Research explores impact of parental relatedness on type 2 diabetes and other common diseases

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A new study finds that consanguinity—unions between close relatives—may increase the risk of common diseases such as type 2 diabetes and post-traumatic stress disorder (PTSD).

Researchers from the Wellcome Sanger Institute and their collaborators at Queen Mary University of London analyzed the genomic data of diverse groups to investigate the relationship between autozygosity—a measure of genetic relatedness between an individual's parents—and the prevalence of common diseases, with a novel method that reduces confounding due to sociocultural factors.

They focused their analysis on the Genes & Health cohort, which consists of British individuals of Pakistani and Bangladeshi descent, as well as individuals of both European and South Asian descent from the UK Biobank.

The Genes & Health Community Advisory Board worked with the researchers to produce a publicly accessible document aimed at the lay public, explaining the study's motivations, methodology, and findings.

The findings, published in *Cell*, help shed light on the complex interplay between genetics and health outcomes, especially among populations with higher rates of consanguinity.

Consanguinity is the social and cultural practice of marriage between two blood-related individuals who share a recent common ancestor, for example a grandparent or great-grandparent. This practice is observed across the world with varying prevalence. Over 10% of the global population consists of individuals who are the offspring of second cousins or closer. In the UK, consanguinity is more common among some British South Asian communities.

Consanguinity increases the fraction of an individual's genome that is inherited identically from both parents, a phenomenon termed autozygosity. While it is well established that consanguinity increases the risk of rare single-gene disorders by increasing the chance that an individual will inherit the same rare DNA change in a disease-causing

"recessive" gene, its impact on common diseases remains understudied.

British Pakistanis and Bangladeshis have higher rates of several diseases than the UK average—for example a four-to-six-fold increased risk of developing type 2 diabetes compared to individuals of European ancestry. However, these diseases involve a complex interplay of genetic and environmental factors, and, prior to this study, it was unknown whether consanguinity plays a role.

In this new study, researchers from the Wellcome Sanger Institute and their collaborators set out to assess the impact of consanguinity on complex genetic diseases.

The teams analyzed genomic data to describe different patterns of consanguinity in distinct populations, including 23,978 British individuals of Pakistani and Bangladeshi descent from the Genes & Health cohort, and 397,184 individuals of European or South Asian descent from the UK Biobank cohort.

They found that ~33% of individuals in Genes & Health were offspring of second cousins or closer, versus 2% of individuals of European descent in UK Biobank.

They then investigated the relationship between autozygosity and the prevalence of common diseases. For this, they restricted their analysis to a set of ~5,700 individuals in Genes & Health and UK Biobank with parents who were inferred to be first cousins based on the genetic data.

Within this restricted "highly consanguineous" group, the precise level of autozygosity is randomly determined, between 4–15%, and the researchers showed that it is not correlated with sociocultural and environmental factors, such as religiosity, education or diet, which might themselves influence health traits. This novel method helped ensure any

observed links between autozygosity and diseases were biological in cause, rather than due to confounding.

Among the 61 complex genetic diseases examined in the Genes & Health and UK Biobank cohorts, researchers identified 12 diseases and disorders associated with increased autozygosity resulting from consanguinity. These included type 2 diabetes, asthma, and PTSD. The associations with type 2 diabetes and PTSD were then validated in a separate dataset from the consumer genetic company 23andMe Inc., using a between-sibling analysis technique.

Analysis suggested that consanguinity may account for approximately 10% of type 2 diabetes cases among British Pakistanis and around 3% of cases among British Bangladeshis. However, any health risks of consanguinity should be balanced with the positive social benefits of the practice as well as considered alongside other, more substantial modifiable risk factors, such as exercise, smoking and body mass index.

This research reveals important insights into the factors influencing health outcomes and the associations between autozygosity and complex diseases within British Pakistani and Bangladeshi communities. It suggests that genetic studies of complex diseases should be broadened to pinpoint specific variants and genes with recessive effects.

Daniel Malawsky, first author of the study and Ph.D. student at the Wellcome Sanger Institute, said, "While consanguinity has a smaller role in common diseases compared to other factors, it is still essential to understand its specific influence on health in these communities. Our new method exploring the natural variation in expected autozygosity among offspring of first cousins was a key breakthrough in helping us to test its impact."

"Some of our results suggested that cultural and environmental factors

associated with consanguinity can sometimes exaggerate associations between autozygosity and health-related traits, or even mask truly causal associations. Our results suggest that some findings from previous studies linking autozygosity to complex traits in humans may have been misleading."

Cllr Ahsan Khan, chair of the Genes & Health community advisory board and councilor at Waltham Forest, said, "This work underscores the significance of culturally sensitive approaches in health research, acknowledging the delicate balance between social benefits and any potential risks."

"The research team actively engaged community members, taking into account our traditions, cultures, and religious practices. By empowering people with the knowledge to make informed health decisions, we can help tackle the health disparities in our communities, especially in diseases like type 2 diabetes."

Prof Sarah Finer, author of the study, co-lead of the Genes & Health research program from Queen Mary, University of London, said, "This research would not have been possible without the many thousands of volunteers who generously agreed to participate in the Genes & Health study and UK Biobank."

Dr. Hilary Martin, senior author of the paper and group leader at the Wellcome Sanger Institute, said, "The findings have the potential to inform disease risk prediction as well as future research efforts to identify specific genetic variants associated with these diseases, not only within these specific communities but also globally, particularly across populations where consanguinity rates are higher. This could be used to help stratify individuals for earlier screening and identify potential drug targets."

Researchers conducted a within-sibling analysis using the consumer genetics company 23andMe Inc. cohort. This involved 545,806 research-consented individuals with at least one genetically-inferred full sibling also in the cohort, using self-reported phenotypes. This between-sibling analysis technique is considered gold-standard in the field for inferring causality of genetic factors.

More information: D.S. Malawsky, H.C. Martin et al., Influence of autozygosity on common disease risk across the phenotypic spectrum, *Cell* (2023). DOI: 10.1016/j.cell.2023.08.028.
www.cell.com/cell/fulltext/S0092-8674(23)00918-2

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