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Excess of Rare Non-coding Variants in Diabetic Families with Low Burden of Polygenic Risk

Abstract:

Type 2 diabetes (T2D) etiology is highly complex due to its multiple roots of origin. Polygenic risk scores (PRS) based on genome-wide association studies (GWAS) can only partially explain the T2D risk. Asian Indians have up to six times higher risk of developing T2D than Europeans. However, the underlying causes of this disparity are unknown. Here, we have performed targeted sequencing of ten T2D GWAS/candidate regions using endogamous Punjabi Sikh families and replication studies using unrelated Sikhs and families from three other Indian endogamous ethnic groups (EEGs). We detected several rare and ultra-rare variants (RVs) in KCNJ11-ABCC8 and HNF4A (MODY genes) that cosegregated with late-onset T2D. In addition, we identified RV enrichment in two novel genes, SLC38A11 and ANPEP, associated with T2D. Gene-burden analysis revealed the highest RV burden contributed by HNF4A ($p=0.0003$), followed by KCNJ11/ABCC8 ($p=0.0061$) and SLC38A11 ($p=0.03$). Some RVs detected in Sikhs were also found in Agarwals from Jaipur, both from Northern India. Still, they were monomorphic in the other two EEGs from South India. Despite carrying a high burden of T2D and RVs, most members of Sikh families had a significantly low burden of polygenic risk scores (PRS). Functional studies confirm the regulatory role of an intronic RV in ABCC8, which abolishes binding sites of Nf-kβ and Pax4 transcription factors influencing the regulation of downstream genes. The enrichment of noncoding RVs from multiple MODY and other genes in these families with high disease burden suggests the oligogenic inheritance of T2D. These findings urge deeper evaluations of such families for potential novel therapeutics.

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Biography:
Dr. Sanghera is a Professor of Pediatrics and the Dr. Altshuler Endowed Chair of Genetics at the University of Oklahoma Health Sciences Center. Her research focuses on the genetic, environmental, and cultural factors affecting diabetes and cardiovascular diseases, as well as health disparities among ethnic groups in the U.S. She teaches two graduate courses in “Pharmacogenetics” and “Cardiovascular Genomics” at the University of Oklahoma Health Sciences Center.