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Genome-wide association study indicates variants associated with insulin signaling and inflammation mediate lipoprotein responses to fenofibrate

Alexis C. Frazier-Wood[a,b,c], **Stella Aslibekyan**[a], **Ingrid B. Borecki**[d], **Paul N. Hopkins**[e], **Chao-Qiang Lai**[f], **Jose M. Ordovas**[f,h,i], **Robert J. Straka**[g], **Hemant K. Tiwari**[b], and **Donna K. Arnett**[a]

[a]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama

[b]Section on Statistical Genetics, Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama

[c]Department of Energetics, University of Alabama at Birmingham, Birmingham, Alabama

[d]Department of Genetics, Washington University School of Medicine, St Louis, Missouri

[e]Department of Internal Medicine, University of Utah, Salt Lake City, Utah

[f]Nutrition and Genomics Laboratory, Jean Mayer-US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts

[g]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, USA

[h]The Department of Epidemiology and Population Genetics, Centro Nacional Investigación Cardiovasculares (CNIC), Madrid, Spain

[i]IMDEA Food, Madrid, Spain

Abstract

Objective—A shift towards overall larger very low-density lipoprotein (VLDL), and smaller low-density lipoprotein and high-density lipoprotein (HDL) diameters occurs in insulin resistance (IR), which reflects shifts in the distribution of the subfraction concentrations. Fenofibrate, indicated for hypertriglyceridemia, simultaneously reduces IR and shifts in lipoprotein diameter. Individual responses to fenofibrate vary, and we conducted a genome-wide association study to identify genetic differences that could contribute to such differences.

Methods—Association analysis was conducted between single nucleotide polymorphisms (SNPs) on the Affymetrix 6.0 array and fasting particle diameter responses to a 12-week fenofibrate trial, in 817 related Caucasian participants of the Genetics of Lipid Lowering Drugs and Diet Network. Linear models were conducted, which adjusted for age, sex and study center as fixed effects, and pedigree as a random effect. The top three SNPs associated with each fraction were examined subsequently for associations with changes in subfraction concentrations.

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Correspondence to: Alexis C. Frazier-Wood, PhD, Department of Epidemiology, University of Alabama at Birmingham, RPHB 230P, Birmingham, Alabama 35294, USA Tel: + 1 205 975 9198; fax: + 1 205 934 8665; lekkiwood@gmail.com.

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Conflicts of interest
There are no conflicts of interest.

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Results—SNPs in *AHCYL2* and *CD36* genes reached, or closely approached, genome-wide levels of significance with VLDL and HDL diameter responses to fenofibrate, respectively (P=4 × 10^{-9} and 8 × 10^{-8}). SNPs in *AHCYL2* were associated with a decrease in the concentration of the large VLDL subfraction only (P = 0.002). SNPs associated with HDL diameter change were not associated with a single subfraction concentration change (P > 0.05) indicating small shifts across all subfractions.

Conclusion—We report novel associations between lipoprotein diameter responses to fenofibrate and the *AHCYL2* and *CD36* genes. Previous associations of these genes with IR emphasize the role of IR in mediating lipoprotein response to fenofibrate.

Keywords

AHCYL2; *CD36*; fenofibrate; inflammation; insulin resistance; insulin signaling; lipoprotein diameter; methylation; *PPARγ*; subclass

Introduction

Lipoproteins within the fractions of very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are heterogenous in their composition. Within a given fraction, the constituent lipoprotein particles can be subdivided into several subfractions, based on size. Recent research indicates that the subfraction distribution within each fraction may be more informative in understanding lipoprotein metabolism and its associations with disease risk than traditional lipid measures [1]. As lipoprotein diameters are modifiable through drug, exercise, and dietary interventions [2–4], they may thus present an important epidemiological tool to understand the pathways to insulin resistance (IR) and atherosclerosis, and a clinical target for preventing the development of these conditions.

