Post-GWAS follow-up of candidate genes of diabetic dyslipidemia using NGS and transgenic zebrafish

Statement of the Problem: Dyslipidemia is a well-known risk factor for cardiovascular disease and a principal cause of mortality in individuals with type 2 diabetes. Despite, the high heritability (50-80%) of lipid traits, previous genome-wide association studies (GWAS) have only been able to account for a fraction of this heritability (<10%) in genes involved in lipid metabolism. In this study, we aim to identify the rare functional variants in known candidate genes for diabetic dyslipidemia.

Methodology & Results: We performed targeted sequencing of 14 candidate genes (~215 kb) for 940 diabetic dyslipidemia individuals [572 cases with high serum triglycerides (TG) (>150 mg/dl) and 368 controls with low TG (<100 mg/dl)] from the Asian Indians Diabetic Heart Study of 2,361 high-quality variants analyzed, 40% of variants were unique to high TG cases and 13.6% variants were unique to controls. Further analysis of variants within the GCKR gene using the Combined Multivariate and Collapsing methods revealed clustering of 13 functionally damaging and deleterious rare mutations near fructose binding site and glucokinase (GCK) binding sites at the sugar isomerase domains. The GCKR encodes glucokinase regulatory protein that regulates GCK by forming a complex, which plays a role in the control of blood glucose homeostasis. The lead variant with a missense mutation of Serine/Asparagine was restricted to individuals with high TG. More than 60% of the carriers were diabetic and 90% of carriers had high TG (ranging from 182 mg/dl to 560 mg/dl). We have designed a transgenic zebrafish (Danio rerio) with human GCKR and tested the phenotypic effects of three functionally disruptive variants to evaluate their metabolic consequences in vivo.

Conclusion & Significance: Our results suggest the potential for detecting novel pathways in diabetes linked with hypertriglyceridemia using NGS technology and humanized zebrafish model.

Biography
Dharambir Sanghera's research specializes in the study of molecular and genetic-disease, obesity, and metabolic syndrome. Using expertise in wide range of molecular and statistical genetics concepts, her laboratory is studying the interplay between environmental and genetic factors involved in complex disease pathogenesis on family- and population-based datasets. The long-term goals of her research are: To identify the underlying molecular mechanisms associated with cardiovascular disorders, to improve the classification of the disease process by identifying genome-wide patterns associated with ethnic variation, and to discover new therapeutic targets which can inform the design of early prevention and treatment therapy among disparate populations.

Dharambir-sanghera@ouhsc.edu

Notes: