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High-Risk Gene Variant Profiling Models Ethnic Disparities in Diabetes Vulnerability

Authors : Jianhua Zhang, Weiping Chen, Guanjie Chen, Jason Flannick, Emma Fikse, Glenda Smerin, Yanqin Yang, Yulong Li, John A. Hanover, William F. Simonds

Abstract : Ethnic disparities in many diseases are well recognized and reflect the consequences of genetic, behavior, and environmental factors. However, direct scientific evidence connecting the ethnic genetic variations and the disease disparities has been elusive, which may have led to the ethnic inequalities in large scale genetic studies. Through the genome-wide analysis of data representing 185,934 subjects, including 14,955 from our own studies of the African America Diabetes Mellitus, we discovered sets of genetic variants either unique to or conserved in all ethnicities. We further developed a quantitative gene function-based high-risk variant index (hrVI) of 20,428 genes to establish profiles that strongly correlate with the subjects' self-identified ethnicities. With respect to the ability to detect human essential and pathogenic genes, the hrVI analysis method is both comparable with and complementary to the well-known genetic analysis methods, pLI and VIRlof. Application of the ethnicity-specific hrVI analysis to the type 2 diabetes mellitus (T2DM) national repository, containing 20,791 cases and 24,440 controls, identified 114 candidate T2DM-associated genes, 8.8-fold greater than that of ethnicity-blind analysis. All the genes identified are defined as either pathogenic or likely-pathogenic in ClinVar database, with 33.3% diabetes-associated and 54.4% obesity-associated genes. These results demonstrate the utility of hrVI analysis and provide the first genetic evidence by clustering patterns of how genetic variations among ethnicities may impede the discovery of diabetes and foreseeably other disease-associated genes.

Keywords : diabetes-associated genes, ethnic health disparities, high-risk variant index, hrVI, T2DM
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