Increases in the number of small LDL and HDL particles are associated with the development of IR and atherosclerosis [5–7]. These changes in concentration are reflected as shifts to a smaller average LDL and HDL diameter [8], and research has supported similar associations between IR and smaller average LDL/HDL diameters, as well as between these conditions and larger average VLDL diameter [8,9]. Fenofibrate is an efficacious therapeutic agent indicated in hypertriglyceridemia, which reduces plasma triglyceride (TG) levels by 35–50% while conferring additional benefits on HDL-C concentrations and markers of inflammation [10–15]. In addition, fenofibrate is associated with shift towards larger more buoyant LDL particles in a variety of populations, which is associated with a decreased progression of coronary artery disease [16–19]. The effect of fenofibrate on changes in diameter in the other lipoprotein fractions is less well studied, although increases in the average HDL diameter have been reported in mice [20].

There is, however, a significant interindividual variation in the response to fenofibrate across a range of lipid phenotypes [21]. Although several genes have been associated with interindividual variations in the lipid-lowering effects of fenofibrate [22–24], studies have yet to examine which genetic variants may mediate the effects of fenofibrate on the change in the distribution of the lipoprotein subfractions, reflected as a change in the average particle diameter. Genome-wide association studies (GWAS) are advantageous in understanding individual variations as the method is hypothesis free and designed to generate new hypothesis regarding underlying biological pathways. In this study, we performed association tests between single nucleotide polymorphisms (SNPs) and lipoprotein particle diameters, for each fraction of lipoprotein, before and after 3 weeks of daily treatment with fenofibrate in genetically homogeneous Caucasian participants of the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study. In addition, we

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examined the association of the top three loci associated with the diameter response to fenofibrate for each of VLDL, LDL, and HDL with changes in the concentration of the various subtractions, to further examine the biological change driving the SNP–phenotype associations found.

Methods

Study population

GOLDN is part of the PROgram for GENetic Interaction Network, a group of family intervention studies focusing on gene–environment interactions. The participants in the GOLDN study were mainly rerecruited from two NHLBI Family Heart Study field centers: Minneapolis (Minnesota) and Salt Lake City (Utah). All participants were of European ancestry. Eligibility criteria were: (a) at least 18 years of age; (b) fasting TGs less than 1500mg/dl; (c) willing to participate in the study and attend the scheduled clinic exams; (d) member of a family with at least two members in a sibship; (e) ASTand ALTresults within normal range; and (f) creatinine less than or equal to 2.0mg/dl. Exclusion criteria were: (a) history of liver, kidney, pancreas, gall bladder disease, or malabsorption; (b) current pregnancy; (c) insulin use; (d) use of lipid lowering drugs (including prescription, OTC and nutraceuticals; participants taking these agents were withdrawn from them 4 weeks before the study with physician's approval); (e) use of warfarin; (f) women of childbearing potential not using an acceptable form of contraception; (g) known hypersensitivity to fenofibrate; and (h) history of pancreatitis within 12 months before enrollment. Previous data on these conditions were available from the parent study, and individuals not fulfilling inclusion criteria were not invited to participate. A medication questionnaire was administered on the first visit, which confirmed eligibility for inclusion. A previous study demonstrated that Caucasians in Utah and Minnesota were homogeneous and pooling data across centers would not threaten the validity of this study [25]. From an initial sample size of 1 238 participants 817 agreed to undergo the fenofibrate trial and are included in the analysis.

The details of the GOLDN visits are published elsewhere [26] and depicted in Fig. 1. After granting informed consent, participants underwent a baseline screening visit. This visit included a fasting blood draw and pregnancy test, if applicable. The day before the first clinical exam, participants came to the clinic for a fasting blood draw. The fenofibrate intervention consisted of a 3-week treatment period, in which participants took fenofibrate (160mg) daily. Lipoproteins were measured twice on the last 2 days of the treatment period after a minimum 8-h fast.

