-1.619	0.608	-0.674	0.600	2.62E-01	-1.851	0.503
	batch 5	0.033	0.377	9.30E-01	-0.706	0.772	-0.486	0.464	2.95E-01	-1.396	0.424	-1.300	0.662	4.97E-02	-2.597	-0.002
	batch 6	-0.548	0.370	1.38E-01	-1.273	0.176	-0.968	0.532	6.91E-02	-2.011	0.076	-1.528	0.962	1.12E-01	-3.413	0.357
	batch 7	-1.275	0.742	8.58E-02	-2.729	0.180	-2.061	0.725	4.46E-03	-3.482	-0.640	-2.677	1.017	8.47E-03	-4.671	-0.684
	intercept	20.330	157.888	8.98E-01	-289.125	329.784	52.867	187.217	7.78E-01	-314.072	419.806	162.185	229.589	4.80E-01	-287.800	612.170
	<i>apoba</i>	-0.470	0.923	6.11E-01	-2.278	1.339	-0.523	1.012	6.06E-01	-2.507	1.461	-0.572	1.353	6.73E-01	-3.223	2.080
	<i>apobb.2</i>	-0.205	0.494	6.78E-01	-1.173	0.762	-0.180	0.536	7.38E-01	-1.229	0.870	0.175	0.536	7.45E-01	-0.876	1.225
	<i>ldlrbb</i>	-42.152	396.237	9.15E-01	-818.763	734.458	-123.631	468.918	7.92E-01	-1000.000	795.432	-398.212	576.562	4.90E-01	-1500.000	731.829
		Vascular infiltration by neutrophils														
		240 vs. 37 larvae with 2 vs. 0 mutated alleles (n=277)					208 vs. 34 larvae with 2 vs. 0 mutated alleles (n=242)					208 vs. 34 larvae with 2 vs. 0 mutated alleles (n=242)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	2 vs. 0 mutated alleles	0.100	0.179	5.77E-01	-0.251	0.451	0.163	0.192	3.96E-01	-0.214	0.540	0.128	0.192	5.06E-01	-0.249	0.505
	<i>apoea</i>	-0.032	0.085	7.08E-01	-0.199	0.135	-0.049	0.091	5.90E-01	-0.227	0.129	-0.073	0.091	4.22E-01	-0.253	0.106
	<i>apobb.1</i>	0.125	0.095	1.89E-01	-0.061	0.311	0.104	0.101	3.02E-01	-0.093	0.301	0.106	0.102	2.96E-01	-0.093	0.305
	<i>ldlra</i>	-0.083	0.073	2.58E-01	-0.227	0.061	-0.078	0.080	3.32E-01	-0.236	0.079	-0.099	0.080	2.18E-01	-0.256	0.058
	body length (in SD)	-	-	-	-	-	-0.027	0.081	7.42E-01	-0.186	0.132	-0.018	0.081	8.26E-01	-0.177	0.141
	dorsal body surface area (in SD)	-	-	-	-	-	0.070	0.070	3.17E-01	-0.068	0.209	0.076	0.070	2.80E-01	-0.062	0.213
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.071	0.058	2.22E-01	-0.043	0.185
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.138	0.069	4.47E-02	0.003	0.272
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.012	0.079	8.77E-01	-0.167	0.143
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.019	0.060	7.48E-01	-0.098	0.137
	time of day (in hours since 9AM)	0.041	0.046	3.69E-01	-0.049	0.132	0.002	0.052	9.72E-01	-0.100	0.104	0.006	0.052	9.02E-01	-0.095	0.108
	intercept_random	53.743	56.805	3.44E-01	-57.594	165.079	26.564	62.657	6.72E-01	-96.241	149.369	35.841	62.150	5.64E-01	-85.971	157.654
	<i>apoba</i>	0.077	0.330	8.15E-01	-0.570	0.725	0.102	0.353	7.73E-01	-0.590	0.794	0.131	0.351	7.09E-01	-0.557	0.820
	<i>apobb.2</i>	0.042	0.211	8.44E-01	-0.373	0.456	0.070	0.225	7.55E-01	-0.371	0.512	0.012	0.228	9.59E-01	-0.435	0.459
	<i>ldlrbb</i>	-135.183	142.138	3.42E-01	-413.770	143.403	-67.148	156.701	6.68E-01	-374.276	239.980	-90.157	155.444	5.62E-01	-394.822	214.507
random factors	variance by batch	0.407	0.115	-	0.234	0.708	0.395	0.118	-	0.220	0.709	0.343	0.108	-	0.186	0.634
	residual	0.838	0.036	-	0.770	0.912	0.842	0.039	-	0.768	0.922	0.834	0.039	-	0.762	0.914

continued Supplementary Table 21

		Vascular co-localization of lipids with neutrophils									
		168 vs. 27 larvae with 2 vs. 0 mutated alleles (n=195)					143 vs. 24 larvae with 2 vs. 0 mutated alleles (n=167)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	-0.389	0.565	4.91E-01	-1.495	0.717	0.227	0.643	7.24E-01	-1.033	1.488
	<i>apoea</i>	-0.241	0.339	4.77E-01	-0.906	0.423	0.048	0.373	8.99E-01	-0.684	0.779
	<i>apobb.1</i>	1.748	0.280	4.46E-10	1.198	2.297	1.812	0.380	1.90E-06	1.066	2.557
	<i>ldlra</i>	0.240	0.315	4.46E-01	-0.377	0.858	0.092	0.322	7.76E-01	-0.540	0.723
	body length (in SD)	-	-	-	-	-	0.071	0.504	8.88E-01	-0.917	1.060
	dorsal body surface area (in SD)	-	-	-	-	-	-0.177	0.246	4.71E-01	-0.659	0.305
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-
	time of day (in hours since 9AM)	0.062	0.169	7.16E-01	-0.270	0.393	0.188	0.195	3.36E-01	-0.195	0.570
	batch 2	-1.617	0.813	4.68E-02	-3.211	-0.023	-1.605	1.080	1.37E-01	-3.722	0.511
	batch 3	-0.752	0.834	3.67E-01	-2.387	0.882	-0.720	0.791	3.63E-01	-2.269	0.830
	batch 4	-0.887	0.621	1.53E-01	-2.104	0.330	-0.638	0.817	4.35E-01	-2.240	0.964
	batch 5	-0.277	0.510	5.87E-01	-1.277	0.722	-0.327	0.550	5.52E-01	-1.405	0.751
	batch 6	-2.640	0.635	3.23E-05	-3.885	-1.395	-2.827	0.837	7.28E-04	-4.467	-1.187
	intercept	-101.955	224.820	6.50E-01	-542.594	338.684	7.020	339.258	9.83E-01	-657.913	671.953
	<i>apoba</i>	0.531	1.282	6.79E-01	-1.982	3.045	1.061	1.155	3.58E-01	-1.203	3.324
	<i>apobb.2</i>	0.600	0.670	3.71E-01	-0.714	1.913	-0.122	0.678	8.57E-01	-1.451	1.206
	<i>ldlr</i>	251.587	564.907	6.56E-01	-855.610	1358.785	-23.731	850.679	9.78E-01	-1700.000	1643.569

		Vascular co-localization of macrophages with neutrophils									
		236 vs. 37 larvae with 2 vs. 0 mutated alleles (n=273)					205 vs. 34 larvae with 2 vs. 0 mutated alleles (n=239)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	0.504	0.278	7.02E-02	-0.042	1.050	0.498	0.280	7.53E-02	-0.051	1.047
	<i>apoea</i>	-0.111	0.148	4.54E-01	-0.400	0.179	-0.100	0.157	5.26E-01	-0.407	0.208
	<i>apobb.1</i>	0.111	0.164	5.00E-01	-0.211	0.432	0.142	0.163	3.84E-01	-0.178	0.462
	<i>ldlra</i>	-0.181	0.126	1.50E-01	-0.428	0.066	-0.178	0.121	1.41E-01	-0.415	0.059
	body length (in SD)	-	-	-	-	-	0.471	0.145	1.16E-03	0.187	0.755
	dorsal body surface area (in SD)	-	-	-	-	-	0.289	0.133	3.01E-02	0.028	0.550
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-
	time of day (in hours since 9AM)	0.112	0.077	1.43E-01	-0.038	0.263	0.117	0.090	1.93E-01	-0.059	0.293
	batch 1	0.658	0.409	1.07E-01	-0.143	1.459	0.246	0.463	5.95E-01	-0.661	1.154
	batch 2	0.750	0.544	1.68E-01	-0.316	1.817	0.756	0.498	1.29E-01	-0.221	1.732
	batch 3	-0.204	0.517	6.93E-01	-1.216	0.809	-0.543	0.525	3.01E-01	-1.573	0.486
	batch 4	1.501	0.490	2.20E-03	0.540	2.462	1.571	0.519	2.46E-03	0.554	2.587
	batch 5	0.456	0.449	3.10E-01	-0.424	1.335	-0.114	0.493	8.17E-01	-1.080	0.852
	batch 6	-1.210	0.466	9.40E-03	-2.123	-0.297	-2.083	0.588	3.99E-04	-3.236	-0.930
	batch 7	-0.190	0.604	7.53E-01	-1.374	0.994	-1.063	0.767	1.66E-01	-2.567	0.441
	intercept	69.161	106.517	5.16E-01	-139.609	277.931	-25.456	109.673	8.16E-01	-240.411	189.499
	<i>apoba</i>	-0.102	0.538	8.50E-01	-1.157	0.953	-0.007	0.546	9.90E-01	-1.076	1.063
	<i>apobb.2</i>	0.017	0.337	9.61E-01	-0.644	0.678	-0.223	0.379	5.57E-01	-0.965	0.520
	<i>ldlr</i>	-164.973	266.850	5.36E-01	-687.989	358.042	73.008	274.916	7.91E-01	-465.817	611.833

