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Diabetes GWAS in understudied populations: Beauty is in the eyes of the beholder

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Genome wide association studies (GWAS) have identified several SNPs associated with monogenic and polygenic diseases, including diabetes. Delineating biological insights and causal links with disease from these associations are challenging and have been successful only in limited cases. Nevertheless, GWAS remains as a popular tool. This abstract highlights the design features for GWAS in understudied populations from the State of Kuwait which is part of the Arabian Peninsula. Kuwait is characterized by a mixture of settlers from Saudi Arabia, Iran, and nearby regions. Analysis for genetic features conforms to Kuwait's geographical location at the nexus of Africa, Europe, and Asia. Runs of homozygosity (ROH) analysis suggests existence of both modern outbred and consanguineous individuals, and identity by descent (IBD) analysis shows existence of both recent and ancient shared ancestries. As many as approximately 2500 exonic SNPs show significant allele frequency differences with continental populations, high prevalence of recessive disorders (due to consanguinity) and lifestyle disorders (due to rapid nutrition transition in the post-oil era) that increase risk of diabetes, is seen in the Peninsula. For above such reasons, design of appropriate GWA studies in Kuwait poses many challenges the primary being modeling the population stratifications and choice of appropriate analytic models for association tests. We show that while classical additive models have been successful in Caucasian populations, recessive models are effective with populations from the Peninsula. Combined use of recessive and additive models identifies markers of significant associations with traits related to type 2 diabetes. Such markers are from genes coding for regulators of key metabolic pathways such as NOTCH signaling, mTOR, and lipid mobilization & transport.

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