Biochemical measurements

All plasma samples used for this analysis were collected after an 8-h fast. All samples were analyzed for lipoprotein profiles once all collections were carried out in each study. Measurements of VLDL, LDL, and HDL diameter were determined by nuclear magnetic resonance (NMR) spectroscopy. NMR detects the signal emitted by lipoprotein methyl-group protons when in the field of a magnet charged at 400MHz. The NMR signal is decoded to obtain estimates of particle numbers for each of several lipoprotein fractions. The weighted average particle diameter for each lipoprotein fraction (VLDL, LDL, and HDL) is calculated as the sum of the average lipoprotein particle diameters multiplied by the relative mass percentage, based on the amplitude of the methyl NMR signal (nm). NMR groups intermediate-density lipoproteins as a subclass of LDL [27,28]. Details of the range of diameters within each subfraction are given in Table 1.

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Genotyping

DNA extraction and purification in the GOLDN study has been described in detail by Irvin *et al.* [29]. A total of 9 06 600 SNPs were genotyped using the Affymetrix Genome-Wide Human 6.0 array (Affymetrix Inc., Santa Clara, California, USA) and the Birdseed calling algorithm (Broad Institute, Cambridge, Massachusetts, USA) [30]. The samples were processed in two different batches by two different technicians. After the imputation, we created a hybrid dataset that included 2 543 887 SNPs, of which 584 029 were initially genotyped in the GOLDN population. SNPs that were monomorphic (55 530) or had a call rate less than 96% (82 462) were removed from the analysis. In addition, SNPs were excluded from the analysis based on the number of families with Mendelian errors as follows: for minor allele frequency (MAF) of at least 20%, removed if errors were present in more than three families (1486 SNPs); for 20%>MAF 10%, removed if errors were present in more than two families (1338 SNPs); for 10%>MAF 5%, removed if errors were present in more than one family (1767 SNPs); for MAF less than 5%, removed if any errors were present (9592 SNPs). In families with remaining errors, the SNPs that showed a Mendelian error were considered as missing (31 595 SNPs). Furthermore, 16 participants with call rates less than 96% were also removed from any subsequent analyses. Subsequently, 748 SNPs failing the Hardy–Weinberg equilibrium test at *P*-value less than 10^{-6} were excluded from association analyses. Finally, after excluding markers with MAF less than 1%, Hardy–Weinberg equilibrium ($P<10^{-6}$), missing strand information, or discrepancies with the *mlinfo* file, we used the MACH software (version 1.0.16) to impute untyped SNPs using Human Genome Build 36, CEU population, as the reference [31,32]. Missing typed data were considered as missing in the final genotype dataset.

Statistical methods

Outcomes were defined using predicted values from linear regression models (slopes). Where necessary, data were monotonically transformed prefenofibrate and postfenofibrate to normalize the distribution (further details found in Supplementary Table 1, http://links.lww.com/FPC/A496). For raw or normalized data, fasting data from visit 4 (prefenofibrate; Fig. 1) was the outcome, and fasting data from visit 2 (postfenofibrate; Fig. 1) along with age, sex, number of fenofibrate tablets taken per day, and data collection center were predictors.

Tests of genome-wide association—For the initial GWAS, the associations of interest were assessed using linear mixed models, adjusted for sex, age, and center as fixed effects, and phenotypic dependence among family members as a function of their kinship (R software, *kinship* package [33]). The additive assumption was used to model genotypes. Population substructure was assessed using principal components generated using EIGENSOFT 3.0 software (http://www.genepath.med.harvard.edu/~reich/Software.htm). As the first 10 principal components did not show a significant association with any outcome ($P<0.001$), they were not included in the mixed models that tested for genotype–phenotype associations. For the initial GWAS, the Bonferroni correction was used to establish genome-wide significance, with the threshold of P less than 2×10^{-8}. Genome-wide Manhattan plots were generated to visualize the results (Supplementary Fig. 1, http://links.lww.com/FPC/A498). Quantile–quantile plots were constructed to evaluate deviations from the expected test statistic distribution (Supplementary Fig. 2, http://links.lww.com/FPC/A499). Plots of the top three hits for each phenotype were completed using LocusZoom [34] (Supplementary Fig. 3, http://links.lww.com/FPC/A500).