continued Supplementary Table 21

		<i>apobb.1</i>														
		Vascular lipid deposition														
		Model 1					Model 2					Model 3				
		20 vs. 113 larvae with 2 vs. 0 mutated alleles (n=133)					20 vs. 95 larvae with 2 vs. 0 mutated alleles (n=115)					20 vs. 95 larvae with 2 vs. 0 mutated alleles (n=115)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	1.765	0.360	9.32E-07	1.060	2.470	2.914	0.809	3.17E-04	1.328	4.499	2.482	0.850	3.50E-03	0.816	4.147
	<i>apoea</i>	-0.406	0.264	1.24E-01	-0.923	0.111	-0.282	0.331	3.95E-01	-0.930	0.367	-0.299	0.339	3.78E-01	-0.964	0.366
	<i>apoeb</i>	0.191	0.190	3.14E-01	-0.181	0.563	0.271	0.230	2.40E-01	-0.181	0.722	0.311	0.247	2.07E-01	-0.173	0.795
	<i>ldlra</i>	0.200	0.174	2.51E-01	-0.142	0.542	0.105	0.193	5.88E-01	-0.274	0.483	0.088	0.199	6.59E-01	-0.303	0.479
	body length (in SD)	-	-	-	-	-	0.704	0.296	1.74E-02	0.124	1.284	0.549	0.337	1.03E-01	-0.111	1.210
	dorsal body surface area (in SD)	-	-	-	-	-	0.510	0.185	5.93E-03	0.147	0.874	0.425	0.201	3.44E-02	0.031	0.819
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.051	0.135	7.09E-01	-0.316	0.215
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.147	0.227	5.16E-01	-0.593	0.298
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.317	0.203	1.19E-01	-0.081	0.715
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.060	0.140	6.69E-01	-0.333	0.214
	time of day (in hours since 9AM)	-0.075	0.114	5.09E-01	-0.299	0.148	-0.155	0.148	2.96E-01	-0.445	0.136	-0.066	0.171	6.98E-01	-0.402	0.270
	batch 2	-1.216	0.674	7.13E-02	-2.538	0.106	-0.149	0.900	8.68E-01	-1.913	1.615	-0.215	0.960	8.23E-01	-2.096	1.666
	batch 3	-1.276	0.499	1.06E-02	-2.255	-0.297	-0.998	0.595	9.38E-02	-2.164	0.169	-1.209	0.651	6.32E-02	-2.484	0.066
	batch 4	-0.845	0.467	7.07E-02	-1.761	0.071	-0.047	0.624	9.40E-01	-1.269	1.175	-0.399	0.722	5.80E-01	-1.815	1.016
	batch 5	-0.211	0.387	5.85E-01	-0.970	0.547	-0.011	0.561	9.85E-01	-1.111	1.090	-0.654	0.712	3.59E-01	-2.050	0.743
	batch 6	-0.162	0.381	6.70E-01	-0.910	0.585	-0.524	0.419	2.11E-01	-1.345	0.297	-1.131	0.595	5.72E-02	-2.297	0.034
	batch 7	-1.058	0.462	2.19E-02	-1.963	-0.153	-1.057	0.544	5.19E-02	-2.122	0.009	-1.729	0.830	3.72E-02	-3.355	-0.103
	intercept	183.351	148.640	2.17E-01	-107.977	474.679	174.210	171.135	3.09E-01	-161.209	509.629	131.729	171.727	4.43E-01	-204.849	468.307
	<i>apoba</i>	0.954	0.808	2.37E-01	-0.629	2.537	0.769	0.923	4.05E-01	-1.040	2.577	0.695	0.964	4.71E-01	-1.195	2.584
	<i>apobb.2</i>	-0.031	0.473	9.48E-01	-0.958	0.895	-0.008	0.509	9.88E-01	-1.006	0.990	0.307	0.554	5.80E-01	-0.779	1.394
	<i>ldlrbb</i>	-450.568	372.285	2.26E-01	-1200.000	279.096	-427.256	428.905	3.19E-01	-1300.000	413.383	-321.569	430.563	4.55E-01	-1200.000	522.320
		Vascular infiltration by macrophages														
		26 vs. 143 larvae with 2 vs. 0 mutated alleles (n=169)					26 vs. 126 larvae with 2 vs. 0 mutated alleles (n=152)					26 vs. 126 larvae with 2 vs. 0 mutated alleles (n=152)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	2 vs. 0 mutated alleles	-0.270	0.214	2.08E-01	-0.690	0.150	-0.300	0.255	2.39E-01	-0.799	0.199	-0.092	0.264	7.28E-01	-0.609	0.426
	<i>apoea</i>	-0.110	0.122	3.66E-01	-0.350	0.129	-0.178	0.135	1.89E-01	-0.443	0.087	-0.229	0.134	8.83E-02	-0.492	0.034
	<i>apoeb</i>	-0.089	0.113	4.30E-01	-0.311	0.132	-0.098	0.125	4.35E-01	-0.343	0.148	-0.143	0.125	2.54E-01	-0.387	0.102
	<i>ldlra</i>	0.067	0.112	5.47E-01	-0.152	0.286	0.086	0.122	4.79E-01	-0.153	0.326	0.104	0.120	3.87E-01	-0.132	0.340
	body length (in SD)	-	-	-	-	-	-0.046	0.121	7.06E-01	-0.284	0.192	0.010	0.123	9.36E-01	-0.231	0.251
	dorsal body surface area (in SD)	-	-	-	-	-	-0.194	0.098	4.73E-02	-0.386	-0.002	-0.157	0.100	1.16E-01	-0.352	0.039
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.120	0.085	1.57E-01	-0.046	0.286
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.055	0.101	5.87E-01	-0.144	0.254
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.258	0.117	2.79E-02	-0.488	-0.028
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.063	0.088	4.76E-01	-0.110	0.236
	time of day (in hours since 9AM)	0.103	0.063	1.01E-01	-0.020	0.225	0.117	0.069	9.19E-02	-0.019	0.253	0.068	0.069	3.23E-01	-0.067	0.203
	intercept_random	11.258	88.626	8.99E-01	-162.446	184.962	-2.079	99.580	9.83E-01	-197.253	193.094	1.267	98.915	9.90E-01	-192.603	195.136
	<i>apoba</i>	-0.485	0.450	2.81E-01	-1.367	0.397	-0.542	0.478	2.58E-01	-1.479	0.396	-0.539	0.470	2.51E-01	-1.460	0.382
	<i>apobb.2</i>	-0.189	0.269	4.82E-01	-0.715	0.337	-0.389	0.303	1.99E-01	-0.983	0.204	-0.606	0.314	5.36E-02	-1.221	0.010
	<i>ldlrbb</i>	-24.951	221.876	9.10E-01	-459.821	409.919	9.325	249.131	9.70E-01	-478.963	497.613	2.196	247.481	9.93E-01	-482.857	487.250
random factors	variance by batch	0.574	0.172	-	0.319	1.031	0.490	0.173	-	0.245	0.980	0.366	0.143	-	0.170	0.787
	residual	0.899	0.050	-	0.805	1.003	0.931	0.055	-	0.828	1.046	0.918	0.055	-	0.817	1.031

continued Supplementary Table 21

		Vascular co-localization of lipids with macrophages														
		20 vs. 108 larvae with 2 vs. 0 mutated alleles (n=128)					20 vs. 92 larvae with 2 vs. 0 mutated alleles (n=112)					20 vs. 92 larvae with 2 vs. 0 mutated alleles (n=112)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	2.295	0.547	2.72E-05	1.223	3.367	4.048	1.068	1.50E-04	1.956	6.141	3.351	1.013	9.44E-04	1.365	5.337
	<i>apoea</i>	-0.269	0.419	5.21E-01	-1.089	0.552	-0.374	0.514	4.66E-01	-1.381	0.632	-0.199	0.538	7.12E-01	-1.253	0.856
	<i>apoeb</i>	-0.236	0.256	3.57E-01	-0.738	0.266	-0.311	0.283	2.72E-01	-0.867	0.244	-0.408	0.276	1.40E-01	-0.950	0.133
	<i>ldlra</i>	0.360	0.208	8.28E-02	-0.047	0.767	0.256	0.220	2.45E-01	-0.175	0.686	0.408	0.233	7.91E-02	-0.047	0.864
	body length (in SD)	-	-	-	-	-	1.231	0.470	8.75E-03	0.311	2.151	1.121	0.485	2.08E-02	0.170	2.071
	dorsal body surface area (in SD)	-	-	-	-	-	0.847	0.259	1.07E-03	0.339	1.354	0.792	0.300	8.21E-03	0.205	1.380
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.363	0.280	1.95E-01	-0.911	0.186
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.033	0.288	9.10E-01	-0.597	0.532
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.096	0.427	8.22E-01	-0.741	0.932
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.232	0.248	3.50E-01	-0.718	0.254
	time of day (in hours since 9AM)	0.215	0.148	1.48E-01	-0.076	0.505	0.313	0.164	5.67E-02	-0.009	0.634	0.437	0.176	1.29E-02	0.092	0.782
	batch 2	0.570	1.135	6.16E-01	-1.655	2.795	1.855	1.345	1.68E-01	-0.782	4.491	1.208	1.298	3.52E-01	-1.337	3.753
	batch 3	-1.739	0.589	3.14E-03	-2.893	-0.585	-1.631	0.721	2.37E-02	-3.045	-0.218	-1.931	0.799	1.57E-02	-3.498	-0.364
	batch 4	-0.373	0.601	5.35E-01	-1.550	0.805	0.295	0.854	7.30E-01	-1.379	1.968	0.269	0.934	7.73E-01	-1.561	2.099
	batch 5	-0.139	0.595	8.16E-01	-1.306	1.028	-0.859	0.762	2.60E-01	-2.353	0.635	-0.795	0.879	3.66E-01	-2.518	0.928
	batch 6	-0.716	0.577	2.14E-01	-1.846	0.414	-2.288	0.702	1.12E-03	-3.664	-0.912	-2.405	1.136	3.43E-02	-4.631	-0.178
	batch 7	-0.845	0.788	2.84E-01	-2.390	0.701	-2.164	0.826	8.77E-03	-3.782	-0.546	-2.372	1.171	4.27E-02	-4.667	-0.078
	intercept	108.949	133.134	4.13E-01	-151.988	369.886	105.728	213.116	6.20E-01	-311.971	523.427	251.845	259.958	3.33E-01	-257.664	761.353
	<i>apoba</i>	-0.919	1.185	4.38E-01	-3.242	1.405	-0.768	1.116	4.92E-01	-2.956	1.420	-0.610	1.095	5.77E-01	-2.757	1.536
	<i>apobb.2</i>	0.031	0.591	9.59E-01	-1.127	1.188	0.132	0.639	8.36E-01	-1.121	1.385	0.210	0.725	7.73E-01	-1.212	1.631
	<i>ldlr</i>	-263.818	334.248	4.30E-01	-918.933	391.296	-256.522	532.363	6.30E-01	-1300.000	786.891	-623.857	649.781	3.37E-01	-1900.000	649.691
		Vascular infiltration by neutrophils														
		26 vs. 147 larvae with 2 vs. 0 mutated alleles (n=173)					26 vs. 129 larvae with 2 vs. 0 mutated alleles (n=155)					26 vs. 129 larvae with 2 vs. 0 mutated alleles (n=155)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	2 vs. 0 mutated alleles	0.428	0.206	3.77E-02	0.024	0.832	0.281	0.235	2.31E-01	-0.179	0.742	0.466	0.245	5.72E-02	-0.014	0.947
	<i>apoea</i>	-0.152	0.116	1.92E-01	-0.380	0.076	-0.217	0.124	8.05E-02	-0.460	0.026	-0.236	0.124	5.78E-02	-0.479	0.008
	<i>apoeb</i>	0.008	0.108	9.40E-01	-0.204	0.220	0.021	0.115	8.58E-01	-0.205	0.247	-0.014	0.116	9.05E-01	-0.241	0.213
	<i>ldlra</i>	-0.088	0.107	4.10E-01	-0.297	0.121	-0.042	0.112	7.08E-01	-0.261	0.177	-0.019	0.111	8.62E-01	-0.237	0.198
	body length (in SD)	-	-	-	-	-	-0.112	0.110	3.08E-01	-0.328	0.103	-0.061	0.112	5.89E-01	-0.280	0.159
	dorsal body surface area (in SD)	-	-	-	-	-	0.040	0.089	6.53E-01	-0.135	0.215	0.074	0.092	4.19E-01	-0.105	0.253
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.054	0.076	4.76E-01	-0.095	0.204
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.049	0.094	6.02E-01	-0.135	0.232
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.186	0.107	8.18E-02	-0.395	0.023
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.122	0.082	1.34E-01	-0.038	0.282
	time of day (in hours since 9AM)	0.029	0.059	6.29E-01	-0.088	0.145	0.017	0.064	7.95E-01	-0.108	0.141	-0.015	0.064	8.14E-01	-0.140	0.110
	intercept_random	-182.126	85.408	3.30E-02	-349.522	-14.729	-203.375	92.181	2.74E-02	-384.047	-22.702	-198.131	92.230	3.17E-02	-378.899	-17.363
	<i>apoba</i>	0.233	0.431	5.89E-01	-0.612	1.078	0.169	0.441	7.02E-01	-0.695	1.033	0.163	0.436	7.09E-01	-0.693	1.018
	<i>apobb.2</i>	0.004	0.259	9.87E-01	-0.503	0.511	0.142	0.280	6.12E-01	-0.407	0.692	0.045	0.292	8.77E-01	-0.527	0.617
	<i>ldlr</i>	454.749	213.818	3.34E-02	35.674	873.823	507.788	230.619	2.77E-02	55.782	959.793	495.311	230.758	3.18E-02	43.035	947.588
random factors	variance by batch	0.468	0.142	-	0.258	0.850	0.407	0.140	-	0.207	0.798	0.308	0.126	-	0.138	0.686
	residual	0.867	0.048	-	0.778	0.966	0.862	0.051	-	0.769	0.967	0.856	0.050	-	0.763	0.961

