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Common and rare variant analysis of fibrate drug response in type-2 diabetics in the ACCORD clinical trial

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Cardio-Vascular Disease (CVD) is the leading cause of death worldwide. Individuals with type-2 diabetes are at an increased risk of CVD and alterations in total cholesterol (TC), LDL, HDL and triglycerides (TG) are known risk factors of CVD. Fenofibrate is a commonly prescribed cholesterol lowering drug but there is heterogeneity in treatment response. Here we conduct a genome-wide association study to investigate common and rare genetic variants associated with lipid changes in 1261 diabetics from the ACCORD clinical trial for ~90 days of fenofibrate treatment. Analysis was also stratified by white (n=773) and black (n=123) subjects. A total of 26, 35 and 120 common variants, mapping to 5, 7 and 24 genes were associated with change in TC, LDL, HDL and or TG in all races, white and black respectively ($p<1\times10^{-6}$). In addition, 7 genes were associated with changes in TG in the rare variant analysis ($q<0.05$). Significant genes in the common and rare variant analysis were tested for gene expression changes in mice treated with fenofibrate. The validation study found 3 genes in the common variant analysis (SMAD3, ATP13A1 and IPO11) displayed significantly decreased gene expression in mice treated with fenofibrate ($q<0.25$). RAB27B and DCUN1D4 were significantly associated with TG in the rare variant analysis and displayed significantly decreased and increased gene expression respectively. SMAD3 is an intracellular mediator of TGFβ and SMAD3-KO mice have been known to have increased insulin sensitivity and reduced adiposity. These results may provide new biomarkers for fenofibrate drug response and lead to new therapeutic targets.

Biography

Daniel Rotroff is a Post-doctoral Research Scholar working with Motsinger-Reif in the Bioinformatics Research Center at NCSU. He has obtained a Master of Science degree in Public Health in 2010 and a PhD in Environmental Science and Engineering from the University of North Carolina at Chapel Hill in 2013. He has authored 20 publications that have accrued over 800 academic citations and his current research focuses on Assessing *in utero* epigenetic modification due to maternal smoking, using metabolomics approaches for biomarker discovery and identifying genetic variants associated with drug-response phenotypes.

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