Post-hoc associations with subfractions—The same models were used in R, with the kinship package. Because of the strong *a priori* hypothesis a false discovery rate (FDR)

correction was used on all significant results ($P<0.05$) within each fraction and corrected Q values are additionally presented [35].

Gene set-based analysis—A pathway analysis on the results of the GWAS were analyzed using the program gene set-based analysis of polymorphisms (GeSBAP [36]). GeSBAP maps SNPs onto gene (±5 kb) using HapMap data. A gene set-based test is conducted [37] whereby the SNPs that fall within a category defined by Gene Ontology (GO [38]) are combined into a single *P*-value for that category, corrected for multiple testing using an FDR correction [35]. In addition, the percentage of genes within the GO category that are significantly associated with the phenotype in a gene-based test is given (Supplementary Fig. 4, http://links.lww.com/FPC/A502). To avoid overinterpreting the data, although all results are presented, we discuss only those where the *P*-value for the biological pathway was significant at an FDR corrected *P* less than 0.01 and 100% of the genes within the GO biological pathway were significantly associated with the phenotype at an FDR-corrected *P* less than 0.01.

Results

General characteristics of the GOLDN study population are summarized in Table 2. Half of the participants were female (50.8%). All participants were of European ancestry. In both the prefenofibrate and postfenofibrate conditions, there were no significant differences between men and women for demographic variables or fasting VLDL diameter; however, fasting LDL and HDL diameters varied significantly by sex (both $P<0.001$). Change in lipoprotein diameter from prefenofibrate to postfenofibrate was significantly different for LDL ($\Delta=0.12\pm0.80$ nm; $P<0.0001$) and HDL ($\Delta=0.12\pm0.23$nm; $P<0.0001$) diameter, but not VLDL diameter ($\Delta=0.49\pm9.17$nm; $P=0.12$).

Initial GWAS

The top three loci for SNP associations with the prefenofibrate to postfenofibrate treatment differences for each lipoprotein diameter are described in Table 3. Variants in the S-adenosylhomocysteine hydrolase-like 2 isoform (*AHCYL2*) gene, and the CD36 antigen (*CD36*) genes reached (or nearly approached) genome-wide levels of significance with VLDL and HDL diameter responses to fenofibrate, respectively ($P=3.95\times10^{-9}$ and 7.52×10^{-8}). The next top two loci reported for each of the fraction are within the cytokinesis 4 (*DOCK4*) gene with VLDL diameter response ($P=1.39\times10^{-7}$ and 1.45×10^{-7}), and within the peroxisome proliferator-activated receptor (*PPARγC1B*) gene for HDL diameter response to fenofibrate ($P=2.87\times10^{-7}$). Although there were no associations reaching genome-wide levels of significance with LDL diameter response to fenofibrate, the top three loci were in the jumonji domain containing 1C isoform a (*JMJD1C*) gene ($P=1.81\times10^{-6}$), the phosphodiesterase 10A (*PDE10*) gene ($P=2.01\times10^{-6}$) and near the neurexophilin-1 (*NXPH1*) gene ($P=1.45\times10^{-06}$). As the two SNPs in the DOCK4 gene were in high LD ($r>0.8$) conditional analysis was run whereby both SNPs were simultaneously modeled as predictors. In this model, neither SNP remained significant (rs10428959: $P=0.32$; rs6466397: $P=0.34$), suggesting that either could be causal or they could be tagging the causal variant. There were no other SNPs in LD>$r=0.03$ in our data, and therefore this question remains open.