continued Supplementary Table 21

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

		Vascular co-localization of macrophages with neutrophils														
		26 vs. 143 larvae with 2 vs. 0 mutated alleles (n=169)					26 vs. 126 larvae with 2 vs. 0 mutated alleles (n=152)					26 vs. 126 larvae with 2 vs. 0 mutated alleles (n=152)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	0.080	0.279	7.73E-01	-0.467	0.628	0.002	0.312	9.96E-01	-0.609	0.613	0.101	0.328	7.58E-01	-0.542	0.743
	<i>apoea</i>	-0.230	0.158	1.45E-01	-0.540	0.080	-0.287	0.172	9.53E-02	-0.624	0.050	-0.435	0.181	1.63E-02	-0.790	-0.080
	<i>apoeb</i>	-0.011	0.149	9.41E-01	-0.302	0.280	-0.040	0.162	8.03E-01	-0.359	0.278	-0.066	0.156	6.72E-01	-0.371	0.239
	<i>ldlra</i>	-0.041	0.137	7.66E-01	-0.310	0.228	-0.042	0.132	7.52E-01	-0.301	0.218	0.047	0.132	7.21E-01	-0.212	0.307
	body length (in SD)	-	-	-	-	-	-0.026	0.165	8.73E-01	-0.350	0.297	-0.019	0.201	9.23E-01	-0.414	0.375
	dorsal body surface area (in SD)	-	-	-	-	-	0.123	0.142	3.86E-01	-0.155	0.401	0.103	0.150	4.92E-01	-0.191	0.397
	LDL cholesterol levels (in SD)	-	-	-	-	-	0.271	0.142	-	-	-	0.012	0.143	9.35E-01	-0.268	0.292
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.166	0.147	2.60E-01	-0.454	0.122
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.284	0.219	1.95E-01	-0.714	0.145
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.304	0.112	6.68E-03	0.084	0.524
	time of day (in hours since 9AM)	0.253	0.079	1.25E-03	0.099	0.407	0.235	0.086	6.31E-03	0.066	0.404	0.185	0.093	4.62E-02	0.003	0.367
	batch 1	-0.542	0.505	2.83E-01	-1.533	0.448	-0.413	0.576	4.74E-01	-1.542	0.717	-0.276	0.782	7.24E-01	-1.809	1.257
	batch 2	-0.959	0.494	5.22E-02	-1.927	0.009	-1.027	0.525	5.05E-02	-2.057	0.002	-0.697	0.619	2.60E-01	-1.910	0.515
	batch 3	-1.403	0.500	4.99E-03	-2.383	-0.424	-1.360	0.508	7.39E-03	-2.354	-0.365	-1.238	0.639	5.27E-02	-2.489	0.014
	batch 4	0.258	0.523	6.23E-01	-0.768	1.284	0.275	0.520	5.96E-01	-0.743	1.294	0.232	0.632	7.13E-01	-1.007	1.471
	batch 5	-0.934	0.444	3.53E-02	-1.804	-0.064	-1.058	0.501	3.46E-02	-2.040	-0.076	-0.619	0.603	3.04E-01	-1.800	0.562
	batch 6	-2.488	0.504	7.97E-07	-3.476	-1.500	-2.571	0.611	2.54E-05	-3.767	-1.374	-2.227	0.664	8.01E-04	-3.529	-0.925
	batch 7	-2.134	0.793	7.15E-03	-3.689	-0.579	-2.135	0.849	1.19E-02	-3.799	-0.471	-2.588	1.027	1.17E-02	-4.600	-0.575
	intercept	-185.934	104.046	7.39E-02	-389.861	17.993	-142.067	123.760	2.51E-01	-384.633	100.498	-147.810	126.894	2.44E-01	-396.517	100.898
	<i>apoba</i>	-0.090	0.607	8.82E-01	-1.281	1.100	0.110	0.598	8.54E-01	-1.063	1.282	0.303	0.577	5.99E-01	-0.827	1.434
	<i>apobb.2</i>	-0.339	0.366	3.55E-01	-1.056	0.379	-0.520	0.407	2.02E-01	-1.318	0.279	-0.419	0.388	2.79E-01	-1.179	0.340
	<i>ldlr</i>	477.129	261.076	6.76E-02	-34.570	988.829	367.600	310.089	2.36E-01	-240.163	975.364	380.686	317.971	2.31E-01	-242.525	1003.897

continued Supplementary Table 21

		<i>ldlra</i>														
		Vascular lipid deposition														
		Model 1					Model 2					Model 3				
		130 vs. 90 larvae with 2 vs. 0 mutated alleles (n=220)					117 vs. 80 larvae with 2 vs. 0 mutated alleles (n=197)					117 vs. 80 larvae with 2 vs. 0 mutated alleles (n=197)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	0.111	0.251	6.58E-01	-0.381	0.603	0.104	0.266	6.97E-01	-0.418	0.626	0.073	0.275	7.91E-01	-0.466	0.612
	<i>apoea</i>	-0.189	0.195	3.32E-01	-0.571	0.193	-0.183	0.212	3.89E-01	-0.598	0.233	-0.172	0.209	4.10E-01	-0.582	0.238
	<i>apoeb</i>	0.308	0.164	6.09E-02	-0.014	0.629	0.394	0.186	3.46E-02	0.029	0.759	0.392	0.191	4.03E-02	0.017	0.768
	<i>apobb.1</i>	0.996	0.161	5.70E-10	0.681	1.310	0.937	0.198	2.13E-06	0.549	1.324	0.898	0.210	1.91E-05	0.486	1.310
	body length (in SD)	-	-	-	-	-	-0.071	0.167	6.70E-01	-0.398	0.256	-0.041	0.175	8.16E-01	-0.384	0.302
	dorsal body surface area (in SD)	-	-	-	-	-	0.197	0.141	1.63E-01	-0.080	0.474	0.213	0.145	1.43E-01	-0.072	0.498
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.015	0.107	8.85E-01	-0.225	0.194
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.045	0.144	7.53E-01	-0.327	0.237
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.140	0.178	4.33E-01	-0.209	0.489
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.042	0.121	7.30E-01	-0.279	0.195
	time of day (in hours since 9AM)	-0.062	0.094	5.07E-01	-0.246	0.122	-0.107	0.117	3.60E-01	-0.335	0.122	-0.086	0.118	4.66E-01	-0.318	0.146
	batch 2	-1.659	0.483	5.94E-04	-2.606	-0.712	-1.871	0.575	1.13E-03	-2.998	-0.745	-1.705	0.605	4.79E-03	-2.890	-0.520
	batch 3	-0.467	0.382	2.21E-01	-1.216	0.282	-0.569	0.399	1.54E-01	-1.351	0.213	-0.644	0.442	1.45E-01	-1.509	0.222
	batch 4	-0.714	0.416	8.63E-02	-1.529	0.102	-0.820	0.449	6.77E-02	-1.699	0.060	-0.818	0.467	8.02E-02	-1.734	0.098
	batch 5	0.372	0.321	2.46E-01	-0.257	1.001	0.208	0.367	5.72E-01	-0.512	0.928	-0.019	0.503	9.70E-01	-1.005	0.967
	batch 6	0.156	0.281	5.80E-01	-0.395	0.707	0.092	0.318	7.72E-01	-0.531	0.716	-0.232	0.535	6.64E-01	-1.281	0.816
	batch 7	-0.554	0.363	1.27E-01	-1.266	0.157	-0.730	0.377	5.27E-02	-1.468	0.008	-0.959	0.554	8.37E-02	-2.046	0.128
	intercept	280.829	147.422	5.68E-02	-8.113	569.772	320.998	153.007	3.59E-02	21.110	620.886	319.158	154.393	3.87E-02	16.554	621.762
	<i>apoba</i>	-0.166	0.630	7.92E-01	-1.401	1.069	-0.357	0.644	5.79E-01	-1.619	0.905	-0.211	0.668	7.52E-01	-1.520	1.098
	<i>apobb.2</i>	-0.046	0.404	9.10E-01	-0.837	0.746	-0.138	0.409	7.36E-01	-0.940	0.665	-0.060	0.419	8.86E-01	-0.881	0.761
	<i>ldlr</i>	-690.958	368.791	6.10E-02	-1400.000	31.859	-789.795	382.814	3.91E-02	-1500.000	-39.493	-785.887	386.208	4.19E-02	-1500.000	-28.933
		Vascular infiltration by macrophages														
		174 vs. 117 larvae with 2 vs. 0 mutated alleles (n=291)					158 vs. 102 larvae with 2 vs. 0 mutated alleles (n=260)					158 vs. 102 larvae with 2 vs. 0 mutated alleles (n=260)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	2 vs. 0 mutated alleles	0.077	0.136	5.70E-01	-0.189	0.343	0.029	0.152	8.50E-01	-0.269	0.327	0.000	0.152	1.00E+00	-0.297	0.297
	<i>apoea</i>	-0.126	0.087	1.48E-01	-0.297	0.045	-0.184	0.094	5.13E-02	-0.369	0.001	-0.197	0.094	3.66E-02	-0.382	-0.012
	<i>apoeb</i>	-0.181	0.090	4.53E-02	-0.357	-0.004	-0.170	0.099	8.64E-02	-0.365	0.024	-0.167	0.099	9.21E-02	-0.362	0.027
	<i>apobb.1</i>	-0.190	0.096	4.64E-02	-0.378	-0.003	-0.186	0.106	7.95E-02	-0.393	0.022	-0.207	0.107	5.29E-02	-0.417	0.003
	body length (in SD)	-	-	-	-	-	-0.004	0.083	9.63E-01	-0.167	0.159	-0.009	0.084	9.12E-01	-0.175	0.156
	dorsal body surface area (in SD)	-	-	-	-	-	-0.069	0.068	3.11E-01	-0.202	0.064	-0.071	0.069	3.00E-01	-0.206	0.063
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.086	0.061	1.57E-01	-0.033	0.204
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.073	0.068	2.86E-01	-0.061	0.207
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.060	0.085	4.82E-01	-0.106	0.226
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.074	0.064	2.47E-01	-0.199	0.051
	time of day (in hours since 9AM)	0.008	0.047	8.71E-01	-0.084	0.099	0.012	0.052	8.18E-01	-0.091	0.115	0.017	0.053	7.53E-01	-0.087	0.120
	intercept_random	0.946	1.148	4.10E-01	-1.304	3.196	1.163	1.212	3.37E-01	-1.212	3.538	1.342	1.209	2.67E-01	-1.027	3.711
	<i>apoba</i>	-0.123	0.336	7.14E-01	-0.782	0.535	-0.127	0.365	7.28E-01	-0.841	0.588	-0.186	0.363	6.08E-01	-0.897	0.525
	<i>apobb.2</i>	-0.173	0.218	4.27E-01	-0.601	0.254	-0.228	0.238	3.38E-01	-0.695	0.239	-0.278	0.239	2.45E-01	-0.747	0.191
	<i>ldlr</i>	-0.088	2.256	9.69E-01	-4.511	4.334	-0.312	2.335	8.94E-01	-4.889	4.266	-0.245	2.333	9.16E-01	-4.817	4.327
random factors	variance by batch	0.442	0.129	-	0.249	0.784	0.421	0.130	-	0.230	0.773	0.396	0.128	-	0.211	0.744
	residual	0.878	0.037	-	0.808	0.954	0.903	0.040	-	0.828	0.986	0.896	0.040	-	0.821	0.979

