Genetics inMedicine | NEWS

NEWS

Diverse GWAS reveals value of multiethnic participants

KTSDESIGN/Getty

Major advances in drug development, clinical guidelines, and the biology of complex traits are thanks in large part to genome-wide association studies (GWAS). Most GWAS, however, focus on data from populations with European ancestry and miss potentially crucial variants that are specific to populations of different race/ethnicity. Such biases have critical implications for precision medicine and can intensify current disease and health-care disparities. In a recent article in *Nature* (https://doi.org/10.1038/s41586-019-1310-4) Wojcik et al. show the value of including multiethnic individuals in large genomic studies. The recent work is part of the Population Architecture using Genomics and Epidemiology (PAGE) study initiated by the National Human Genome Research Institute and the National Institute on Minority Health and Health Disparities. The study's aim is to perform genetic epidemiological research in ancestrally diverse populations in the United States. It draws on three existing population-based cohorts—the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the Women's Health Initiative (WHI), and the Multiethnic Cohort (MEC)—in addition to the Icahn School of Medicine at Mount Sinai BioMe biobank (BioMe). The researchers first genotyped nearly 50,000 individuals who self-identified as Hispanic/Latino, African American, Asian, Native Hawaiian, Native American, or "other" on the Multi-Ethnic Genotyping Array (MEGA), a platform developed to objectively capture diverse genetic variation. Wojcik and colleagues then performed genome-wide association analyses on 26 clinical and behavioral traits. Utilizing a framework optimized for investigating diverse populations, the analysis identified 27 novel loci: 16 with significant trait–variant associations and 11 low-frequency loci with suggestive associations. The study additionally found 38 secondary signals at known loci. Correlations between the risk allele genotype and principal components, such as self-identified race/ethnicity, uncovered population differences in the frequency of risk alleles. For example, one newly identified single-nucleotide polymorphism (SNP) (rs182996728) associated not only with the number of cigarettes smoked per day among smokers but also with a principal component representing Native Hawaiian/Pacific Islander ancestry. Although this variant is rare or absent in most populations, it was found in 17% of Native Hawaiian participants. Findings such as this highlight the need for including diverse groups in GWAS studies, according to the authors. The team then compared effect sizes of PAGE analyses with effect sizes from the GWAS catalog. They found that effect sizes from the PAGE study for Hispanic/Latino and African American populations were greatly reduced. The finding indicates that effect sizes at known variants differ between ancestries. The authors conclude that diverse, multiethnic studies are necessary to attenuate health disparities, and they recommend that the research community follow in the steps of the United States' All of Us Research Program, which stresses the recruitment of underrepresented populations. —*V. L. Dengler, News Editor*

Family history of intellectual disability in males may not signal X-linkage

Blackjack3D/Getty

An X-linked mode of inheritance is often assumed in families in which more than one male has intellectual disability. As a result, genetic studies in these circumstances concentrate on variants in X-linked genes. Yet, a genetic cause for the developmental disorder remains unknown in about half of affected individuals. In a recent article in *Frontiers in Genetics* (https://doi.org/10.3389/fgene.2019.00578) Sanchis-Juan et al. reveal that genetic etiologies beyond X-linkage are frequent in families with more than one male with intellectual disability. The researchers sequenced the genomes of 274 individuals with moderate to severe nonsyndromic intellectual disability from 135 nonconsanguineous families. Most families had at least two affected males, suggesting an X-linked mode of inheritance. The analysis uncovered 66 variants in 38% of participants (103/274). Three-quarters of the variants were novel. Single-nucleotide variants were the most common variant type (61%), followed by indels (27%) and copy-number variants (12%). The analysis further identified pathogenic or likely pathogenic variants in 19% (25/135) of families and variants of uncertain significance in 24% of families (33/135), for a total of reportable variants identified in 43% of families. In most cases (72%), participants from the same family reported shared variants (42/58), but in 13 families variants were reported for only one individual and in a few families (3/58) affected individuals had distinct variants. The finding is perhaps unsurprising, the authors note, since many highly penetrant genes associate with intellectual disability. However, based on the findings, the researchers advise cautious use and interpretation of American College of Medical Genetics and Genomic (ACMG) guidelines that suggest that lack of segregation in affected family members indicates benign impact. Although more than half of families reported variants in X-linked recessive genes (55%, 32/58), 22 families (38%) had variants in autosomal genes and 4 families (7%) had multiple variants with different modes of inheritance. When Sanchis-Juan and colleagues examined the variants in autosomal genes, they found 15 genes acting in a dominant manner whereas 7 showed recessive effects. The findings corroborate previous evidence that intellectual disability is not often recessive in outbred populations. The results further highlight that autosomal inheritance as well as discrete variants between family members may underlie disorders that appear initially to have an X-linked mode of inheritance. Altogether, the findings emphasize the importance of distinguishing X-linkage from other modes of inheritance to provide the best clinical management for families as well as offer the most accurate risk assessments, according to the researchers. The authors conclude that more extensive genetic testing is warranted in families in which X-linked inheritance is possible when causation has not been proven. —*V. L. Dengler, News Editor*