Post-hoc associations with subfractions

The decrease in VLDL diameter, associated with variants in the *AHCYL2* and *DOCK4* genes reflected an association of these variants with a decrease in the concentration of large VLDL particles ($P=0.002$–0.02; $Q=0.01$–0.06); these variants were not associated with changes in the concentration of medium or small VLDL particles ($P>0.05$; Table 4). The top

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three loci associated with an increase in LDL diameter reflected similar associations between these loci and changes across all five subfractions of the LDL fraction (all $P<0.02$; $Q<0.02$; Table 5). Finally, the associations of HDL diameter response to fenofibrate with variants in the *CD36* and *PPARγC1B* genes seem to reflect small changes across all subfraction concentrations, and are not driven by significant changes in the concentration of any of the HDL subfractions (all $P>0.05$; Table 6).

There were no associations (FDR corrected $Q>0.10$) between any of our lipoprotein diameter responses to fenofibrate with the 95 SNPs recently reported as being associated with fasting HDL-cholesterol, LDL-cholesterol, total cholesterol, or TG levels in a recent meta-analysis of 46 GWAS of these traits ([39]; Supplementary Table 2, http://links.lww.com/FPC/A503).

Gene-based analysis

GeSBAP identified a number of biological pathways implicated in lipoprotein diameter response to fenofibrate (Supplementary Fig. 4, http://links.lww.com/FPC/A502). Gene sets where 100% of the GO biological pathways were significantly associated with one of the phenotypes showed that neuron adhesion pathways ($P=4.1 \times 10^{-2}$) were associated with the response of LDL diameter to fenofibrate, and pathways regulating insulin receptor signaling ($P=1.9 \times 10^{-2}$) and interleukin-6 (IL-6; $P=4.6 \times 10^{-3}$) were associated with HDL diameter responses to fenofibrate. There were no gene categories where 100% of the included genes were significantly associated with VLDL diameter response to fenofibrate.

Discussion

This is, to our knowledge, the first study to look at genetic associations with lipoprotein subfraction responses to fenofibrate. We used the GWAS data as a discovery mechanism to reveal associations between a variant in the *AHCYL2* gene with VLDL diameter response to fenofibrate, which reached genome-wide levels of significance. In addition, variants in the *CD36*, *PPARγC1B,* and *JMJD1C* genes were associated with HDL (*CD36*, *PPARγC1B*) and LDL (*JMJD1C*) diameter responses to fenofibrate, at levels approaching genome-wide significance, and may have biological relevance through previous associations with NMR and IR phenotypes.

We saw one locus that was associated with particle diameter responses to fenofibrate at genome-wide levels of significance. The response of VLDL diameter to fenofibrate was significantly associated with a single variant (rs11766298) in the *AHCYL2* gene on chromosome 7. The association of *AHCYL2* with VLDL diameter change results from decreases in the concentration of large VLDL particles also associated with *AHCYL2.* The protein encoded by *AHCYL2* acts as a homotetramer and may be involved in the conversion of S-adenosylhomocysteine to L-homocysteine and adenosine. High levels of S-adenosylhomocysteine inhibit methylation [40], are associated with IR [41] and may be a sensitive indicator of CVD [42].

An intronic variant of the *CD36* gene (rs11574703) was suggestively associated with a change in diameter for HDL particles, in that the association approached genome-wide levels of significance. The various subfractions of lipoprotein compete to bind in their oxidized state to the CD36 receptor, which thus may contribute to the regulation of lipid metabolism, and to the pathogenesis of atherosclerosis [43]. Null mutations in the *CD36* gene, in mice, are associated with an increase in cholesterol, mainly within the HDL fraction, and additionally an increase in triacylglycerol within the very small LDL fraction [44]. Our study is the first study to suggest that CD36 mutations may affect the response of the content of HDL lipoproteins to fenofibrate, in humans.