continued Supplementary Table 21

		Vascular co-localization of lipids with macrophages														
		128 vs. 89 larvae with 2 vs. 0 mutated alleles (n=217)					115 vs. 79 larvae with 2 vs. 0 mutated alleles (n=194)					115 vs. 79 larvae with 2 vs. 0 mutated alleles (n=194)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	2 vs. 0 mutated alleles	0.184	0.338	5.87E-01	-0.479	0.846	0.244	0.377	5.19E-01	-0.496	0.983	0.208	0.380	5.84E-01	-0.536	0.952
	<i>apoae</i>	-0.008	0.252	9.76E-01	-0.502	0.487	-0.147	0.270	5.87E-01	-0.676	0.382	-0.168	0.269	5.31E-01	-0.696	0.359
	<i>apoeb</i>	0.023	0.231	9.22E-01	-0.431	0.476	0.141	0.254	5.80E-01	-0.358	0.639	0.136	0.260	6.01E-01	-0.373	0.645
	<i>apobb.1</i>	1.145	0.230	6.01E-07	0.696	1.595	0.895	0.296	2.49E-03	0.315	1.474	0.799	0.363	2.75E-02	0.088	1.510
	body length (in SD)	-	-	-	-	-	-0.164	0.238	4.90E-01	-0.631	0.302	-0.215	0.281	4.45E-01	-0.766	0.336
	dorsal body surface area (in SD)	-	-	-	-	-	0.319	0.150	3.34E-02	0.025	0.613	0.308	0.149	3.88E-02	0.016	0.601
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.094	0.171	5.83E-01	-0.241	0.429
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.118	0.224	5.98E-01	-0.321	0.558
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.178	0.275	5.18E-01	-0.362	0.717
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.088	0.162	5.86E-01	-0.406	0.229
	time of day (in hours since 9AM)	0.091	0.112	4.16E-01	-0.128	0.310	0.088	0.132	5.04E-01	-0.170	0.347	0.117	0.141	4.07E-01	-0.160	0.394
	batch 2	-2.643	0.693	1.38E-04	-4.002	-1.284	-3.005	0.793	1.50E-04	-4.559	-1.452	-3.007	0.802	1.77E-04	-4.579	-1.435
	batch 3	-1.141	0.418	6.35E-03	-1.961	-0.322	-1.133	0.497	2.27E-02	-2.107	-0.158	-1.092	0.549	4.67E-02	-2.169	-0.016
	batch 4	-0.119	0.500	8.12E-01	-1.099	0.861	-0.367	0.567	5.18E-01	-1.477	0.744	-0.283	0.635	6.56E-01	-1.528	0.961
	batch 5	0.440	0.405	2.76E-01	-0.353	1.233	0.151	0.506	7.65E-01	-0.840	1.143	0.003	0.757	9.97E-01	-1.482	1.487
	batch 6	-0.124	0.392	7.52E-01	-0.891	0.644	-0.142	0.452	7.53E-01	-1.028	0.744	-0.318	0.969	7.42E-01	-2.217	1.580
	batch 7	-0.761	0.790	3.35E-01	-2.309	0.787	-1.260	0.764	9.92E-02	-2.758	0.238	-1.208	0.973	2.14E-01	-3.115	0.699
	intercept	563.870	199.665	4.74E-03	172.534	955.207	660.449	204.076	1.21E-03	260.468	1060.430	696.194	205.187	6.91E-04	294.035	1098.352
	<i>apoba</i>	-0.860	1.155	4.57E-01	-3.122	1.403	-1.185	1.185	3.18E-01	-3.508	1.138	-0.979	1.236	4.28E-01	-3.401	1.443
	<i>apobb.2</i>	-0.139	0.519	7.89E-01	-1.156	0.878	-0.355	0.519	4.94E-01	-1.372	0.663	-0.287	0.561	6.09E-01	-1.386	0.813
	<i>ldlr</i>	-1400.000	498.871	4.96E-03	-2400.000	-423.915	-1600.000	509.990	1.30E-03	-2600.000	-640.783	-1700.000	512.929	7.40E-04	-2700.000	-725.512
		Vascular infiltration by neutrophils														
		175 vs. 118 larvae with 2 vs. 0 mutated alleles (n=293)					159 vs. 103 larvae with 2 vs. 0 mutated alleles (n=262)					159 vs. 103 larvae with 2 vs. 0 mutated alleles (n=262)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	2 vs. 0 mutated alleles	-0.224	0.131	8.60E-02	-0.480	0.032	-0.222	0.141	1.14E-01	-0.498	0.053	-0.218	0.140	1.21E-01	-0.493	0.057
	<i>apoae</i>	-0.033	0.083	6.88E-01	-0.197	0.130	-0.071	0.087	4.18E-01	-0.242	0.100	-0.067	0.087	4.42E-01	-0.238	0.104
	<i>apoeb</i>	-0.053	0.087	5.38E-01	-0.223	0.116	-0.014	0.092	8.81E-01	-0.194	0.166	-0.030	0.092	7.45E-01	-0.210	0.150
	<i>apobb.1</i>	0.126	0.092	1.71E-01	-0.054	0.306	0.034	0.098	7.28E-01	-0.158	0.225	0.057	0.099	5.62E-01	-0.137	0.251
	body length (in SD)	-	-	-	-	-	-0.161	0.076	3.44E-02	-0.310	-0.012	-0.138	0.078	7.50E-02	-0.290	0.014
	dorsal body surface area (in SD)	-	-	-	-	-	0.007	0.062	9.06E-01	-0.114	0.129	0.030	0.063	6.39E-01	-0.094	0.153
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.033	0.055	5.50E-01	-0.141	0.075
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.053	0.063	4.00E-01	-0.070	0.177
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.096	0.077	2.10E-01	-0.247	0.054
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.065	0.059	2.67E-01	-0.050	0.181
	time of day (in hours since 9AM)	-0.014	0.044	7.59E-01	-0.100	0.073	-0.036	0.048	4.48E-01	-0.129	0.057	-0.043	0.048	3.69E-01	-0.137	0.051
	intercept_random	0.244	1.101	8.25E-01	-1.914	2.402	-0.103	1.119	9.27E-01	-2.297	2.091	-0.103	1.119	9.26E-01	-2.296	2.089
	<i>apoba</i>	0.488	0.323	1.30E-01	-0.144	1.120	0.557	0.337	9.81E-02	-0.103	1.218	0.584	0.336	8.20E-02	-0.074	1.243
	<i>apobb.2</i>	-0.169	0.210	4.21E-01	-0.581	0.243	-0.093	0.221	6.73E-01	-0.526	0.340	-0.094	0.222	6.72E-01	-0.529	0.341
	<i>ldlr</i>	-1.665	2.175	4.44E-01	-5.927	2.598	-1.151	2.169	5.96E-01	-5.403	3.100	-1.232	2.173	5.71E-01	-5.492	3.027
random factors	variance by batch	0.343	0.102	-	0.192	0.615	0.314	0.098	-	0.171	0.578	0.303	0.096	-	0.163	0.563
	residual	0.847	0.036	-	0.780	0.919	0.839	0.037	-	0.769	0.915	0.834	0.037	-	0.765	0.910

continued Supplementary Table 21

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

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

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

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

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

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

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

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

Supplementary Table 23 - The additive effect of mutated alleles in *apoEa*, *apoEb*, *apoBb.1* and *ldlr* on

