Cardiometabolic disease

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Genetic insights into global heterogeneity of type 2 diabetes

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In people of South Asia ancestry, specific genetic mechanisms may drive diabetes development, as revealed by a new study offering insights into global diabetes heterogeneity and potential avenues toward precision medicine.

The clinical characteristics of people with type 2 diabetes vary markedly across global populations. Depending on where they live and their genetic ancestry, individuals with type 2 diabetes differ in mean age of diagnosis, body-mass index (BMI) and response to treatment, among other factors[1,2]. Such differences remain incompletely delineated and poorly understood, and this knowledge gap represents a substantial barrier to the delivery of precision medicine in diabetes[3].

Many factors likely contribute to the observed global diversity in diabetes phenotypes, including differences related to social determinants of health, diet, physical activity, culture and the type of medical care available[4]. Importantly, the contribution of genetic factors has been increasingly elucidated, facilitating the process of disentangling genetic from non-genetic factors while aspiring to avoid exacerbation of potential health disparities or biases[5]. But key questions remain: for example, what are the pathophysiological mechanisms that explain the different diabetes clinical phenotypes? Can these pathophysiological differences inform optimal management strategies? In this issue of *Nature Medicine*, Hodgson et al.[6] address these questions.

By analyzing data from over 51,000 British Pakistani and British Bangladeshi individuals in the Genes & Health study, the authors investigated how common genetic risk factors for type 2 diabetes contribute to the clinical phenotype of diabetes in people of South Asian descent. They utilized recently developed multi-ancestry 'partitioned polygenic scores' (pPS)[7] that each aim to capture an individual's genetic risk (based on common variants) for a particular type 2 diabetes mechanistic process – such as diminished pancreatic beta cell function or increased adiposity (Fig. 1). They find that pPS related to mechanisms of body fat distribution (referred to as 'lipodystrophy') and insulin deficiency were most strongly associated with risk of type 2 diabetes and gestational diabetes. These same pPS were also associated with lower BMI and younger age at the time of type 2 diabetes diagnosis. Individuals of South Asian genetic ancestry had a higher burden of genetic variants relating to these disease mechanisms than individuals of European ancestry in the UK Biobank. Additionally, in South Asians, pPS were associated with differences in response to treatment, progression to insulin dependence and the risk of developing diabetes-related complications.

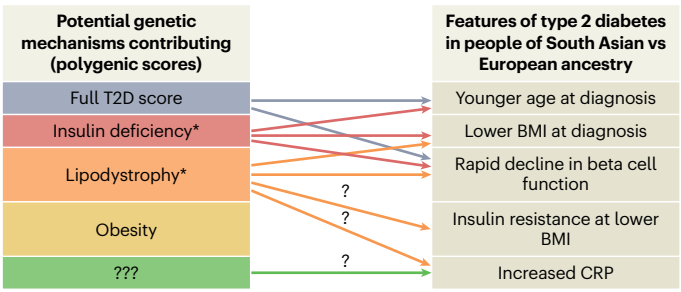

Fig. 1 | Clinical features and genetic drivers of type 2 diabetes in people of South Asian ancestry. People of South Asian ancestry with type 2 diabetes (T2D) have distinctive clinical features compared to individuals of European ancestry[2]. Hodgson et al.[6] found that several of these clinical features appear to be driven by type 2 diabetes partitioned polygenic scores (pPS). The pPS related to mechanisms of body fat distribution (lipodystrophy) and insulin deficiency drive several of the characteristic features of type 2 diabetes in South Asian individuals. Compared to individuals of European genetic ancestry, individuals of South Asian ancestry also had a higher burden of genetic variants relating to these two disease mechanisms (noted with asterisks). Other studies have mapped the alleles in the insulin deficiency pPS to DNA regulatory activity in pancreatic islet cells and the alleles in the lipodystrophy pPS to adipose tissue[7,12]. With increasing genetic discovery in South Asians via analyses of growing datasets, additional type 2 diabetes pPS are expected to be identified and may contribute to other classic clinical features of type 2 diabetes in South Asians. CRP, C-reactive protein.

