PPARA Polymorphism Influences the Cardiovascular Benefit of Fenofibrate in Type 2 Diabetes: Findings From ACCORD-Lipid

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The cardiovascular benefits of fibrates have been shown to be heterogeneous and to depend on the presence of atherogenic dyslipidemia. We investigated whether genetic variability in the *PPARA* gene, coding for the pharmacological target of fibrates (PPAR-α), could be used to improve the selection of patients with type 2 diabetes who may derive cardiovascular benefit from addition of this treatment to statins. We identified a common variant at the *PPARA* locus (rs6008845, C/T) displaying a study-wide significant influence on the effect of fenofibrate on major cardiovascular events (MACE) among 3,065 self-reported white subjects treated with simvastatin and randomized to fenofibrate or placebo in the ACCORD-Lipid trial. T/T homozygotes (36% of participants) experienced a 51% MACE reduction in response to fenofibrate (hazard ratio 0.49; 95% CI 0.34–0.72), whereas no benefit was observed for other genotypes ($P_{interaction} = 3.7 \times 10^{-4}$). The rs6008845-by-fenofibrate interaction on MACE was replicated in African Americans from ACCORD ($N = 585$, $P = 0.02$) and in external cohorts (ACCORD-BP, ORIGIN, and TRIUMPH, total $N = 3059$, $P = 0.005$). Remarkably, rs6008845 T/T homozygotes experienced a cardiovascular benefit from fibrate even in the absence of atherogenic dyslipidemia. Among these individuals, but not among carriers of other genotypes, fenofibrate treatment was associated with lower circulating levels of CCL11—a proinflammatory and atherogenic chemokine also known as eotaxin (P for rs6008845-by-fenofibrate interaction = 0.003). The GTEx data set revealed regulatory functions of rs6008845 on *PPARA* expression in many tissues. In summary, we have found a common *PPARA* regulatory variant that influences the cardiovascular effects of fenofibrate and that could be used to identify patients with type 2 diabetes who would derive benefit from fenofibrate treatment, in addition to those with atherogenic dyslipidemia.

Cardiovascular events due to accelerated atherogenesis are major determinants of morbidity and mortality in patients with type 2 diabetes (1). The causes of increased atherogenesis in type 2 diabetes are complex and include, in addition to exposure to hyperglycemia, the presence

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of other cardiovascular risk factors that frequently accompany type 2 diabetes such as dyslipidemia and hypertension (2). The current recommendations to prevent major adverse cardiovascular events (MACE) in patients with type 2 diabetes include lifestyle modifications, improvement of glycemic control, treatment of hypertension, and use of cholesterol-lowering therapies (1).

Treatment with fibrates as an additional intervention to further improve cardiovascular outcomes in type 2 diabetes has been studied several times in the last decades (3–7). Fibrates are agonists of peroxisome proliferator–activated receptor-α (PPAR-α)—a transcription factor that functions as a master regulator of lipid homeostasis, cardiac energy metabolism, vascular inflammation, and cell differentiation. PPAR-α activation reduces serum triglycerides, raises plasma HDL cholesterol (HDL-c) levels, and reduces systemic inflammation (8,9). However, despite such beneficial effects, clinical trials of fibrates have shown inconsistent benefit of this treatment in preventing MACE (4,5,10), including among subjects with type 2 diabetes (4,5). At the same time, analyses of these trials have consistently shown that fibrates might have a beneficial effect among subjects with atherogenic dyslipidemia (defined by low HDL-c and high triglycerides levels) (11–14). For these reasons, fibrates are not currently recommended as a standard treatment to prevent MACE in type 2 diabetes but may be considered as second- or third-line treatments in patients with atherogenic dyslipidemia (1,15,16).

The lipid and inflammatory responses to fibrates vary in the population, in part due to genetic factors (17,18). Thus, one can hypothesize that the inconclusive results from clinical trials may be partly due to an underlying genetic heterogeneity in the cardiovascular response to fibrates. A corollary of this hypothesis is that it may be possible to develop genetic tests that can help distinguish individuals who would benefit from fibrates from those who would not. We have tested these postulates in the Action to Control Cardiovascular Risk in Diabetes lipid study (ACCORD-Lipid) (4), the largest randomized clinical trial to date on fibrate treatment as add-on to statin therapy in type 2 diabetes. We specifically directed our attention to *PPARA*—the gene that codes for the molecule (PPAR-α) through which fibrates are believed to exert their pharmacological effects.

RESEARCH DESIGN AND METHODS

Study Populations

Accord-Lipid Trial

ACCORD-Lipid was part of ACCORD, a clinical trial that tested the effectiveness of intensive versus standard glycemic control in preventing MACE (a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) among 10,251 subjects with type 2 diabetes at high risk of atherosclerotic cardiovascular disease (19). The trial had a double, 2 × 2 factorial design, with 4,733 patients additionally randomized to a blood pressure trial (ACCORD-BP) (20) and 5,518 to a lipid trial (ACCORD-Lipid) (4). Subjects were specifically enrolled in ACCORD-Lipid if they had HDL-c <55 mg/dL for women and blacks or <50 mg/dL for all other groups, LDL cholesterol level between 60 and 180 mg/dL, and fasting triglycerides <750 mg/dL without triglyceride-lowering treatment or <400 mg/dL if they were receiving triglyceride-lowering treatment. ACCORD-Lipid investigated whether fenofibrate, given in addition to statins, was more effective than statins alone in preventing MACE. This trial showed a modest, nonsignificant trend toward a benefit of fenofibrate (hazard ratio [HR] 0.92; 95% CI 0.79–1.08) (4). Genetic data were available for 4,414 ACCORD-Lipid participants (80% of the total), who had provided consent for genetic studies. For avoidance of race/ethnicity confounding, genetic analyses were initially restricted to self-reported non-Hispanic whites (n = 3,065) and then extended to self-reported African Americans (n = 585). Other racial/ethnic groups were too sparse to be considered individually.

ACCORD-BP, ORIGIN, and TRIUMPH Cohorts

ACCORD-BP (blood pressure) (20) investigated whether reducing systolic blood pressure to <120 mmHg was more effective than standard treatment (target <140 mmHg) in preventing MACE among 4,733 subjects with type 2 diabetes at high cardiovascular risk. After a median follow-up time of 4.7 years, the study reported lack of significant cardiovascular effect of this treatment.

The Outcome Reduction With Initial Glargine Intervention (ORIGIN Trial) (21) investigated, in a 2 × 2 factorial design, the effect of titrated basal insulin versus standard care and of n-3 fatty acid supplements versus placebo on

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MACE occurrence among 12,537 subjects with impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes and high cardiovascular risk. After a median follow-up time of 6.2 years, the study reported lack of significant cardiovascular effect of these two treatments.

The Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health status (TRIUMPH) study is a large, prospective, observational cohort study of 4,340 consecutive patients, (31% with type 2 diabetes), designed to examine the complex interactions between genetic and environmental determinants of post–myocardial infarction outcomes (22).

The current study included 1,407, 1,244, and 408 self-reported white participants from ACCORD-BP, ORIGIN, and TRIUMPH, respectively, who had type 2 diabetes or dysglycemia and were on concomitant statin + fibrate or statin alone therapies before the occurrence of cardiovascular events or before being censored and for whom genetic data were available.

ACCORD-MIND Study

The ACCORD Memory in Diabetes (ACCORD-MIND) study included 2,977 participants from the overall ACCORD trial, and 562 of these participants, with available serum samples, participated in an ancillary biomarker study (23). This study included 133 self-reported white subjects from this ancillary study (24), who were also included in the ACCORD-Lipid trial and for whom genetic data were available.

Outcomes

In this post hoc study, the primary outcome was a three-point MACE (a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death), defined according to the prespecified primary end point definitions in ACCORD (19) and ORIGIN (21) clinical trials. In TRIUMPH, the primary outcome was mortality after acute myocardial infarction.

Data Analysis

Effect of PPARA Single Nucleotide Polymorphism × Fenofibrate Treatment Interaction on MACE Risk

For identification of common variants in or around the candidate gene *PPARA* that modulated the effect of fenofibrate on the ACCORD primary outcome (MACE), genotype data for 360 genotyped or imputed single nucleotide polymorphisms (SNPs) having minor allele frequencies (MAFs) >5% and spanning the entire *PPARA* gene plus 40 Kb on either side (GRCh37/hg19 base pair coordinates of chromosome 22: 46,506,499–46,679,653) were extracted from the ACCORD genetic data set. Detailed DNA extraction, genotyping, quality control methods, and imputation can be found in the previously published supplemental material of the article in which this data set was first reported (25). Separate analyses were conducted in the two genotyping subsets that compose the ACCORD genetic data set (ANYSET, including patients who gave consent to genetic studies by any investigator, and ACCSET, including patients who gave consent only to genetic studies by ACCORD investigators), and results were meta-analyzed as previously described (25). When the two subsets were analyzed together, an indicator variable for the genotyping platform was used as covariate. The SNPs were analyzed according to an additive genetic model. The effect of interaction between fenofibrate treatment and each of the 360 SNPs on MACE risk was assessed by means of Cox proportional hazards models, each including the SNP minor allele dosage, fenofibrate assignment (yes/no), and a SNP × fenofibrate interaction term along with assignment to intensive or standard glycemic control group, clinical center network, presence of cardiovascular disease (CVD) at baseline, age, and sex as covariates. The number of independent tests that were conducted by analyzing these 360 SNPs was estimated by means of the simpleM method (26), which considers the correlation, or linkage disequilibrium (LD), among variants. Based on the results of this analysis (81 independent comparisons), the Bonferroni-adjusted threshold for significance was set to $P = 6.2 \times 10^{-4}$ ($\alpha = 0.05/81$) (Supplementary Fig. 1).

All self-reported white ($N = 3{,}065$) and African American ($N = 585$) participants randomized to fenofibrate or placebo for whom genetic data were available were included in the study. All 360 SNPs were analyzed for their interaction with fenofibrate in whites. SNPs found to have a significant effect in whites were then analyzed in African Americans. A summary estimate of the interaction effect across the two races was obtained by means of a fixed effects meta-analysis using an inverse variance approach.

The number of patients who need to be treated to prevent one additional MACE event over 5 years (number needed to treat) with fenofibrate + statin compared with statin alone treatments was calculated as previously described (27).

Replication of the rs6008845 × Fenofibrate Treatment Interaction

The SNP showing a significant interaction with fenofibrate in ACCORD-Lipid (rs6008845) was further investigated in the ACCORD-BP trial (20) by contrasting 87 participants who were on concomitant fibrate + statin therapy with 1,320 participants who were only on concomitant statin therapy, in ORIGIN (21) by contrasting 82 participants who were on concomitant fibrate + statin therapy with 1,162 participants who were only on concomitant statin therapy, and in TRIUMPH (22) by contrasting 21 participants who were on concomitant fibrate + statin therapy with 387 participants who were only on concomitant statin therapy. The SNP × fenofibrate interaction on the primary outcome was evaluated by Cox proportional hazards models including treatment arms, age, sex, and history of CVD as covariates (in TRIUMPH, since all subjects were in secondary prevention by study design, history of CVD was not included in the analyses). Results were meta-analyzed with a fixed effects inverse variance approach.

Effect of rs6008845 × Fenofibrate Treatment Interaction on Other Clinical Features

The association between rs6008845 and baseline characteristics was evaluated by means of ANCOVA or logistic regression models. Presence of atherogenic dyslipidemia was defined by the same previously used cutoff (4) of having both low HDL-c (≤34 mg/dL, i.e., the first tertile of HDL-c distribution) and high triglyceride levels (≥204 mg/dL, i.e., in the third tertile of triglyceride distribution). The influence of rs6008845 on the effect of fenofibrate (SNP × fenofibrate interaction) on change from baseline to the average on-trial value of plasma lipids was tested by ANCOVA with the baseline biomarker level included as a covariate along with the predictors included in the Cox regression models.

Effect of rs6008845 × Fenofibrate Treatment Interaction on Chemokines Levels

Data on serum levels of seven chemokines (CCL2, CCL3, CCL4, CCL11, CXCL8, CXC10, and CXC3CR1) were available from the ACCORD-MIND ancillary study, in which biomarkers were measured in a subset of ACCORD participants by means of multiplexing kits from Millipore and Luminex using a single lot of reagent and quality control material. Baseline and 12-month levels were log transformed, and the influence of rs6008845 on the effect of fenofibrate (SNP × fenofibrate interaction) on 12-month levels was tested by ANCOVA with the baseline chemokine level included as a covariate along with the same predictors included in the Cox regression models.

Expression Studies and Functional Annotation

The association between rs6008845 and *PPARA* expression was tested using RNA sequencing data from 44 tissues collected from up to 449 donors as part of the Genotype-Tissue Expression (GTEx) project (release version V6p) (28). In single-tissue expression quantitative trait locus analysis, the SNP effect size (β) was estimated as the slope of the linear regression of normalized expression data versus the three genotype categories coded as 0, 1, and 2 (www.gtexportal.org/home/documentationPage). Trans–expression quantitative trait locus analyses of the influence of rs6008845 on PPAR-α target genes were performed using the same approach. Results across tissues were summarized, as in the GTEx portal, by means of Han and Eskin's random effects model (RE2) with METASOFT (29). Additional functional annotations were derived using two Web-based tools integrating data from ENCODE, RegulomeDB (https://regulomedb.org/), and the Roadmap Epigenomics project (HaploReg) (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php). Additional information on the association between the top significant SNPs and other phenotypes of interest was obtained by browsing the GWAS catalog (https://www.ebi.ac.uk/gwas/).

Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). Graphs were edited with GraphPad Prism (version 7.02).

Institutional Review Board Approval

The institutional review board or ethics committee at each ACCORD center approved the ACCORD study protocol prior to data collection.

Data and Resource Availability

The ACCORD database is available upon request from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository (https://biolincc.nhlbi.nih.gov/studies/accord/). The ACCORD genetic data are deposited in dbGAP, accession: phs0001411.

RESULTS

PPARA Variant Modulating the Fenofibrate Effect on MACE in Whites

Among 3,065 self-reported white subjects from ACCORD-Lipid (Supplementary Table 1), fenofibrate treatment was associated with a nonsignificant reduction of MACE risk during a median follow-up of 4.7 years (HR 0.82; 95% CI 0.66–1.02). In this population, a total of 360 SNPs in the *PPARA* gene region were tested for a modulatory influence on the effect of fenofibrate treatment on MACE risk. Results are shown in Fig. 1 as a function of the SNP positions along the genome. Evidence of interaction with fenofibrate meeting study-wide significance ($P < 6.2 \times 10^{-4}$ based on a Bonferroni adjustment for the 81 independent comparisons that were made by analyzing those 360 SNPs) was observed for SNP rs6008845: a T to C substitution placed ~25 Kb upstream of the *PPARA* transcription start site ($P = 3.7 \times 10^{-4}$) (Table 1). The interaction was such that the T allele conferred protection among subjects treated with statin + fenofibrate (HR 0.75; 95% CI 0.60–0.95), whereas it was associated with a higher risk of MACE among those randomized to statin alone (HR 1.27; 95% CI 1.01–1.60) (Fig. 2).

Transethnic and External Validation of the Gene × Fenofibrate Interaction

The interaction between rs6008845 and fenofibrate treatment was internally validated among 585 self-reported African Americans enrolled in ACCORD-Lipid. Despite the lower frequency of the T allele in this racial group (0.21 vs. 0.60 in whites [Supplementary Fig. 2]), the interaction was in the same direction as in whites, with the T allele being associated with MACE prevention in subjects randomized to fenofibrate + statin (HR 0.31; 95% CI 0.11–0.90) but not among those randomized to statin + placebo (odds ratio 1.37; 95% CI 0.74–2.53, P for rs6008845 × fenofibrate interaction = 0.02 [Fig. 2]). Meta-analyses of results from self-reported whites and African Americans led to a P value for rs6008845 × fenofibrate interaction of 6×10^{-5} (Supplementary Table 2).

A similar synergism between rs6008845 T allele and fenofibrate was observed in an observational setting by analyzing data on concomitant medications among self-reported whites from ACCORD-BP and ORIGIN and from the TRIUMPH cohort (Fig. 2). In a combined analysis of the three cohorts (see baseline clinical characteristics in

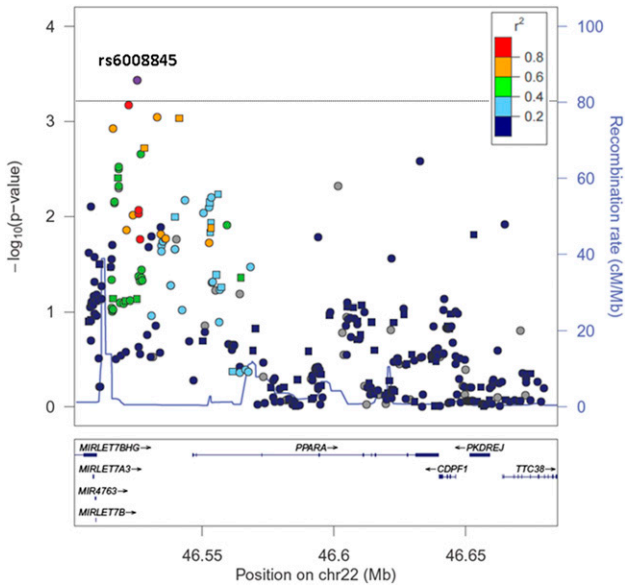

Figure 1—Regional plot of the *PPARA* gene region. Each point represents one SNP. The base pair position on chromosome (chr) 22 (from 46.5 to 46.7 Mb) is on the *x*-axis, and the negative log transformation of the *P* value for interaction between each SNP and fenofibrate on the primary outcome is on the *y*-axis. The significance threshold ($P = 6.2 \times 10^{-4}$) after adjustment for multiple comparisons is indicated by the dashed line. Colors indicate the amount of linkage disequilibrium between plotted SNPs and rs6008845 (specific information of top SNPs can be found in Supplementary Table 2). Plots were generated using LocusZoom v1.1 (Abecasis Laboratory, University of Michigan School of Public Health).

Supplementary Table 3), the T allele was associated with a significantly lower risk of events among subjects on concomitant fibrate + statin therapy (HR 0.45; 95% CI 0.25–0.79), whereas no association was present among participants on statin alone (HR 1.03; 95% CI 0.89–1.20). The summary *P* value for interaction was 0.0046. The meta-analysis of results from ACCORD-Lipid (whites and African American), combined with those from observational studies, yielded a *P* value for interaction of 1×10^{-6} (Fig. 2).

Fenofibrate Effect on MACE According to rs6008845 Genotype and Lipid Profile

The top panel of Fig. 3 shows the interaction described above from a different perspective, that is, as the effect of fenofibrate on MACE risk reduction across genotypes, which is more meaningful from a clinical viewpoint. Among whites from ACCORD-Lipid, T/T homozygotes (approximately one-third of the cohort) experienced a 51% reduction in MACE risk when randomized to fenofibrate (HR 0.49; 95% CI 0.34–0.72), while no beneficial response was observed among heterozygotes (HR 0.98; 95% CI 0.72–1.34) or C/C homozygotes (HR 1.38; 95% CI 0.79–2.48). As shown in the bottom panel of Fig. 3, this interaction was only evident among participants without overt atherogenic dyslipidemia, resulting in a beneficial effect of fenofibrate among T/T homozygotes even in the absence of the combination of both low HDL-c and high triglycerides. Among participants with atherogenic dyslipidemia, the known beneficial effect of fenofibrate on MACE risk reduction was confirmed with no significant modulation by rs6008845 genotypes. Notably, in the group of participants without overt atherogenic dyslipidemia and with rs6008845 T/T genotype, the HR of fenofibrate and the number needed to treat to prevent one MACE over 5 years were similar to those for subjects with atherogenic dyslipidemia, for whom fibrates are currently indicated (Table 2). As shown in Supplementary Table 4, results were similar using an alternative definition of atherogenic dyslipidemia (HDL-c <50.2 mg/dL or 1.3 mmol/L for women and <38.7 mg/dL or 1.0 mmol/L for men combined with triglycerides >203.7 mg/dL or 2.3 mmol/L, regardless of sex [16]).

rs6008845 Effect on Lipid and Chemokine Response to Fenofibrate

As shown in Table 3, the larger cardiovascular benefit of fenofibrate among T/T homozygotes was not paralleled by differences in clinical characteristics at baseline, the only nominally significant difference being in the age of onset of diabetes. The lipid response to fenofibrate treatment, in terms of increase in HDL-c and decrease in triglycerides and total cholesterol, was also equivalent in the three genotypes (Fig. 4). Consistent with the lack of association with lipid profile in ACCORD, rs6008845 was not in LD with any of the *PPARA* variants previously reported to be associated with lipid profile at GWAS levels (30). Rather, a recent genome-wide association study reported an association between genetic variants in the *PPARA* region, including rs6008845, and serum levels of a proinflammatory chemokine (CCL27) (31). Thus, we evaluated the effect of the "rs6008845-by-fenofibrate" interaction on circulating levels of seven chemokines available for 133 subjects from ACCORD-Lipid included in the ACCORD-MIND ancillary study (24). This subset had slightly different clinical characteristics compared with the whole ACCORD-Lipid cohort; in particular, they were characterized by shorter duration of diabetes; lower blood pressure, HbA_{1c}, and LDL-cholesterol levels; and lower prevalence of CVD at baseline (Supplementary Table 5). As shown in Fig. 5 and Supplementary Table 6, we found a significant interaction between rs6008845 and fenofibrate in the circulating levels of CCL11 (also known as eotaxin), in the sense that fenofibrate was associated with lower levels of CCL11 levels ($P = 0.01$) among T/T homozygotes but not among T/C or C/C subjects. Though not reaching statistical significance, a similar pattern of interaction was observed for CLL3 and CXCL8 (Supplementary Table 7).

rs6008845 Regulatory Function

In an analysis of RNA sequencing data from the GTEx project, the rs6008845 T allele was significantly associated with lower *PPARA* expression in skin ($P = 6 \times 10^{-17}$), whole blood ($P = 9 \times 10^{-3}$), skeletal muscle ($P = 2 \times 10^{-2}$),

Table 1—Characteristics of the top SNPs modulating the fenofibrate effectiveness in ACCORD among the self-reported non-Hispanic whites (with $P_{interaction} < 5 \times 10^{-3}$)

SNP	Position	Minor allele	Ref. allele	MAF	*P*	Effect R_{GE}	SE	IMP/GEN	LD with rs6008845
rs6008845	**46525357**	**C**	**T**	**40%**	**3.7E-04**	**0.59**	**0.17**	**IMP**	**ref.**
rs6007904	46521999	G	A	42%	6.4E-04	0.56	0.16	IMP	0.78
rs135570	46532781	G	A	46%	9.0E-04	0.54	0.16	IMP	0.72
rs135557	46541227	G	A	44%	9.3E-04	0.54	0.16	IMP	0.61
rs9306519	46516140	G	A	39%	1.2E-03	0.54	0.17	IMP	0.76
rs2105914	46527955	G	A	48%	1.9E-03	0.50	0.16	GEN	0.67
rs135577	46526617	A	G	28%	2.2E-03	0.56	0.18	IMP	0.58
rs9615264	46632589	A	G	8%	2.6E-03	0.95	0.32	IMP	0.008
rs6008801	46518278	G	C	28%	3.1E-03	0.54	0.18	IMP	0.57
rs6008799	46518189	C	T	28%	3.2E-03	0.54	0.18	IMP	0.57
rs6008798	46518082	C	T	27%	3.9E-03	0.52	0.18	GEN	0.55
rs552533545	46601416	In/del	In/del	14%	4.9E-03	−0.74	0.26	IMP	0.02
rs6008800	46518260	G	T	27%	4.9E-03	0.51	0.18	IMP	0.55

Boldface type indicates the SNP passing the study-wide significant threshold of $P = 6 \times 10^{-4}$ (rs6008845 [IMPUTE2 info score >0.95]). Effect R_{GE}, β for SNP by fenofibrate interaction; GEN, genotyped SNP; IMP, imputed SNP; In/del, insertion/deletion; SE, SE of the β.

vagina ($P = 3 \times 10^{-3}$), and esophageal mucosa ($P = 4 \times 10^{-4}$). The association also approached significance in liver ($P = 7 \times 10^{-2}$) despite the smaller sample size. In a meta-analysis across all 44 tissues available in GTEx, rs6008845 was significantly associated with *PPARA* mRNA levels ($P = 3 \times 10^{-21}$ [Supplementary Fig. 3]), although these results should be interpreted with caution due to the correlation between expression measurements in different tissues obtained from the same donors. Of note, consistent with its influence on *PPARA* mRNA levels, rs6008845 was also associated in the above tissues with the expression of multiple PPAR-α targets (24 genes yielding $P < 0.05$ out of 98 tested, binomial *P* value $= 6 \times 10^{-11}$ [Supplementary Table 8]). The regulatory role of rs6008845 was also supported by data from ENCODE and the Roadmap Epigenomics project (Supplementary Fig. 4 and Supplementary Table 9), indicating that SNP rs6008845 is placed in a DNAse I hypersensitivity cluster in the 5′ flanking region of the *PPARA* gene where chromatin immunoprecipitation experiments have shown binding of several transcription factors in different cell types (mainly white blood cell derived). Histone modification chromatin immunoprecipitation sequencing peaks confirmed the occurrence of rs6008845 in a regulatory locus in multiple cell lines, as this variant was found to be placed inside epigenetic peaks for histone 3 (H3K4Me1, H3K4Me1, and H3K27Ac—as shown in Supplementary Fig. 5), which suggests an active enhancer region.

DISCUSSION

Clinical trials assessing the effect of fibrates on cardiovascular risk among patients with type 2 diabetes (4,5) have demonstrated small, if any, cardiovascular benefits of these drugs (10). These studies, however, have shown a highly variable response to these agents (3–7,11,12), suggesting the possibility of designing precision medicine algorithms to identify patients who have a higher probability of deriving cardiovascular benefit from fibrates (32). In this study, we have identified a genetic variant near the gene coding for the pharmacological target of fenofibrate (PPAR-α) that could be used for this purpose. Among homozygotes for the major allele of this variant (approximately one-third of ACCORD-Lipid participants), randomization to fenofibrate + statin rather than statin alone yielded a 50% reduction in MACE—much larger than in the overall study population. Importantly, this benefit was present in the absence of overt atherogenic dyslipidemia—the only condition that today represents an indication for the addition of fenofibrate to statins for cardiovascular prevention (16). If the results of this study were brought to the clinic, they would translate into more than a doubling in the number of patients with type 2 diabetes who would benefit from treatment with fenofibrate as an add-on to statins.