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

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

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

continued Supplementary Table 23

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

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

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

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

		Vascular lipid deposition														
		Model 1 (n=306)					Model 2 (n=272)					Model 3 (n=272)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	<i>apoea</i>	-0.120	0.158	4.47E-01	-0.431	0.190	-0.169	0.173	3.28E-01	-0.509	0.170	-0.124	0.172	4.71E-01	-0.462	0.214
	<i>apoeb</i>	0.189	0.146	1.96E-01	-0.098	0.476	0.231	0.160	1.49E-01	-0.083	0.546	0.227	0.162	1.61E-01	-0.090	0.545
	<i>apoba</i>	0.003	0.508	9.95E-01	-0.993	0.999	-0.093	0.521	8.58E-01	-1.114	0.928	0.113	0.515	8.26E-01	-0.896	1.122
	<i>apobb.1</i>	0.972	0.144	1.52E-11	0.690	1.255	0.972	0.183	1.02E-07	0.614	1.329	0.947	0.196	1.30E-06	0.564	1.331
	<i>apobb.2</i>	-0.330	0.410	4.20E-01	-1.133	0.473	-0.341	0.412	4.09E-01	-1.148	0.467	-0.152	0.405	7.07E-01	-0.946	0.641
	<i>ldlra</i>	0.007	0.137	9.62E-01	-0.261	0.274	0.018	0.142	8.98E-01	-0.260	0.296	0.001	0.144	9.95E-01	-0.280	0.282
	body length (in SD)	-	-	-	-	-	-0.030	0.158	8.47E-01	-0.340	0.279	0.017	0.161	9.16E-01	-0.299	0.333
	dorsal body surface area (in SD)	-	-	-	-	-	0.176	0.126	1.61E-01	-0.070	0.423	0.196	0.128	1.25E-01	-0.055	0.447
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.060	0.092	5.18E-01	-0.241	0.121
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.118	0.126	3.49E-01	-0.364	0.128
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.193	0.170	2.56E-01	-0.140	0.527
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.049	0.104	6.40E-01	-0.254	0.156
	time of day (in hours since 9AM)	-0.107	0.080	1.81E-01	-0.263	0.050	-0.177	0.099	7.39E-02	-0.372	0.017	-0.148	0.104	1.56E-01	-0.352	0.056
	batch 1	2.477	0.423	4.67E-09	1.648	3.305	2.692	0.492	4.40E-08	1.728	3.656	2.861	0.549	1.90E-07	1.784	3.937
	batch 2	1.303	0.517	1.17E-02	0.290	2.315	1.415	0.531	7.69E-03	0.374	2.455	1.764	0.613	3.99E-03	0.563	2.965
	batch 3	1.771	0.500	3.96E-04	0.791	2.752	1.970	0.524	1.69E-04	0.943	2.996	1.986	0.545	2.69E-04	0.918	3.055
	batch 4	1.559	0.513	2.38E-03	0.553	2.565	1.753	0.528	8.92E-04	0.719	2.788	1.914	0.541	4.06E-04	0.853	2.975
	batch 5	2.972	0.518	9.40E-09	1.957	3.986	3.193	0.592	6.96E-08	2.032	4.353	2.949	0.656	6.99E-06	1.663	4.235
	batch 6	2.623	0.443	3.33E-09	1.754	3.492	2.794	0.553	4.44E-07	1.709	3.878	2.462	0.596	3.55E-05	1.295	3.629
	batch 7	1.974	0.515	1.25E-04	0.965	2.982	2.088	0.611	6.26E-04	0.892	3.285	1.827	0.631	3.76E-03	0.591	3.063
	intercept	-4.563	1.643	5.47E-03	-7.783	-1.344	-4.567	1.623	4.90E-03	-7.748	-1.385	-5.112	1.615	1.55E-03	-8.276	-1.947
	<i>ldlr</i>	17.601	3.301	9.70E-08	11.131	24.070	18.155	3.236	2.01E-08	11.813	24.496	17.829	3.207	2.72E-08	11.543	24.115
		Vascular infiltration by macrophages														
		Model 1 (n=368)					Model 2 (n=328)					Model 3 (n=328)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	<i>apoea</i>	-0.067	0.075	3.70E-01	-0.213	0.079	-0.111	0.081	1.67E-01	-0.269	0.047	-0.126	0.081	1.20E-01	-0.285	0.033
	<i>apoeb</i>	-0.145	0.082	7.49E-02	-0.305	0.015	-0.125	0.089	1.59E-01	-0.299	0.049	-0.129	0.089	1.49E-01	-0.303	0.046
	<i>apoba</i>	-0.144	0.275	6.02E-01	-0.683	0.396	-0.165	0.295	5.76E-01	-0.743	0.413	-0.178	0.294	5.44E-01	-0.754	0.398
	<i>apobb.1</i>	-0.222	0.080	5.54E-03	-0.379	-0.065	-0.208	0.087	1.72E-02	-0.379	-0.037	-0.222	0.089	1.23E-02	-0.396	-0.048
	<i>apobb.2</i>	-0.300	0.193	1.21E-01	-0.678	0.079	-0.373	0.209	7.41E-02	-0.782	0.036	-0.425	0.211	4.37E-02	-0.838	-0.012
	<i>ldlra</i>	0.034	0.063	5.91E-01	-0.090	0.158	0.013	0.070	8.50E-01	-0.124	0.150	-0.002	0.070	9.74E-01	-0.139	0.135
	body length (in SD)	-	-	-	-	-	0.045	0.072	5.36E-01	-0.097	0.186	0.046	0.073	5.25E-01	-0.097	0.190
	dorsal body surface area (in SD)	-	-	-	-	-	-0.044	0.061	4.67E-01	-0.163	0.075	-0.045	0.061	4.67E-01	-0.165	0.076
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.058	0.055	2.87E-01	-0.049	0.165
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.079	0.061	1.91E-01	-0.040	0.199
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.034	0.074	6.50E-01	-0.112	0.179
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.043	0.054	4.32E-01	-0.149	0.064
	time of day (in hours since 9AM)	0.031	0.041	4.41E-01	-0.048	0.111	0.030	0.046	5.16E-01	-0.060	0.120	0.032	0.046	4.87E-01	-0.058	0.122
	intercept	1.063	1.075	3.23E-01	-1.044	3.170	1.346	1.122	2.30E-01	-0.853	3.544	1.478	1.121	1.87E-01	-0.719	3.675
	<i>ldlr</i>	-0.104	2.197	9.62E-01	-4.411	4.202	-0.347	2.258	8.78E-01	-4.773	4.079	-0.329	2.258	8.84E-01	-4.755	4.097
random factors	variation by batch	0.514	0.140	-	0.301	0.877	0.509	0.143	-	0.293	0.884	0.479	0.138	-	0.272	0.844
	residual	0.858	0.032	-	0.798	0.923	0.878	0.035	-	0.812	0.949	0.874	0.035	-	0.809	0.944

continued Supplementary Table 24

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=301)					Model 2 (n=269)					Model 3 (n=269)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	<i>apoEa</i>	-0.299	0.234	2.02E-01	-0.758	0.160	-0.410	0.246	9.58E-02	-0.893	0.073	-0.351	0.244	1.51E-01	-0.830	0.128
	<i>apoEb</i>	-0.142	0.180	4.31E-01	-0.496	0.212	-0.123	0.198	5.34E-01	-0.512	0.265	-0.113	0.198	5.67E-01	-0.501	0.275
	<i>apoBa</i>	0.123	0.760	8.71E-01	-1.367	1.613	0.108	0.745	8.85E-01	-1.353	1.569	0.456	0.805	5.71E-01	-1.122	2.035
	<i>apobB.1</i>	1.049	0.204	2.71E-07	0.649	1.449	0.963	0.248	1.05E-04	0.476	1.449	0.881	0.273	1.27E-03	0.345	1.416
	<i>apobB.2</i>	-0.154	0.475	7.46E-01	-1.086	0.778	-0.233	0.499	6.41E-01	-1.211	0.746	0.002	0.496	9.96E-01	-0.970	0.975
	<i>ldlrA</i>	-0.096	0.193	6.22E-01	-0.475	0.284	-0.079	0.191	6.79E-01	-0.454	0.296	-0.102	0.191	5.95E-01	-0.476	0.273
	body length (in SD)	-	-	-	-	-	-0.093	0.245	7.05E-01	-0.574	0.388	-0.060	0.256	8.14E-01	-0.563	0.442
	dorsal body surface area (in SD)	-	-	-	-	-	0.096	0.152	5.30E-01	-0.203	0.394	0.068	0.154	6.58E-01	-0.233	0.369
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.086	0.151	5.69E-01	-0.382	0.210
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.009	0.170	9.58E-01	-0.325	0.343
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.316	0.235	1.78E-01	-0.144	0.776
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.116	0.137	3.95E-01	-0.384	0.151
	time of day (in hours since 9AM)	0.031	0.090	7.32E-01	-0.146	0.208	0.026	0.115	8.23E-01	-0.199	0.250	0.092	0.122	4.48E-01	-0.146	0.331
	batch 1	1.673	0.598	5.14E-03	0.501	2.845	1.703	0.705	1.57E-02	0.321	3.086	1.674	0.786	3.32E-02	0.134	3.214
	batch 2	1.054	0.863	2.22E-01	-0.637	2.745	0.884	0.862	3.05E-01	-0.805	2.574	0.758	0.928	4.14E-01	-1.060	2.577
	batch 3	0.934	0.618	1.30E-01	-0.277	2.145	0.910	0.646	1.59E-01	-0.356	2.176	0.785	0.664	2.37E-01	-0.517	2.086
	batch 4	1.449	0.652	2.62E-02	0.171	2.727	1.271	0.677	6.02E-02	-0.055	2.598	1.260	0.720	7.98E-02	-0.150	2.671
	batch 5	2.334	0.705	9.37E-04	0.951	3.717	2.246	0.827	6.64E-03	0.624	3.867	1.773	0.883	4.46E-02	0.043	3.504
	batch 6	1.190	0.648	6.62E-02	-0.080	2.460	1.252	0.865	1.48E-01	-0.443	2.947	0.663	0.932	4.77E-01	-1.164	2.489
	batch 7	0.737	0.971	4.48E-01	-1.166	2.640	0.545	1.090	6.17E-01	-1.592	2.682	0.141	1.122	9.00E-01	-2.057	2.340
	intercept	-5.120	1.899	7.02E-03	-8.842	-1.398	-4.899	1.863	8.54E-03	-8.550	-1.248	-5.421	1.971	5.95E-03	-9.284	-1.558
	<i>ldlrB</i>	14.867	3.709	6.11E-05	7.598	22.136	15.184	3.380	7.03E-06	8.560	21.808	14.218	3.406	2.98E-05	7.543	20.893
		Vascular infiltration by neutrophils														
		Model 1 (n=371)					Model 2 (n=330)					Model 3 (n=330)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	<i>apoEa</i>	-0.047	0.076	5.36E-01	-0.196	0.102	-0.076	0.081	3.52E-01	-0.234	0.083	-0.083	0.082	3.11E-01	-0.244	0.078
	<i>apoEb</i>	0.001	0.084	9.87E-01	-0.162	0.165	0.028	0.090	7.54E-01	-0.147	0.204	0.010	0.090	9.09E-01	-0.166	0.186
	<i>apoBa</i>	0.099	0.281	7.25E-01	-0.452	0.650	0.111	0.296	7.07E-01	-0.469	0.692	0.110	0.295	7.10E-01	-0.469	0.689
	<i>apobB.1</i>	0.103	0.082	2.07E-01	-0.057	0.264	0.042	0.088	6.32E-01	-0.130	0.214	0.061	0.089	4.96E-01	-0.114	0.235
	<i>apobB.2</i>	-0.056	0.198	7.79E-01	-0.443	0.332	0.021	0.210	9.19E-01	-0.391	0.434	0.006	0.212	9.76E-01	-0.410	0.423
	<i>ldlrA</i>	-0.074	0.064	2.51E-01	-0.200	0.052	-0.066	0.070	3.47E-01	-0.204	0.072	-0.069	0.070	3.29E-01	-0.207	0.069
	body length (in SD)	-	-	-	-	-	-0.111	0.071	1.19E-01	-0.250	0.028	-0.098	0.072	1.71E-01	-0.239	0.043
	dorsal body surface area (in SD)	-	-	-	-	-	0.050	0.060	4.00E-01	-0.067	0.168	0.067	0.060	2.67E-01	-0.051	0.186
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.006	0.054	9.15E-01	-0.099	0.111
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.083	0.060	1.72E-01	-0.036	0.201
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.054	0.072	4.50E-01	-0.195	0.086
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.062	0.054	2.55E-01	-0.045	0.169
	time of day (in hours since 9AM)	0.016	0.041	6.95E-01	-0.064	0.095	-0.020	0.045	6.63E-01	-0.107	0.068	-0.022	0.045	6.28E-01	-0.109	0.066
	intercept	0.777	1.093	4.77E-01	-1.364	2.919	0.584	1.122	6.03E-01	-1.615	2.782	0.617	1.122	5.82E-01	-1.582	2.815
	<i>ldlrB</i>	-2.049	2.254	3.63E-01	-6.467	2.369	-1.571	2.281	4.91E-01	-6.041	2.900	-1.525	2.285	5.05E-01	-6.005	2.954
random factors	variation by batch	0.352	0.100	-	0.201	0.615	0.323	0.097	-	0.179	0.583	0.296	0.092	-	0.161	0.543
	residual	0.882	0.033	-	0.820	0.948	0.888	0.035	-	0.822	0.959	0.885	0.035	-	0.819	0.956

continued Supplementary Table 24

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

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

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

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

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

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

Associations are shown for criteria that resulted in the exclusion of at least 10 larvae. Many false positives: >20% of true negative objects were falsely detected by the quantification pipeline.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

