

Hints of Unique Genetic Effects for Type 2 Diabetes in India

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The prevalence of type 2 diabetes (T2D) is rising rapidly worldwide. In September 2012, the World Health Organization reported a global prevalence exceeding 300 million people, predicting a further 60–70% increase by the year 2030 (1). One of the largest absolute increases is expected to occur in India, with the International Diabetes Federation estimating that India alone will have 100 million people with diabetes by 2030 (2). About 90% of these will have T2D.

Increased food consumption and decreased physical activity represent major contributors to the growing Indian T2D epidemic, reflecting ongoing economic transitions and widespread embrace of a Western lifestyle. But T2D risk also has a substantial genetic component and evidence indicates that Indians may be more susceptible to developing insulin resistance and T2D compared with European-ancestry individuals of equivalent age and BMI (3–5), suggesting the possibility of population-specific genetic or epigenetic risk factors.

A recent, comprehensive genetic study provided compelling evidence for global genetic differentiation of T2D risk. In a survey of thousands of confirmed genetic associations, risk alleles for T2D demonstrated the most extreme population frequency differentiation among twelve common diseases studied (6). A clear gradient of T2D risk allele frequencies along continental paths of early human migration was evident, suggesting potential population-specific evolutionary adaptation to agricultural developments, dietary patterns, or food availability. The latter is consistent with the “thrifty genotype” hypothesis, which contends that genetic alleles promoting efficient energy storage experienced positive selection in populations that experienced historically inconsistent food supply and now contribute to an increased prevalence of obesity and T2D. However, such selection effects remain unproven, and the population frequency differences may also reflect non-selective factors such as drift.

Regardless of the cause(s), population differences in disease allele frequencies have implications for risk allele identification via association tests, the power of which varies with allele frequency. An early example was provided by the first two genome-wide association studies (GWASs) of T2D conducted in East Asian populations

(7,8), which identified genome-wide association of *KCNQ1* variants. Association of these variants with T2D was not previously detected in large European ancestry studies due to a vastly lower risk allele frequency in Europeans (5 vs. 40%). A European-based meta-analysis (7) subsequently confirmed association of the *KCNQ1* variants in Europeans, but at significance levels far below the thresholds typically motivating replication attempts ($P \sim 0.02$). Studies of distinct ancestral groups may also enhance the detection or localization of genetic risk variants due to population differences in linkage disequilibrium, gene–environment interactions, or the presence of population-specific variants, particularly for recently derived causal mutations of low frequency. Indeed, recent T2D GWAS in East- and South-Asian populations (9–12) show that many T2D risk variants have similar effects across ancestral groups, but have also identified various, seemingly population-specific, risk variants.

For millennia, India has been populated by diverse caste and tribal groups, with intergroup gene flow impeded by a hierarchical caste system, geographical dispersal, and subdivision of the country into different linguistic regions (13). This has led to significantly higher genetic diversity within India, compared with Europe and East Asia (14). Given high genetic differentiation of both Indian populations and T2D risk variants, well-powered GWASs within ethnically homogeneous Indian populations may provide novel insights into genetic effects underlying T2D susceptibility, both in Indians and other populations. One of the few T2D GWASs performed in an exclusively Indian population identified a 2q21 locus showing genome-wide significant association with T2D in a Northern-Indian sample (15). The associated single-nucleotide polymorphisms (SNPs) also showed association with fasting plasma insulin levels in the same population but were not associated with T2D in a large European sample, potentially due to differences in risk allele frequency or linkage disequilibrium.

The study by Saxena et al. (16) in this issue describes a T2D GWAS in Punjabi Sikhs from India, an endogamous North-West Indian population with a high prevalence of T2D and cardiovascular disease in spite of low obesity rates, ~50% vegetarianism, and strict tobacco abstinence. The total Sikh sample included 3,354 T2D case and 3,975 control subjects from three distinct samples, combined GWAS meta-analysis of which identified genome-wide significant association of a SNP within the skeletal muscle-expressed sarcoglycan γ (*SGCG*) gene (rs9552911: $P = 1.8 \times 10^{-8}$). Each additional risk allele was associated with an estimated 50% increase in disease odds, with a 95% CI 30–72%. The association demonstrated excellent consistency across the three Sikh samples, but no association was observed in a large, East Asian replication study. Interestingly, the associated SNP is monomorphic in Europeans, and hence not amenable to statistical analysis.

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Although further study is required to validate and explain these results, it is possible that the detected locus is specific to the Indian Punjabi Sikh population, as a result of India's complex demographic history and cultural diversity.

Strengths of this study were the use of samples from an ethnically homogeneous Indian population, robust phenotyping, and careful sensitivity analyses to exclude the potentially confounding effects of population stratification or consanguinity. Reassuringly, the study also reported highly significant association of a previously reported SNP in *TCF7L2* in Sikhs ($P = 3.3 \times 10^{-19}$) and confirmed a previously reported *IGF2BP2* locus, with these two loci also showing genome-wide significant association with T2D in combined meta-analysis of the Sikh and wider South-Asian populations, and large, multiethnic meta-analyses. A weakness of the study was a lack of independent replication of the novel association in additional Sikh samples, precluding independent evaluation of validity and effect size. However, strong consistency of the signal across the three studied samples lends confidence to the initial finding.

This study suggests a T2D susceptibility locus potentially specific to populations within the Indian subcontinent, contributing to the broadening landscape of shared and unique population genetic effects for this disease. Given the burgeoning prevalence of this disorder in India and evidence for population genetic/epigenetic differences in susceptibility, these results support further comprehensive genetic studies of T2D in diverse Indian and Asian populations. Ancestry-specific characterization of T2D risk alleles may maximize the benefits of gene discovery and future clinical translation for these large, susceptible groups.

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