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In addition, two variants approached genome-wide levels of significance ($P<2 \times 10^{-6}$) and warrant further examination in their association with the fenofibrate responses of particle diameters, because of the previous associations with related phenotypes. We observed associations with markers in the *PPARγC1B* (rs9285640) gene with HDL response to fenofibrate and in the intronic region of *JMJ1C* (rs10995485) gene with LDL diameter response to fenofibrate. *PPARγC1B* has been associated previously with the homeostatic model assessment of IR, lipid-induced IR and type 2 diabetes [45–48]. As our analysis suggests that *PPARγC1B* mediates the effect of fenofibrate, the role of IR, similarly associated with *PPARγC1B*, in mediating the responses of lipoproteins to fenofibrate should be further examined. The preliminary evidence that polymorphisms associated IR may mediate lipoprotein diameter responses to fenofibrate is strengthened by our gene set-based analysis which showed that the insulin signaling receptor biological pathway, as well as the IL-6 inflammation pathway, were associated with HDL diameter response to fenofibrate. The nominal association of *JMJ1C* with VLDL diameter response to fenofibrate is interesting as *JMJC1* has been associated previously with total number of VLDL parameters (particle concentration) in a recent GWAS [49]. This GWAS report represented first lipoprotein-related association with this gene, and here we additionally report that *JMJ1C* may also associate with LDL subfraction response to fenofibrate, whereby the changes in concentration of all subfractions of LDL are mediated by individual differences in variants on the *JMJ1C* gene.

Our study should be seen in the light of a number of possible limitations. First, we limited our analysis to Caucasians of European descent at an *a priori* lower risk of cardiovascular disease, thus generalizations from our findings may be limited. Second, we assumed an additive genetic model, and thus may have missed loci that associate with fenofibrate response through other modes of inheritance, and any epistatic genetic effects. Third, information on covariates that may affect fenofibrate response, such as renal function, was limited in our cohort; therefore, we are unable to more finely understand the biology underlying our top hits. Fourth, while we consider our sample size excellent for a clinical trial, it is more modest for a current day GWAS; therefore lack of power may explain why only one hit reached genome-wide significance, and we hope the data here may inform more targeted follow-up studies. Finally, as this is the first study to examine genome-wide predictors of NMR responses to fenofibrate, replication remains a key issue. However, this is especially challenging in the context of both a clinical trial, and with the use of the newer phenotypes revealed through NMR data, which may be unavailable in existing datasets. We are unaware of any be other studies holding NMR, GWAS, and fenofibrate response data. Thus, as the results from the gene-based analysis support our GWAS findings and fit with previous biological findings from independent groups, they are exploratory and should be considered suggestive only, and a basis for future research paradigms.

Nonetheless, we provide here important evidence that genetic variants in the *AHCLY2*, *PPARγC1B*, and *JMJ1C* genes are suggestively associated with the responses of particle diameters to fenofibrate. In particular, a variant associated previously with the conversion of S-adenosylhomocysteine to L-homocysteine and adenosine, and variants involved in the insulin receptor signaling pathway and the IL-6 inflammation related pathways may be an important mediator of responses to fenofibrate. As lipoprotein diameters could present a therapeutic target in clinical interventions for IR and atherosclerosis, the associations of these genes, and the role these biological pathways may play in preventing incident disease under therapeutic interventions, warrants further research.