continued Supplementary Table 29

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

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

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

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

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

Human gene	ENSG	Zebrafish orthologue	ENSDARG	Chr	Target %identity	Query %identity	Main human protein	Top hit BLAST	%identity (protein)	Conserved genes in locus
<i>LPAR2</i>	ENSG000000064547	<i>lpar2a</i>	ENSDARG000000042338	3	49.16	49.86	ENSP00000384665	ENSDARP00000154087	54.95	<i>PBX4, ATP13A1, GMIP</i>
		<i>lpar2b</i>	ENSDARG000000042561	1	51.76	54.42		ENSDARP00000062425	60.00	none
<i>GMIP</i>	ENSG000000089639	<i>gmip</i>	ENSDARG000000077249	3	36.91	34.02	ENSP00000203556	ENSDARP00000131373	43.92	<i>ATP13A1, PBX4, LPAR2</i>
<i>GATAD2A</i>	ENSG00000167491	<i>gata2ab</i>	ENSDARG000000006192	22	53.16	53.00	ENSP00000351552	ENSDARP00000115930	53.8	<i>GMIP, CILP2, YIEFN3, TSSK6, TM6SF2, HAPLN4, NCAN, NR2C2AP, RFXANK, BORCS8, MEF2B, TMEM161A, SLC25A42, ARMC6, HOMER3</i>
<i>TM6SF2</i>	ENSG00000213996	<i>tm6sf2</i>	ENSDARG00000029057	22	43.32	42.97	ENSP00000374014	ENSDARP00000118571	45.86	<i>GMIP, HAPLN4, NCAN, NR2C2AP, RFXANK, BORCS8, MEF2B, TMEM161A, GATAD2A, TSSK6, YIEFN3,</i>
		<i>zgc:85843</i>	ENSDARG00000105208	2	43.86	39.79		ENSDARP00000130339	45.67	<i>HOMER3, GMIP, SCL25A42, ARMC6</i>

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

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

Human gene	Zebrafish orthologue	CRISPR gRNA target sequence	Genomic location (dabRer11/GRCz11)		Exon	Strand	GC (%)	Self-complementarity	Off-targets				Predicted efficiency	CRISPRscan score	Target activity (NA ^a , no ^b , low, moderate, high or very high ^c)	Forward primer	Reverse primer	product size
			Chr	Pos					0	1	2	3						
LPAR2	lpar2a	GATGCCAGCGAAGAGGTC	3	53,091,511	2 of 3	+	60	0	0	0	6	0.65	-	-	NA	ATTGTCAACCGAAAGTTCCACT	TGAGGCTCATGTTAATCAATGC	175
		GgCACTCATGACTTTGT	3	53,091,654	2 of 3	-	55	1	0	0	1	0.63	53		high	TTAACAGCTGTGAGGCTTTTGA	AGTGGAACTTTCGGTTGACAAT	186
	lpar2b	GGGGACTAAAGCGAAGG	1	59,206,929	2 of 7	-	65	1	0	0	0	0.76	76		very high	TTTCTTCTACAGCATCAGCCA	CCAGCAGGTAATAAATGGGGTA	174
GMIP	gmip	GGTCAAAACAAAGGAGACC	1	59,204,504	3 of 7	-	55	0	0	0	1	0.70	49		high, but only inframe variants	CTACACGCGCATCTTCATTAC	CGCTAAAATGGAAGCTGAATCT	187
		GgTCCACGCCATCCTCGC	3	52,763,869	5 of 20	-	70	1	0	0	0	0.68	-		moderate	GTTGATGCTGATGTGTTGTTT	TCCAGCCTAATACAATGTGTCG	243
	gmip	gGTGAAGATCTGCCGTGAA	3	52,753,647	4 of 20	+	50	0	0	0	1	0.62	-		moderate	TGCCACTGGGAATATTAAAGC	ACGAGTTCTCATCCCAATCTC	205
GATAD2A	gatad2ab	GAGAAGATGTCAGAAGAC	22	18,353,216	2 of 11	+	50	0	0	0	3	0.70	51		NA	GGTCAGACCACTTGTATGTCCA	TCTACAGCTCCAGGTTCTCCTC	207
		GGTGAAGGCCACCATCA	22	18,353,404	2 of 11	+	60	1	0	0	1	0.63	51		moderate/high	GAGGAGAACCTGGAGCTGTAGA	ATGATCGACCCTAGTTAGCAGC	194
	gatad2ab	GTTTATTTCTGAAATTGGC	22	17,790,559	3 of 11	+	40	0	0	0	7	0.60	10		no	ACAACCTCAGCATCCTATTTC	GGATCCTTAGGAGGATTGAAGC	239
TM6SF2	tm6sf2	GAGGTCAATGACACACGTG	22	17,792,919	4 of 11	-	50	1	0	0	0	0.63	62		NA	ACACCACAACACTGAAAGCAAT	ACGCTAACCGTTTCTGGTGA	186
		GgGTAGCGAGGTAGACCA	22	17,790,601	3 of 11	-	65	1	0	0	0	0.67	69		very high	ttctatccccacagcaagctaaa	aggatgaaatgcagaatgtgg	229
		GAGGATTGAAGCGCGTAGC	22	17,790,613	3 of 11	-	60	1	0	0	0	0.63	58		very high	ttctatccccacagcaagctaaa	aggatgaaatgcagaatgtgg	229
	zgc:85843	GATGCTGACAAACAGACGTG	2	56,897,287	3 of 10	-	50	0	0	0	4	0.63	54		moderate	GATGGGAGGAGAGGGGAG*	AAAGTCCATGAAGCCTTTGATG*	231
		gGGTCTTACCGTAGAACAG	2	56,896,546	2 of 10	-	45	1	0	0	0	0.57	46		NA	TGGATGTGTTGTGTAATGAT	GCCTAATTATCCTAACCTGCCCA	241
		gGGATGATGAGCTACTGGG	2	56,904,057	4 of 10	+	50	0	0	0	6	0.68	70		very high	CTTGTGCTGTTGTTGTAGGCAC	cacaggagggcgaatagtttag	244
		gGACACTGAGGTTTGCCA	2	56,896,504	2 of 10	-	55	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 capillary electrophoresis while estimating the length of the targeted region of an exon; No: 8 of 8 larvae test-injected with the gRNA only showed wildtype sequences; Low: 8 of 8 larvae showed wildtype sequence and fewer than 4 of 8 also contained indel sequence; Moderate: 8 of 8 larvae showed wildtype sequence and >4 of 8 also contained indel sequence; High: 8 of 8 larvae showed wildtype as well as indel sequence; Very high: Fewer than 4 of 8 larvae showed wildtype sequence and all larvae showed indel sequence. Target sequences highlighted in bold were selected and used to generate multiplexed mutant zebrafish.

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

Zebrafish orthologue	Sequence	Annotation	Number of alleles	mean $\pm$ SD number of reads
<i>lpar2a</i>	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACCACAAAGTCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	142M (wildtype reference)	1083	742 $\pm$ 537
	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACCACAAAGTCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	69M2D71M	8	512 $\pm$ 569
	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	69M8D65M	2	327 $\pm$ 65
<i>lpar2b</i>	TATAGCCGCTATGACCAACATATTGGCCAGGATGATGAAAACACAAATGGGGAGCCCCAGACCGACCACAAAGTCATGAGTGCGCCAGTTTGGACTAATAGGCTTGCCAGTCCTGTTGTAGAAGTAAGACACTGGATTG	66M5D71M	1	673
	GTGAAAGCGCGGTTTCATGAAGATGGCCGCCATCACCAGGATGTTGGTGAAGATGACAAAAACACTGACCAGCAGCCCCATACCCACCACCGCCTTCGCTTTAGTCCCCACGTATCGCTGATGTTCTTA	130M (wildtype reference)	1086	310 $\pm$ 174
	GTGAAAGCGCGGTTTCATGAAGATGGCCGCCATCACCAGGATGTTGGTGAAGATGACAAAAACACTGACCAGCAGCCCCATACCCACCACCTTCGCTTTAGTCCCCACGTATCGCTGATGTTCTTA	89M3D38M	6	278 $\pm$ 91
<i>gatad2ab</i>	TGGACTCAAGACCAAAGCGAACAGGCCAACAAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	150M (wildtype reference)	1062	1091 $\pm$ 567
	TGGACTCAAGACCAAAGCGAACAGGCCAACAAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	64M12D74M	27	584 $\pm$ 349
	TGGACTCAAGACCAAAGCGAACAGGCCAACAAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCACCATCAGGTGGTGACAGCAGCGGTGGTGACAGCAGCAGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	77M1S1M12I1M1S2M1S66M	2	424 $\pm$ 98
	TGAACCTAAGACCAAAGCGAACAGGCCAACAAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCAAAGGTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	2M1S66M6D75M	2	323 $\pm$ 48
	TGGACTCAAGACCAAAGCGAACAGGCCAACAAAGGTGGCGAACATCCTGCGGGCCGGAGAGGTGAAGGCCGTTGGAGGTGCAGACCAGCGACGAGCCCGTGGACATGAGCACATCCAAGAGGTTGGTCATGAAATAAGTCCA	70M8D72M	1	436

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

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

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

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

Supplementary Table 3: Sequencing results expressed in number of mutated alleles for 19 candidate genes

Zebrafish orthologue	Number of mutated alleles			Missing genotypes	Total	Non-missing	Mutant allele freq	P_{HWE_LR}
	0	1	2					
<i>lpar2a</i>	536	11	0	5	552	547	0.010	0.99
<i>lpar2b</i>	540	6	0	6	552	546	0.005	0.02
<i>gata2ab</i>	515	32	0	5	552	547	0.029	0.47

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

Supplementary Table 35 - The effect of a mutated allele in *lpar2a*, *lpar2b* and *gata2ab* on body size

		Body length (n=505)				
		Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	-0.016	0.243	9.47E-01	-0.493	0.460
	<i>lpar2b</i>	1.075	0.490	2.80E-02	0.116	2.035
	<i>gata2ab</i>	-0.161	0.224	4.71E-01	-0.600	0.277
	age (11dpf vs. 10dpf)	0.301	0.101	2.94E-03	0.103	0.500
	time of day (in hours since 9AM)	0.000	0.019	9.79E-01	-0.036	0.037
	intercept	0.114	0.290	6.95E-01	-0.454	0.682
random factors	<i>variance by batch</i>	0.779	0.025	-	0.732	0.829
	<i>residual</i>	0.673	0.200	-	0.376	1.204

		Dorsal body surface area (n=505)				
		Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	0.016	0.263	9.53E-01	-0.500	0.531
	<i>lpar2b</i>	-0.831	0.530	1.17E-01	-1.869	0.207
	<i>gata2ab</i>	0.825	0.242	6.52E-04	0.351	1.299
	age (11dpf vs. 10dpf)	0.214	0.109	4.99E-02	0.000	0.429
	time of day (in hours since 9AM)	0.007	0.020	7.45E-01	-0.033	0.046
	intercept	0.012	0.237	9.58E-01	-0.452	0.477
random factors	<i>variance by batch</i>	0.843	0.027	-	0.792	0.897
	<i>residual</i>	0.527	0.158	-	0.292	0.949