Several aspects of these findings make them especially robust. First, the genetic effect is linked to the gene that codes for the main pharmacological target of fibrates and as such had a very high prior probability of being involved in the modulation of fenofibrate effects. Second, the SNP × fenofibrate interaction was observed in the rigorous setting of a double-blind, randomized, placebo-controlled clinical trial characterized by excellent adherence to the study protocol. Third, the statistical significance of the interaction was robust to adjustment for the number of independent polymorphisms that were tested at the *PPARA* locus. Fourth, the interaction was validated through transethnic replication in African Americans from ACCORD-Lipid and also by using concomitant medication data from three well-characterized cohorts (ACCORD-BP, ORIGIN, and TRIUMPH), through which

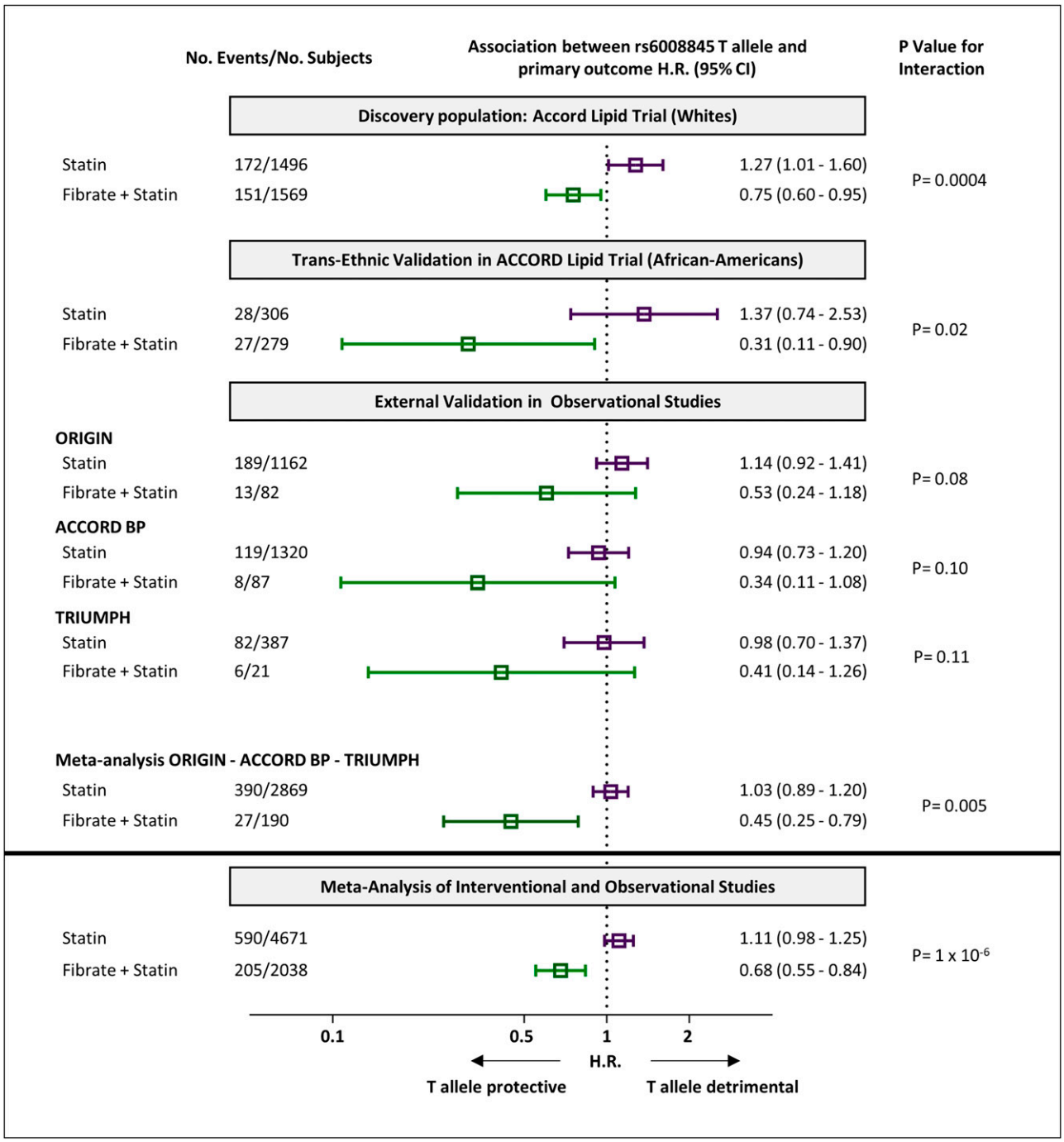

Figure 2—rs6008845 association with primary outcome stratified by fenofibrate treatment in discovery and validation cohorts of subjects with type 2 diabetes and high cardiovascular risk. Note: the association between rs6008845 and the primary outcome is depicted as the effect per each T allele copy.

we were able to reproduce the same exact exposures as in ACCORD-Lipid (fibrate + statin vs. statin alone)—an essential factor for a meaningful replication of genetic findings (33). The fact that we could observe the same rs6008845-by-fibrate interaction in these cohorts as in ACCORD-Lipid is quite remarkable, considering the different clinical characteristics and settings (i.e., observational and interventional) of study populations.

Another critical element in support of the robustness of our findings is the association observed in multiple tissues between the SNP interacting with fenofibrate and mRNA levels of *PPARA* and PPAR-α targets. The decrease in *PPARA* expression associated with the SNP suggests that the latter is functional, providing experimental confirmation of the in silico predictions based on ENCODE and Roadmap Epigenomics project data. The association