Supplementary Material

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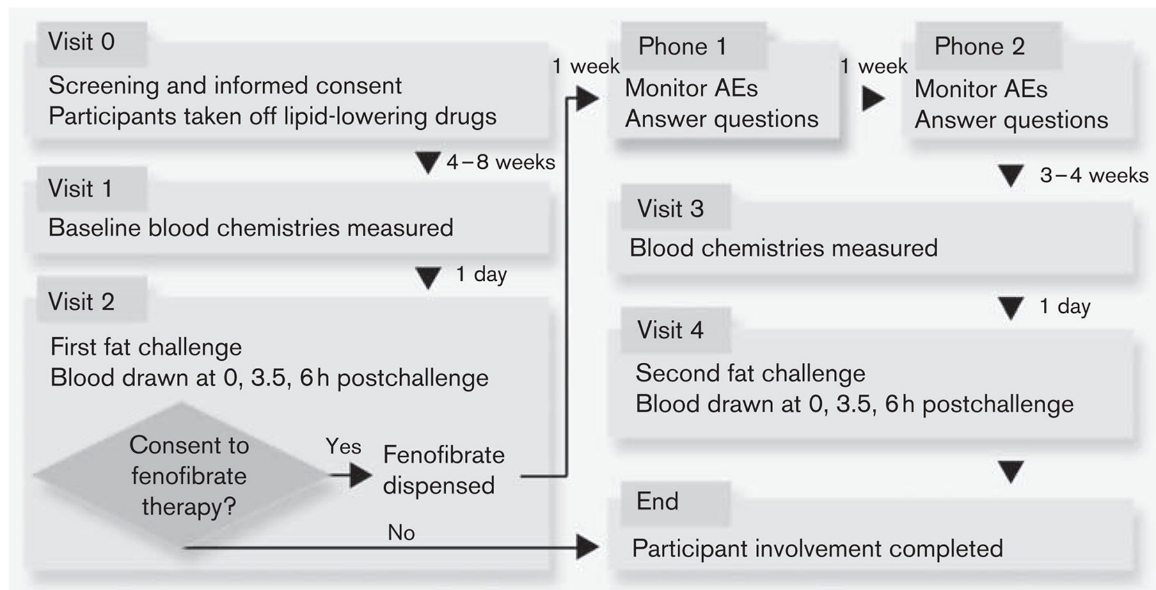

Fig. 1.
Details of the GOLDN study. Reproduced with permission from Frazier-Wood *et al.* [26]. AE, adverse events; GOLDN, Genetics of Lipid Lowering Drugs and Diet Network.

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Table 1

Diameter ranges of lipoprotein subclasses when measured by NMR

NMR lipoprotein parameter	Diameter range (nm)
VLDL	
Large VLDL/chylomicrons	> 60
Medium VLDL	35–60
Small VLDL	27–35
LDL	
Large LDL	21.2–23
Small LDL	18–21.2
Medium–small LDL	19.8–21.2
Very small LDL	18–19.8
HDL	
Large HDL	8.8–13
Medium HDL	8.2–8.8
Small HDL	7.3–8.2

Adapted from Jeyarajah *et al.* [28].

HDL, high-density lipoprotein; LDL, low-density lipoprotein; NMR, nuclear magnetic resonance; VLDL, very low-density lipoprotein.

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Table 2

Means (±SD) or percentages for demographic characteristics and lipoprotein diameters for the GOLDN study participants

	Men	Women		P^a
Age (years)	48.3 (15.6)	48.1 (15.9)		0.57
Field center (% from Minnesota)	49.6	49.6		0.89
Age (years)	48.3 (15.6)	48.1 (15.9)		0.57
	Men and women			
	Prefenofibrate	Postfenofibrate	Δ	
VLDL diameter (nm)	51.39 (7.83)	51.87 (8.73)	0.49 (9.17)	0.12
LDL diameter (nm)	20.80 (0.88)	20.89 (0.58)	0.12 (0.80)	< 0.0001
HDL diameter (nm)	8.85 (0.85)	8.73 (0.40)	0.12 (0.23)	< 0.0001

GOLDN, Genetics of Lipid Lowering Drugs and Diet Network; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

[a] *P*-values examining differences in diameters were derived from *t*-tests.

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Table 3

Top three genetic loci in SNP-phenotype associations with VLDL, LDL and HDL particle diameter changes in response to fenofibrate in GOLDN study participants