		Lateral body surface area (n=502)				
		Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	0.281	0.279	3.14E-01	-0.265	0.827
	<i>lpar2b</i>	0.070	0.561	9.01E-01	-1.030	1.169
	<i>gata2ab</i>	0.710	0.256	5.59E-03	0.208	1.212
	age (11dpf vs. 10dpf)	0.263	0.115	2.27E-02	0.037	0.489
	time of day (in hours since 9AM)	-0.040	0.021	6.13E-02	-0.082	0.002
	intercept	0.170	0.213	4.26E-01	-0.248	0.588
random factors	<i>variance by batch</i>	0.892	0.028	-	0.839	0.950
	<i>residual</i>	0.454	0.140	-	0.248	0.831

		Body volume (n=495)				
		Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	0.200	0.276	4.69E-01	-0.341	0.740
	<i>lpar2b</i>	0.152	0.606	8.03E-01	-1.037	1.340
	<i>gata2ab</i>	0.924	0.254	2.72E-04	0.426	1.421
	age (11dpf vs. 10dpf)	0.286	0.115	1.31E-02	0.060	0.512
	time of day (in hours since 9AM)	-0.005	0.021	8.04E-01	-0.047	0.037
	intercept	0.023	0.220	9.16E-01	-0.408	0.454
random factors	<i>variance by batch</i>	0.883	0.028	-	0.830	0.940
	<i>residual</i>	0.474	0.146	-	0.259	0.866

All outcomes were normalized for length using residuals, and inverse-normally transformed before the analysis. Associations were examined using hierarchical linear models. Effects shown are for the effect of carrying a mutated allele in *lpar2a*, *lpar2b* and *gata2ab*, weighted by the allele's predicted effect on protein function (i.e. additive model, mutually adjusted). All associations were adjusted for age (i.e. 11 vs. 10 days post fertilization (dpf), time of day and batch. Lci and uci are lower and upper boundaries of the 95% confidence interval.

Supplementary Table 36 - The effect of a mutated allele in *lpar2a*, *lpar2b* and *gata2ab* on whole-body lipids

		LDL cholesterol levels (n=513)				
		Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	-0.607	0.310	5.00E-02	-1.215	0.000
	<i>lpar2b</i>	-0.539	0.724	4.57E-01	-1.959	0.881
	<i>gata2ab</i>	-0.159	0.262	5.45E-01	-0.673	0.356
	age (11dpf vs. 10dpf)	-0.263	0.121	2.98E-02	-0.500	-0.026
	time of day (in hours since 9AM)	0.010	0.024	6.86E-01	-0.037	0.056
	intercept	0.108	0.160	5.01E-01	-0.206	0.422
random factors	<i>variance by batch</i>	0.946	0.030	-	0.889	1.006
	<i>residual</i>	0.284	0.101	-	0.141	0.572

		HDL cholesterol levels (n=513)				
		Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	-0.346	0.318	2.77E-01	-0.970	0.278
	<i>lpar2b</i>	-1.264	0.744	8.96E-02	-2.723	0.195
	<i>gata2ab</i>	-0.486	0.269	7.11E-02	-1.014	0.042
	age (11dpf vs. 10dpf)	-0.122	0.122	3.17E-01	-0.362	0.117
	time of day (in hours since 9AM)	0.020	0.024	4.03E-01	-0.027	0.067
	intercept	-0.059	0.144	6.81E-01	-0.341	0.223
random factors	<i>variance by batch</i>	0.972	0.031	-	0.914	1.034
	<i>residual</i>	0.218	0.084	-	0.103	0.462

		Triglyceride levels (n=513)				
		Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	-0.652	0.278	1.92E-02	-1.197	-0.106
	<i>lpar2b</i>	-0.001	0.650	9.99E-01	-1.276	1.274
	<i>gata2ab</i>	0.394	0.236	9.45E-02	-0.068	0.857
	age (11dpf vs. 10dpf)	0.007	0.111	9.52E-01	-0.210	0.224
	time of day (in hours since 9AM)	0.085	0.022	7.12E-05	0.043	0.128
	intercept	-0.328	0.232	1.57E-01	-0.783	0.126
random factors	<i>variance by batch</i>	0.849	0.027	-	0.798	0.903
	<i>residual</i>	0.512	0.156	-	0.282	0.929

		Total cholesterol levels (n=513)				
		Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	-0.739	0.306	1.58E-02	-1.340	-0.139
	<i>lpar2b</i>	0.369	0.716	6.07E-01	-1.035	1.773
	<i>gata2ab</i>	0.118	0.260	6.48E-01	-0.390	0.627
	age (11dpf vs. 10dpf)	-0.487	0.120	4.89E-05	-0.722	-0.252
	time of day (in hours since 9AM)	0.018	0.023	4.39E-01	-0.028	0.064
	intercept	0.034	0.166	8.37E-01	-0.291	0.360
random factors	<i>variance by batch</i>	0.935	0.029	-	0.879	0.994
	<i>residual</i>	0.306	0.105	-	0.156	0.598

continued Supplementary Table 36

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

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

Supplementary Table 37 - The effect of a mutated allele in *lpar2a*, *lpar2b* and *gata2ab* on vascular atherogenic traits

		Vascular lipid deposition														
		Model 1 (n=280)					Model 2 (n=258)					Model 3 (n=233)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	<i>lpar2a</i>	1.870	1.003	6.23E-02	-0.096	3.836	1.622	1.001	1.05E-01	-0.340	3.584	1.795	0.995	7.13E-02	-0.156	3.746
	<i>lpar2b</i>	0.994	1.191	4.04E-01	-1.340	3.328	0.861	1.139	4.50E-01	-1.371	3.093	0.912	1.351	5.00E-01	-1.736	3.560
	<i>gata2ab</i>	-0.006	0.334	9.87E-01	-0.659	0.648	-0.058	0.316	8.55E-01	-0.676	0.561	-0.277	0.313	3.75E-01	-0.890	0.336
	body length (in SD)	-	-	-	-	-	0.152	0.116	1.92E-01	-0.076	0.379	0.194	0.126	1.24E-01	-0.054	0.442
	dorsal body surface area (in SD)	-	-	-	-	-	0.153	0.131	2.44E-01	-0.104	0.410	0.202	0.139	1.46E-01	-0.070	0.474
	age (11dpf vs. 10dpf)	0.263	0.503	6.01E-01	-0.722	1.249	0.328	0.497	5.09E-01	-0.646	1.302	0.229	0.462	6.20E-01	-0.677	1.136
	time of day (in hours since 9AM)	-0.079	0.038	4.00E-02	-0.154	-0.004	-0.075	0.041	7.06E-02	-0.156	0.006	-0.045	0.052	3.93E-01	-0.147	0.058
	batch 1	3.239	0.635	3.42E-07	1.994	4.484	3.299	0.621	1.09E-07	2.082	4.517	3.364	0.580	6.46E-09	2.228	4.500
	batch 2	4.939	0.746	3.50E-11	3.477	6.400	4.771	0.782	1.03E-09	3.239	6.304	4.686	0.744	3.00E-10	3.228	6.144
	batch 3	4.581	0.725	2.66E-10	3.160	6.003	4.361	0.749	5.83E-09	2.893	5.829	4.486	0.683	4.99E-11	3.148	5.824
	batch 4	3.656	0.738	7.39E-07	2.209	5.103	3.855	0.726	1.11E-07	2.431	5.279	3.953	0.653	1.46E-09	2.672	5.234
	batch 5	3.903	0.732	9.59E-08	2.469	5.337	3.705	0.751	8.02E-07	2.233	5.176	3.635	0.689	1.31E-07	2.285	4.985
	intercept	0.802	0.720	2.65E-01	-0.609	2.212	0.766	0.702	2.75E-01	-0.610	2.143	0.597	0.639	3.50E-01	-0.656	1.850
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.189	0.096	4.94E-02	-0.377	0.000
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.084	0.075	2.65E-01	-0.063	0.231
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.070	0.105	5.09E-01	-0.137	0.276
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.016	0.108	8.82E-01	-0.227	0.195
		Vascular infiltration by macrophages														
		Model 1 (n=363)					Model 2 (n=331)					Model 3 (n=305)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	0.307	0.374	4.12E-01	-0.426	1.041	0.282	0.368	4.44E-01	-0.440	1.003	0.238	0.420	5.70E-01	-0.584	1.061
	<i>lpar2b</i>	0.528	0.520	3.09E-01	-0.490	1.546	0.597	0.512	2.43E-01	-0.406	1.601	0.649	0.636	3.08E-01	-0.598	1.896
	<i>gata2ab</i>	0.404	0.254	1.11E-01	-0.093	0.902	0.472	0.261	7.08E-02	-0.040	0.984	0.458	0.267	8.68E-02	-0.066	0.982
	body length (in SD)	-	-	-	-	-	0.020	0.059	7.38E-01	-0.096	0.136	0.029	0.062	6.36E-01	-0.092	0.150
	dorsal body surface area (in SD)	-	-	-	-	-	0.077	0.055	1.63E-01	-0.031	0.186	0.056	0.057	3.28E-01	-0.056	0.168
	age (11dpf vs. 10dpf)	-0.149	0.151	3.24E-01	-0.445	0.147	-0.146	0.148	3.25E-01	-0.436	0.144	-0.124	0.147	3.97E-01	-0.411	0.163
	time of day (in hours since 9AM)	0.042	0.023	6.53E-02	-0.003	0.086	0.043	0.023	6.58E-02	-0.003	0.088	0.010	0.027	7.21E-01	-0.043	0.063
	intercept	-0.101	0.172	5.56E-01	-0.438	0.235	-0.139	0.169	4.12E-01	-0.470	0.193	-0.029	0.157	8.55E-01	-0.336	0.278
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.001	0.048	9.81E-01	-0.095	0.092
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.012	0.046	7.88E-01	-0.103	0.078
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.021	0.052	6.84E-01	-0.123	0.080
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.094	0.057	9.68E-02	-0.017	0.205
random factors	<i>intercept</i>	0.822	0.031	-	0.764	0.885	0.805	0.032	-	0.746	0.870	0.812	0.033	-	0.749	0.879
	<i>variation by batch</i>	0.311	0.103	-	0.162	0.595	0.294	0.099	-	0.151	0.569	0.218	0.086	-	0.100	0.474