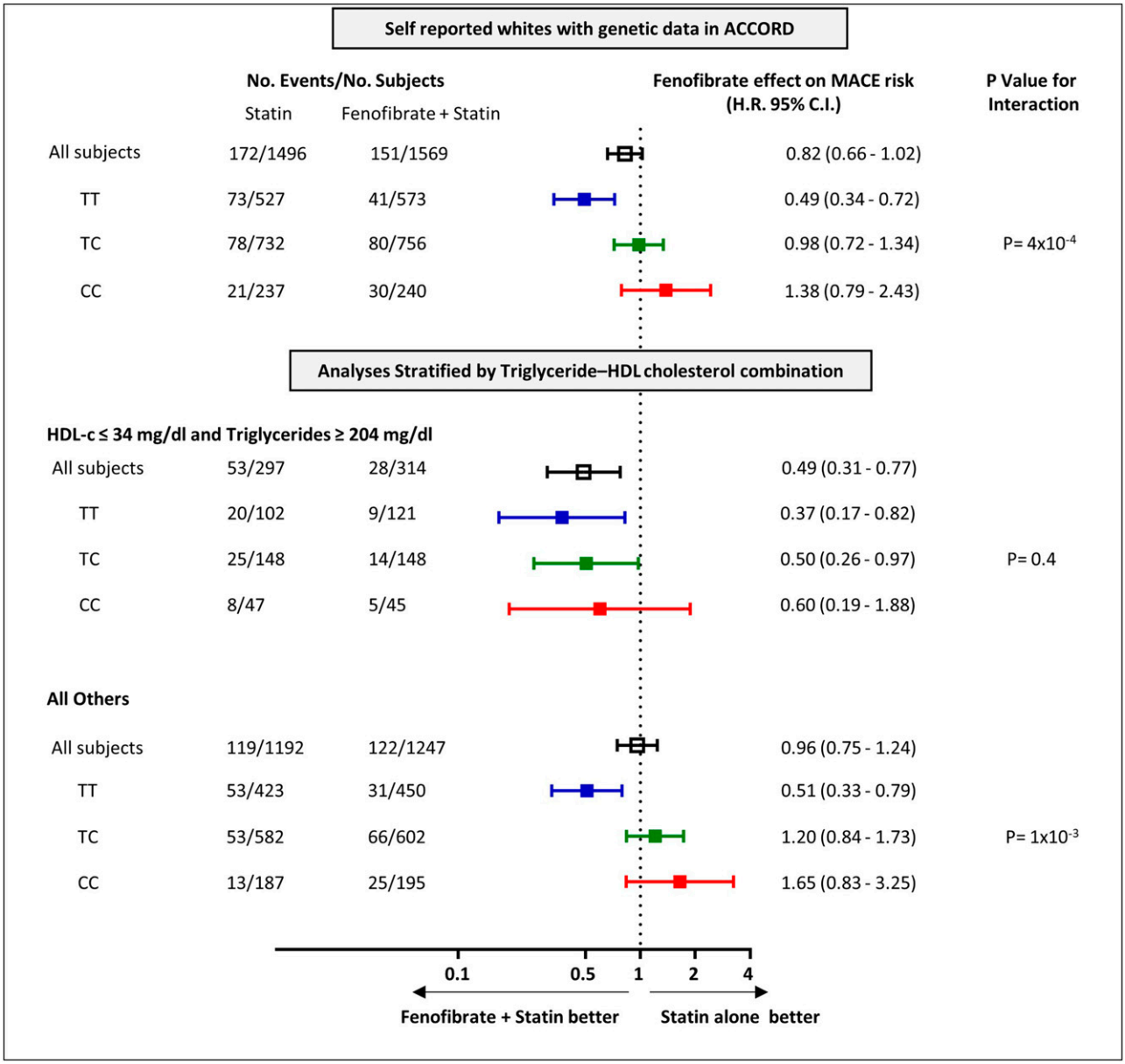

Figure 3—Fenofibrate cardiovascular effectiveness according to rs6008845 genotypes. Top panel: among all self-reported white subjects randomized to fenofibrate or placebo in the ACCORD-Lipid study. Middle and bottom panels: in the same population according to absence or presence of atherogenic dyslipidemia at baseline (a few subjects, $N = 15$, were not included due to missing data on lipid profile at baseline).

with the expression of PPAR-α targets indicates that the effect of the rs6008845 on *PPARA* expression translates into allelic differences in PPAR-α activity that propagate downstream and influence cellular functions. As *PPARA* expression is reduced in rs6008845 T/T homozygotes, one can speculate that carriers of this genotype derive benefit from fibrate treatment because they start from lower PPAR-α activity, whereas C allele carriers derive no benefit because their PPAR-α activity is already optimal. Consistent with this interpretation was the tendency of the T allele to be associated with increased risk of MACE among subjects treated with statins alone, which was reversed to significant protection from MACE by the addition of fenofibrate.

The *PPARA* variant does not appear to act by influencing the effect of fenofibrate on circulating lipids—a finding hardly surprising, considering that changes in plasma lipid profile have been shown to explain <25% of the cardiovascular benefit of fibrates (34). Rather, our finding suggests that the variant exerts its modulatory effects by enhancing the ability of fenofibrate to dampen proinflammatory chemokines such as CCL11. The circulating levels of this chemokine were unaffected by fenofibrate in the overall ACCORD study population. However, T/T subjects,

Table 2—Number of subjects needed to be treated with fenofibrate to prevent one MACE in 5 years in different subgroups

Subgroups	Subjects in each group, *N* (%)	HR (95% CI)	Number needed to treat (95% CI)
By dyslipidemia			
Presence of atherogenic dyslipidemia	611 (20.0)	0.49 (0.31–0.77)	**12 (9–28)**
Absence of atherogenic dyslipidemia	2,439 (80.0)	0.96 (0.75–1.24)	265 (40 to −44), no benefit
By rs6008845 (in the absence of atherogenic dyslipidemia)			
T/T genotype	873 (28.6)	0.51 (0.33–0.79)	**15 (11–36)**
T/C genotype	1,184 (38.8)	1.20 (0.84–1.73)	−58 (72 to −16), no benefit
C/C genotype	382 (16.6)	1.65 (0.83–3.25)	−22 (80 to −7), no benefit

Analyses conducted on 3,050 self-reported white subjects with data on presence or absence of dyslipidemia at baseline. Note: atherogenic dyslipidemia at baseline is defined by cutoff previously used (HDL-c ≤34 mg/dL [0.88 mmol/L] and triglycerides ≥204 mg/dL [2.1 mmol/L]). Numbers needed to treat for subgroups showing a statistically significant benefit of fenofibrate treatment are reported in boldface type.

i.e., those experiencing the cardiovascular benefit of fenofibrate, had significantly lower levels of CCL11 when treated with fenofibrate. CCL11, also known as eotaxin, is a chemokine expressed in multiple tissues, which, in addition to its chemotactic activity on eosinophils, basophils, and Th2 lymphocytes (35,36), has been consistently identified, with its receptor CCR3, as a player in vascular inflammatory processes (37–39). Moreover, several epidemiological studies have found a significant association between higher CCL11 levels and increased cardiovascular risk (40–42), with randomized clinical trials showing that cardioprotective therapies such as metformin and atorvastatin reduce circulating CCL11 (43,44). There are no reports in the literature, besides the present one, describing a similar effect of fenofibrate in humans. However, such an effect is supported by a study in a mouse model, in which upregulation of PPAR-α activity decreased skin expression of CCL11 and other chemokines (45). Such actions may relate to the inhibitory effect of PPAR-α activation on the nuclear factor-κB pathway (e.g., by inducing the nuclear factor-κB inhibitor IκBα) (45–47), which is known to regulate the expression of CCL11 and its receptor CCR3 (48,49). Altogether, our findings provide support for a complex mechanism of action of fibrates on cardiovascular risk, consistent with the pleiotropic effects that activation of PPAR-α has in multiple cell types relevant to atherogenesis including monocytes/macrophages, smooth muscle cells, endothelial cells, platelets, and fibroblasts (9,50,51).