Marker	Chromosome	Position	HWE	Minor allele	β (SE)	Gene	*P*
VLDL diameter							
rs11766298	7	128792083	–	T	4.41 (0.74)	*AHCLY2*	3.95×10^{-9}
rs10428959	7	111465142	–	T	6.00 (1.13)	*DOCK4*	1.39×10^{-7}
rs6466397	7	111454471	–	G	−5.98 (1.13)	*DOCK4*	1.45×10^{-7}
LDL diameter							
rs10952132	7	9033345	> 0.99	T	0.31 (0.64)	*NXPH1*	1.45×10^{-6}
rs10995485	10	64696864	–	G	−1.18 (0.25)	*JMJ1C*	1.81×10^{-6}
rs519595	6	165855411	–	G	−0.60 (0.12)	*PDE10*	2.01×10^{-6}
HDL diameter							
rs11574703	7	80124844	–	T	−3.72 (0.68)	*CD36*	7.52×10^{-8}
rs5001812	2	166412540	–	T	−4.67 (0.89)	–	2.17×10^{-7}
rs9285640	5	149122260	–	G	−29.95 (5.78)	*PPARγC1B*	2.87×10^{-7}

GOLDN, Genetics of Lipid Lowering Drugs and Diet Network; HDL, high-density lipoprotein; HWE, Hardy–Weinberg equilibrium; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

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Table 4

The association of the top three genetic loci in SNP-phenotype associations VLDL particle diameters response to fenofibrate with VLDL subfraction concentration responses to fenofibrate

	Large VLDL			Medium VLDL			Small VLDL		
Marker	**β (SE)**	***P***	**Q**	**β (SE)**	***P***	**Q**	**β (SE)**	***P***	**Q**
rs11766298	1.86 (0.78)	0.02	0.06	−1.40 (0.77)	0.07	–	−1.12 (0.90)	0.21	–
rs10428959	3.58 (1.14)	0.002	0.01	−1.32 (1.16)	0.26	–	−1.02 (1.39)	0.46	–
rs6466397	−3.58 (1.14)	0.002	0.01	1.31 (1.16)	0.26	–	1.02 (1.39)	0.46	–

SNPs, single nucleotide polymorphisms; VLDL, very low-density lipoprotein.

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Table 5

The association of the top three genetic loci in SNP-phenotype associations LDL particle diameters response to fenofibrate with LDL subfraction concentration responses to fenofibrate

	Large LDL			Medium–small LDL			Small LDL			Very small LDL		
Marker	**β (SE)**	***P***	**Q**	**β (SE)**	***P***	**Q**	**β (SE)**	***P***	**Q**	**β (SE)**	***P***	**Q**
rs10952132	0.29 (0.65)	7.31×10^{-6}	3.00×10^{-5}	−0.16 (0.69)	0.02	0.02	−0.29 (0.07)	2.26×10^{-5}	4.8×10^{-5}	−0.29 (0.07)	4.13×10^{-5}	6.85×10^{-5}
rs10995485	−1.04 (0.25)	3.35×10^{-5}	6.00×10^{-5}	1.12 (0.25)	1.16×10^{-5}	3.00×10^{-5}	0.82 (0.26)	0.002	0.002	0.75 (0.27)	0.006	0.007
rs519595	−0.58 (0.13)	5.02×10^{-6}	3.00×10^{-5}	0.44 (0.14)	0.001	0.001	0.58 (0.13)	1.17×10^{-5}	3.00×10^{-5}	0.52 (0.14)	0.0002	3.00×10^{-4}

LDL, low-density lipoprotein; SNPs, single nucleotide polymorphisms.

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Table 6

The association of the top three genetic loci in SNP-phenotype associations HDL particle diameters response to fenofibrate with HDL subfraction concentration responses to fenofibrate

	Large HDL			Medium HDL			Small HDL		
Marker	**β (SE)**	***P***	**Q**	**β (SE)**	***P***	**Q**	**β (SE)**	***P***	**Q**
rs11574703	−0.62 (0.70)	0.38	–	1.85 (1.23)	0.13	–	0.24 (0.69)	0.73	–
rs5001812	−1.09 (0.91)	0.23	–	−0.66 (1.99	0.75	–	2.77 (0.90)	0.002	0.01
rs9285640	3.45 (5.88)	0.56	–	−13.27 (15.73)	0.39	–	7.33 (5.85)	0.21	–

HDL, high-density lipoprotein; SNPs, single nucleotide polymorphisms.