continued Supplementary Table 37

		Vascular co-localization of lipids with macrophages														
		Model 1 (n=263)					Model 2 (n=241)					Model 3 (n=217)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	<i>lpar2a</i>	3.463	1.204	4.02E-03	1.103	5.823	3.511	1.207	3.63E-03	1.145	5.877	3.408	1.167	3.50E-03	1.120	5.696
	<i>lpar2b</i>	0.851	1.083	4.32E-01	-1.270	2.973	0.747	1.018	4.63E-01	-1.248	2.743	0.284	1.368	8.35E-01	-2.396	2.965
	<i>gata2ab</i>	0.248	0.491	6.13E-01	-0.714	1.210	0.495	0.518	3.39E-01	-0.520	1.509	0.404	0.582	4.87E-01	-0.737	1.545
	body length (in SD)	-	-	-	-	-	0.101	0.190	5.94E-01	-0.271	0.473	0.223	0.197	2.57E-01	-0.162	0.609
	dorsal body surface area (in SD)	-	-	-	-	-	-0.063	0.179	7.25E-01	-0.414	0.288	0.059	0.200	7.70E-01	-0.334	0.452
	age (11dpf vs. 10dpf)	0.248	0.642	6.99E-01	-1.010	1.506	0.261	0.634	6.81E-01	-0.981	1.502	-0.196	0.678	7.73E-01	-1.524	1.133
	time of day (in hours since 9AM)	-0.129	0.054	1.65E-02	-0.235	-0.024	-0.150	0.060	1.17E-02	-0.267	-0.033	-0.124	0.087	1.55E-01	-0.294	0.047
	batch 1	4.433	0.824	7.38E-08	2.819	6.048	4.418	0.831	1.06E-07	2.789	6.048	4.521	0.825	4.31E-08	2.904	6.139
	batch 2	5.985	0.974	7.89E-10	4.076	7.893	5.875	0.994	3.37E-09	3.928	7.823	5.222	1.122	3.25E-06	3.023	7.422
	batch 3	5.635	0.928	1.28E-09	3.815	7.454	5.649	0.948	2.51E-09	3.792	7.507	5.258	1.068	8.46E-07	3.165	7.351
	batch 4	4.252	1.026	3.40E-05	2.241	6.262	4.352	1.082	5.73E-05	2.232	6.472	4.120	1.109	2.02E-04	1.947	6.293
	batch 5	4.694	0.939	5.84E-07	2.853	6.535	4.494	0.969	3.55E-06	2.594	6.394	4.039	1.033	9.29E-05	2.014	6.065
	intercept	-1.384	0.956	1.48E-01	-3.258	0.490	-1.303	0.965	1.77E-01	-3.195	0.589	-1.141	1.126	3.11E-01	-3.348	1.066
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.098	0.139	4.82E-01	-0.371	0.175
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.105	0.107	3.23E-01	-0.104	0.314
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.274	0.167	1.01E-01	-0.601	0.053
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.170	0.139	2.22E-01	-0.442	0.103
		Vascular infiltration by neutrophils														
		Model 1 (n=363)					Model 2 (n=334)					Model 3 (n=307)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
fixed factors	<i>lpar2a</i>	0.743	0.387	5.46E-02	-0.015	1.501	0.678	0.386	7.89E-02	-0.078	1.435	0.566	0.423	1.80E-01	-0.262	1.395
	<i>lpar2b</i>	0.130	0.537	8.09E-01	-0.922	1.182	0.035	0.538	9.48E-01	-1.019	1.090	0.045	0.642	9.44E-01	-1.213	1.303
	<i>gata2ab</i>	-0.315	0.267	2.38E-01	-0.837	0.208	-0.452	0.278	1.04E-01	-0.996	0.093	-0.353	0.274	1.97E-01	-0.889	0.183
	body length (in SD)	-	-	-	-	-	0.145	0.061	1.76E-02	0.025	0.264	0.197	0.063	1.72E-03	0.074	0.320
	dorsal body surface area (in SD)	-	-	-	-	-	0.053	0.059	3.68E-01	-0.062	0.168	0.016	0.060	7.88E-01	-0.101	0.134
	age (11dpf vs. 10dpf)	-0.120	0.152	4.30E-01	-0.418	0.178	-0.157	0.150	2.97E-01	-0.451	0.138	-0.159	0.150	2.89E-01	-0.453	0.135
	time of day (in hours since 9AM)	0.025	0.023	2.83E-01	-0.021	0.070	0.025	0.024	2.92E-01	-0.022	0.072	0.019	0.027	4.92E-01	-0.034	0.072
	intercept	0.033	0.195	8.65E-01	-0.348	0.415	0.023	0.179	9.00E-01	-0.329	0.374	0.038	0.186	8.36E-01	-0.325	0.402
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.029	0.048	5.54E-01	-0.066	0.123
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.135	0.046	3.67E-03	-0.226	-0.044
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.033	0.052	5.35E-01	-0.070	0.135
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.049	0.057	3.88E-01	-0.160	0.062
random factors	<i>intercept</i>	0.849	0.032	-	0.789	0.914	0.846	0.033	-	0.783	0.913	0.818	0.033	-	0.755	0.886
	<i>variation by batch</i>	0.379	0.121	-	0.202	0.710	0.320	0.111	-	0.162	0.630	0.329	0.114	-	0.167	0.649

continued Supplementary Table 37

		Vascular co-localization of lipids with neutrophils														
		Model 1 (n=260)					Model 2 (n=242)					Model 3 (n=217)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	<i>lpar2a</i>	2.718	1.321	3.96E-02	0.129	5.307	2.614	1.314	4.67E-02	0.038	5.189	3.548	1.292	6.03E-03	1.016	6.081
	<i>lpar2b</i>	-0.034	1.109	9.75E-01	-2.207	2.139	-0.260	1.167	8.24E-01	-2.547	2.027	-2.627	1.687	1.20E-01	-5.934	0.681
	<i>gata2ab</i>	-1.383	1.031	1.80E-01	-3.403	0.638	-1.613	1.014	1.12E-01	-3.601	0.375	-2.236	1.025	2.91E-02	-4.245	-0.227
	body length (in SD)	-	-	-	-	-	0.260	0.182	1.53E-01	-0.097	0.617	0.178	0.185	3.37E-01	-0.185	0.542
	dorsal body surface area (in SD)	-	-	-	-	-	0.077	0.182	6.72E-01	-0.280	0.434	0.000	0.187	9.98E-01	-0.367	0.368
	age (11dpf vs. 10dpf)	0.838	0.610	1.69E-01	-0.357	2.033	0.853	0.608	1.60E-01	-0.338	2.044	0.390	0.632	5.38E-01	-0.849	1.628
	time of day (in hours since 9AM)	-0.126	0.069	6.76E-02	-0.262	0.009	-0.134	0.068	4.74E-02	-0.267	-0.002	-0.219	0.078	5.16E-03	-0.372	-0.065
	batch 1	3.057	1.022	2.78E-03	1.054	5.060	3.136	0.981	1.39E-03	1.213	5.059	3.287	0.840	9.06E-05	1.641	4.933
	batch 2	4.126	1.202	5.98E-04	1.770	6.482	3.865	1.213	1.44E-03	1.488	6.243	4.036	1.086	2.01E-04	1.908	6.164
	batch 3	3.450	1.162	2.99E-03	1.173	5.727	3.265	1.137	4.09E-03	1.036	5.494	3.350	1.010	9.10E-04	1.371	5.330
	batch 4	3.911	1.181	9.27E-04	1.596	6.225	4.210	1.145	2.36E-04	1.966	6.453	4.467	0.971	4.21E-06	2.564	6.370
	batch 5	2.912	1.171	1.29E-02	0.617	5.208	3.073	1.122	6.16E-03	0.874	5.272	3.193	0.965	9.33E-04	1.303	5.084
	intercept	-1.356	1.157	2.41E-01	-3.624	0.911	-1.388	1.105	2.09E-01	-3.554	0.778	-1.071	0.999	2.83E-01	-3.029	0.886
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.312	0.165	5.79E-02	-0.635	0.010
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.088	0.132	5.05E-01	-0.171	0.347
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.134	0.145	3.53E-01	-0.149	0.417
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	0.135	0.171	4.30E-01	-0.200	0.471

		Vascular co-localization of macrophages with neutrophils														
		Model 1 (n=345)					Model 2 (n=317)					Model 3 (n=291)				
		Effect	SE	P	lci	uci	Effect	SE	P	lci	uci	Effect	SE	P	lci	uci
negative binomial terms	<i>lpar2a</i>	0.219	0.301	4.67E-01	-0.371	0.808	0.185	0.304	5.44E-01	-0.411	0.781	0.023	0.315	9.41E-01	-0.594	0.641
	<i>lpar2b</i>	-0.073	0.473	8.77E-01	-1.000	0.853	0.022	0.452	9.62E-01	-0.864	0.907	0.225	0.513	6.61E-01	-0.780	1.229
	<i>gata2ab</i>	-0.409	0.357	2.52E-01	-1.108	0.290	-0.514	0.417	2.18E-01	-1.330	0.303	-0.676	0.384	7.84E-02	-1.429	0.077
	body length (in SD)	-	-	-	-	-	-0.084	0.073	2.49E-01	-0.226	0.059	-0.027	0.077	7.29E-01	-0.177	0.124
	dorsal body surface area (in SD)	-	-	-	-	-	0.100	0.066	1.26E-01	-0.028	0.229	0.096	0.068	1.60E-01	-0.038	0.230
	age (11dpf vs. 10dpf)	-0.209	0.165	2.05E-01	-0.532	0.114	-0.186	0.165	2.59E-01	-0.510	0.137	-0.199	0.174	2.51E-01	-0.540	0.141
	time of day (in hours since 9AM)	0.019	0.028	4.97E-01	-0.036	0.075	0.021	0.029	4.65E-01	-0.035	0.077	0.030	0.032	3.60E-01	-0.034	0.093
	batch 1	0.026	0.176	8.83E-01	-0.318	0.370	0.084	0.178	6.39E-01	-0.266	0.433	0.038	0.205	8.54E-01	-0.365	0.440
	batch 2	0.491	0.255	5.39E-02	-0.008	0.991	0.528	0.311	8.94E-02	-0.081	1.137	0.512	0.349	1.43E-01	-0.173	1.196
	batch 3	1.144	0.236	1.26E-06	0.681	1.606	1.137	0.267	2.00E-05	0.615	1.660	1.223	0.314	9.78E-05	0.608	1.838
	batch 4	-0.467	0.259	7.09E-02	-0.975	0.040	-0.514	0.258	4.65E-02	-1.021	-0.008	-0.560	0.255	2.78E-02	-1.059	-0.061
	batch 5	-0.311	0.228	1.73E-01	-0.758	0.136	-0.313	0.238	1.88E-01	-0.779	0.153	-0.299	0.264	2.58E-01	-0.816	0.219
	intercept	4.047	0.208	1.95E-84	3.639	4.454	4.021	0.211	8.39E-81	3.607	4.435	3.978	0.253	7.40E-56	3.483	4.473
	HDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.035	0.054	5.11E-01	-0.141	0.070
	LDL cholesterol levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.105	0.060	7.96E-02	-0.222	0.012
	glucose levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.005	0.062	9.36E-01	-0.126	0.116
	triglyceride levels (in SD)	-	-	-	-	-	-	-	-	-	-	-0.024	0.072	7.35E-01	-0.166	0.117

Associations were examined using negative binomial regression for outcomes that showed a negative binomial distribution; and using hierarchical linear models on inverse-normally transformed outcomes for outcomes that were (borderline) normally distributed (i.e. vascular accumulation of macrophages and neutrophils). Effects shown are for the effect of carrying a mutated allele in *lpar2a*, *lpar2b* and *gata2ab*, weighted by the allele's predicted effect on protein function (i.e. additive model, mutually adjusted). Model 1: adjusted for time of day and batch; Model 2: additionally adjusted for body length and dorsal body surface area normalized for length; Model 3: additionally adjusted for whole-body LDL cholesterol, HDL cholesterol, triglyceride and glucose levels normalized for protein level. Lci and uci are lower and upper boundaries of the 95% confidence interval.

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

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

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

continued Supplementary Table 38

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

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

continued Supplementary Table 38

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

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

continued Supplementary Table 38

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

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

continued Supplementary Table 38

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

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

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