Some limitations of our study must be acknowledged. First, this was a post hoc analysis that included only 80% of the subjects in the ACCORD-Lipid trial (i.e., those for

Table 3—Baseline characteristics according to rs6008845 genotype in self-reported whites

	TT	TC	CC	*P*
n	1,100	1,488	477	
Female, *n* (%)	319 (29.0)	433 (29.1)	138 (28.9)	0.9
Age (years)	62.8 ± 6.4	62.7 ± 6.5	62.9 ± 6.8	0.8
Years of diabetes	10.1 ± 6.8	10.9 ± 7.7	11.0 ± 7.5	0.006
Previous CVD, *n* (%)	404 (36.7)	551 (37.0)	176 (36.9)	0.9
HbA_{1c} (%)	8.2 ± 0.9	8.2 ± 0.9	8.1 ± 0.9	0.3
Fasting plasma glucose (mg/dL)	179.4 ± 50.4	176.8 ± 49.7	179.5 ± 51.9	0.7
BMI (kg/m^2)	33.2 ± 5.1	33.0 ± 5.2	33.0 ± 5.0	0.7
Atherogenic dyslipidemia, *n* (%)	223 (20.3)	296 (20.0)	92 (19.4)	0.6
Triglycerides (mg/dL)	177 (125–244)	174 (125–239)	171 (120–249)	0.7
Total cholesterol (mg/dL)	177.4 ± 36.8	175.2 ± 36.9	174.6 ± 37.0	0.07
HDL-c (mg/dL)	37.6 ± 7.5	37.3 ± 7.4	37.6 ± 7.6	0.6
LDL-c (mg/dL)	100.9 ± 30.0	99.2 ± 30.0	98.6 ± 31.1	0.08
Systolic BP (mmHg)	133.3 ± 17.1	132.7 ± 17.2	132.6 ± 16.6	0.3
Diastolic BP (mmHg)	73.7 ± 9.9	72.8 ± 10.3	73.3 ± 10.6	0.2
Serum creatinine (mg/dL)	0.91 ± 0.22	0.92 ± 0.22	0.92 ± 0.21	0.3

Data are mean ± SD or median (interquartile range) unless otherwise indicated. For representation purposes, subjects were considered as major allele homozygotes if the minor allele dosage was <0.5, heterozygotes if the minor allele dosage was ≥0.5 and <1.5, and minor allele homozygotes if the minor allele dosage was ≥1.5. Atherogenic dyslipidemia was defined as HDL-c ≤34 mg/dL and triglycerides ≥204 mg/dL. To convert cholesterol values to millimoles per liter, multiply by 0.02586. To convert triglyceride values to millimoles per liter, multiply by 0.01129. BP, blood pressure; LDL-c, LDL cholesterol.

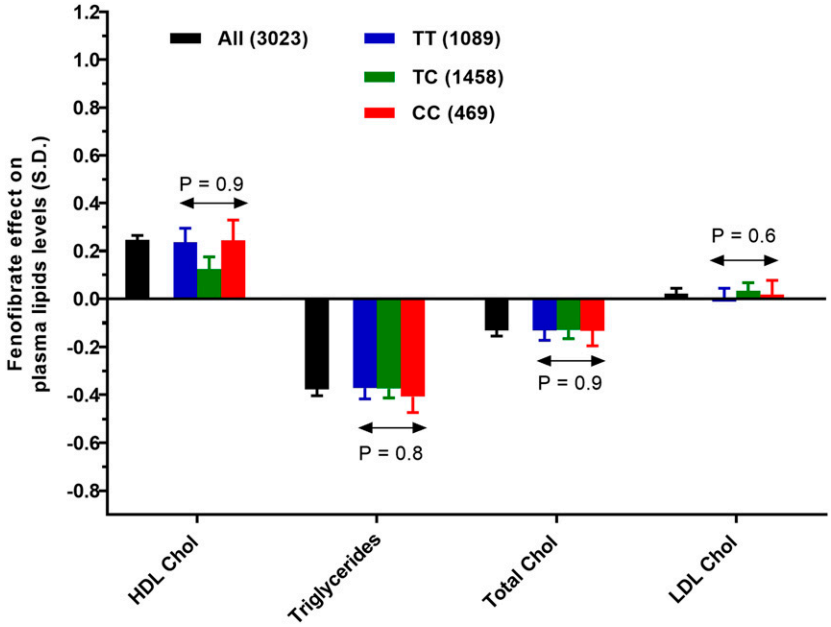

Figure 4—Effects of fenofibrate on changes in lipid levels among self-reported whites in ACCORD-Lipid, stratified by rs6008845 genotypes. Error bars represent SEs. One SD is equal to 5.4 mg/dL for HDL-c, 87.1 mg/dL for triglycerides, 35.2 mg/dL for total cholesterol, and 29.8 mg/dL for LDL cholesterol. To convert cholesterol values to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. Chol, cholesterol.

whom DNA was available). As such, this analysis deviates from an intention-to-treat approach. On the other hand, the lack of differences in baseline clinical characteristics between treatment arms in the subset included in the study, and the external validation in three different cohorts, attenuates the importance of this limitation. While these other cohorts were from observational studies, in which fibrate and statin treatments were not randomized and were based on self-report, the lack of differences in clinical characteristics among rs6008845 genotypes and the fact that results were similar across the three cohorts and consistent with the findings from ACCORD-Lipid provide reassurance about the validity of these data. Second, since ACCORD-Lipid investigated fenofibrate