This study builds on recent work that also showed differences in type 2 diabetes pPS across genetic ancestral subpopulations, whereby individuals of East Asian genetic ancestry had a higher genetic burden of the same lipodystrophy alleles that are enriched in the South Asian population[7]. These lipodystrophy alleles were associated with a predilection toward a metabolically unfavorable body fat distribution, with increased fat storage within visceral rather than subcutaneous regions. Additionally, the lipodystrophy pPS contributed to the lower BMI threshold observed for the development of type 2 diabetes in the East Asian subpopulation as compared to the European subpopulation.

Implicating sets of genetic alleles as contributors to a population's diabetes clinical phenotype provides an exciting initial step toward understanding why there are global differences in the clinical features of diabetes. Further investigation is now needed to expand and build upon these findings and to move from genetic association to causal inference, with elucidation of the relevant pathophysiology and clinical translation. Yet there are several challenges to achieving these goals.

First, efforts to solidify the causal relationship between presumed genetic mechanism and clinical phenotype require diverse multi-ancestry studies with harmonized collection of clinical information, environmental exposures, biomarkers and multi-omics data.

There are currently few such cohort studies completed, limiting the ability to accurately compare characteristics across ancestral subpopulations and investigate how variants relate to actual patient pathophysiology and clinical outcomes. Nevertheless, important progress is being made: for example, a recent study analyzed two distinct patient populations utilizing biomarker measurements in conjunction with genetic and ancestral information, finding that pancreatic beta cell function was indeed lower in South Asian individuals than in European individuals[8]. This concordant finding supports the validity of the results from Hodgson et al.[6]. Comparison of data across studies of people with diabetes from different populations is challenging because of siloed datasets that may or may not contain analogous variables and biomarkers. Therefore, robust comparisons across populations will require ongoing development of international, collaborative studies with diverse representation, unified research protocols and assays, and comprehensive capture of relevant variables.

Second, in addition to the general dearth of well-phenotyped, diverse multi-ancestry studies, there is a particular need for better representation of South Asian (and other under-represented) ancestral subgroups in genetic studies. Genetic discovery in under-represented populations is critical not only for the identification of type 2 diabetes risk alleles but also to identify alleles related to clinical traits and biomarkers, because these association statistics underpin the formation of the pPS. With larger genetic studies of type 2 diabetes and related traits in individuals of South Asian ancestry, it will be possible to generate more robust South Asian–specific pPS that could potentially implicate novel disease mechanisms and improve the predictive ability of pPS in this population.

Third, to understand the molecular mechanisms captured by genetic clusters and pPS, well-designed experimental studies are necessary for connecting genetics to disease pathways. In one elegant example, researchers analyzed cellular profiles of subcutaneous fat biopsies from individuals predominantly of European descent[9]. They connected the lipodystrophy pPS to a subcutaneous adipocyte profile involving reduced lipid droplet size and altered mitochondrial activity; this cellular profile supported a lipodystrophy mechanism involving the shunting of fat storage away from the subcutaneous adipose region. Assessment of similar data in people of diverse ancestries, including South Asian ancestry, could further determine whether and how the identified molecular mechanism varies across ancestral populations.

Finally, clinical translation of any robust determinants of genetic or pathophysiological differences across populations has the potential to inform clinical management and improve patient outcomes, but care must be taken to avoid racism and exacerbation of health disparities. It is important to note that the associations of pPS with clinical phenotypes are currently only able to capture group-level phenotypic differences (that is, between those with high versus low scores) and are not well-powered enough for accurate prediction at the individual level. Nevertheless, insofar as pPS capture disease biology, they offer a superior alternative to other correlates of biology, such as clinician-determined race. An illustrative example is the Duffy-null genotype that causes lower white blood cell counts in people of African as compared to European genetic ancestry[10]: use of the actual causal genotype to interpret white blood cell level in a patient is more accurate and less biased than a clinician using a person's assumed or self-described race as a surrogate[11]. Likewise, preliminary evidence supports the use of pPS for personalized BMI goals for patients at risk of type 2 diabetes — rather than a reliance on assumptions related to race or ethnicity[7].

As future studies build on the findings of Hodgson et al.[6], the pathophysiological basis and clinical implications of the pPS for type 2 diabetes will be further determined. Such developments hold exciting potential for pinpointing how and why type 2 diabetes phenotypes differ across diverse populations and guiding the global delivery of precision medicine.

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Competing interests

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