Objective: Fenofibrate, a peroxisome proliferator-activated receptor-α (PPARα) agonist, reduces triglyceride (TG) concentrations by 25-60%. Given significant interindividual variations in the TG response, we investigated the association of PPARA rare variants with treatment response in the Genetics of Lipid-Lowering Drugs and Diet Network study.

Methods: We calculated the change in the TG concentration (ΔTG) among 861 GOLDN participants treated with fenofibrate (160 mg/day) for 3 weeks. From the distribution of ΔTG adjusted for age and sex, the 150 highest and 150 lowest fenofibrate responders were selected from the tails of the distribution for PPARA resequencing. The resequencing strategy was based on VariantSEQr technology for the amplification of exons and regulatory regions.

Results: We identified 73 variants with an average minor allele frequency of 4.8% (range: 0.2-16%). We tested the association of rare variants located in a coding or a regulatory region (minor allele frequency<1%, 13 variants) with treatment response group by an indicator variable (presence/absence of ≥1 rare variant) using general linear mixed models to allow for adjustment for family relationship. After adjusting for baseline, fasting TG concentration carrying at least one rare variant was associated with a low fenofibrate response (odds ratio=6.46; 95%
confidence interval: 1.4-30.8). Carrier status was also associated with a relative change in the total cholesterol concentration (P=0.02), but not high-density lipoprotein or low-density lipoprotein concentration.

**CONCLUSION:** Rare, potentially functional variants in PPARA may play a role in the TG response to fenofibrate, but future experimental studies will be necessary to replicate the findings and confirm functional effects.

DOI: [10.1097/FPC.0b013e328351a486](http://dx.doi.org/10.1097/FPC.0b013e328351a486)

Alternate Journal: Pharmacogenet. Genomics

PubMed ID: [22336959](http://www.ncbi.nlm.nih.gov/pubmed/22336959)

PubMed Central ID: PMC3325369

Grant List:

**T32 NS054584 / NS / NINDS NIH HHS / United States**

**U01 HL072524-04 / HL / NHLBI NIH HHS / United States**

**U01HL072524-04 / HL / NHLBI NIH HHS / United States**