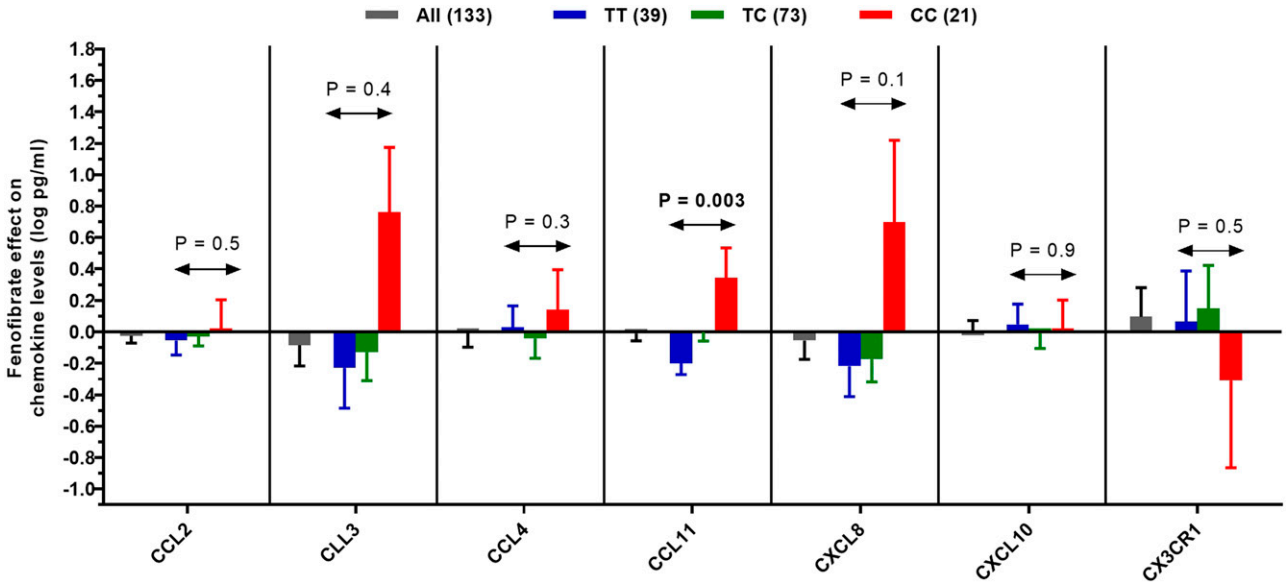

Figure 5—Fenofibrate effects on chemokine levels according to rs6008845 genotypes among self-reported whites from the ACCORD-MIND biomarker study. Error bars represent SEs.

given in combination with a statin and was specifically directed to subjects with type 2 diabetes at high cardiovascular risk (as were the ORIGIN, ACCORD-BP, and TRIUMPH cohorts), caution should be exercised in generalizing these findings to treatment with fenofibrate alone or to subjects having different characteristics. This aspect deserves special attention given the known cross talk between fibrates and statins (52,53). Importantly, although we were able to replicate our findings among African Americans, further evidence should be gathered before extending conclusions to other races or ethnic groups. Third, since only mortality data were available for the TRIUMPH cohort, we could not analyze the effect of the variant on MACE in this study, as was done in the other two cohorts. However, all TRIUMPH participants were enrolled in that study after an acute myocardial infarction; thus, the majority of deaths in this cohort are likely to have had a cardiovascular cause. Fourth, due to the relatively small sample size, our analysis was limited to common polymorphisms (MAF >5%) and we cannot therefore exclude that other, less common variants may exist in the *PPARA* gene region that also modulate the cardiovascular responsiveness to fenofibrate. Finally, given the small number of participants with chemokine data, the finding of association between fenofibrate treatment and reduced CCL11 levels in T/T homozygotes should be interpreted with caution and should be considered at this point as merely hypothesis generating.

Our findings have promising implications for the treatment of patients with diabetes at high cardiovascular risk. Due to the lack of clear cardiovascular benefit, in 2016 the U.S. Food and Drug Administration removed the indication of the addition of fibrates to statins for cardiovascular prevention (54), and current guidelines do not recommended this treatment for that purpose (1,15). The only exceptions are patients with atherogenic dyslipidemia, i.e., with low HDL-c and high triglycerides, for whom this treatment may be considered due to the consistent evidence of benefit in this small subgroup (12–14). Our findings confirm the established benefit of fenofibrate in the presence of atherogenic dyslipidemia but, importantly, suggest that rs6008845 could be used as a marker to identify an additional group of subjects (i.e., those with T/T genotype) for whom therapy with a fibrate as an add-on to statins could be indicated for cardiovascular disease prevention even in the absence of atherogenic dyslipidemia. The use of this marker would at least double the proportion of patients eligible for fenofibrate therapy, with obvious public health implications. However, before this approach can be brought into clinical practice, our findings will require validation through specifically designed pharmacogenetics clinical trials, in which randomization to fibrate or placebo is stratified by *PPARA* genotype. In the case of fenofibrate, the low cost and the well-documented safety profile of this drug may facilitate this goal by making pragmatic clinical trials possible. Our findings may also prompt ancillary studies of ongoing cardiovascular clinical trials of new fibrates, such as the PROMINENT (Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With DiabeTes) clinical trial of pemafibrate (ClinicalTrials.gov: NCT03071692).

In conclusion, we have identified a genetic variant at the *PPARA* locus that modulates the cardiovascular response to fenofibrate in patients with type 2 diabetes. These findings suggest a precision medicine approach to prescribe fenofibrate optimally, rescuing a drug that would be otherwise dismissed as ineffective and offering a cardioprotective drug to those patients that are most likely to experience a robust benefit from this medication.

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Author Contributions. M.L.M. designed the study; acquired, analyzed, and interpreted the data; and wrote the manuscript. H.S.S. designed the study; acquired, analyzed, and interpreted the data; and reviewed the manuscript. A.A.M.-R. and H.G. acquired and interpreted data and reviewed the manuscript. J.S., P.A.L., H.C., L.L., and G.P. acquired and analyzed data and reviewed the manuscript. S.P., A.P., M.G.P., D.M.R., E.P., L.M., and V.T. interpreted the data and reviewed the manuscript. R.J.S. and E.Y.C. designed the study and reviewed the manuscript. S.C. and H.C.G. designed the study, acquired and interpreted data, and reviewed the manuscript. S.M.M., J.B.B., and M.J.W. acquired and interpreted data and reviewed the manuscript. P.K. designed the study, interpreted the data, and reviewed the manuscript. H.N.G. designed the study, acquired and interpreted the data, and reviewed the manuscript. J.C.M. designed the study; acquired, analyzed, and interpreted the data; and reviewed the manuscript. A.D. designed the study; acquired, analyzed, and interpreted the data; and wrote the manuscript. A.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Preliminary data of this study were presented at the National Congress of the Italian Society for the Study of Atherosclerosis (SISA), Palermo, Sicily, 19–21 November 2017.

Appendix

Members of the ACCORD Data Safety Monitoring Board. Antonio M. Gotto. Jr. (chair), Kent Bailey, Dorothy Gohdes, Steven Haffner, Roland Hiss, Kenneth Jamerson, Kerry Lee, David Nathan, James Sowers, and LeRoy Walters.

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