Medical Xpress

Genomic study revealing among diverse populations with inherited retinal disease

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An international team of researchers, led by scientists at University of California San Diego and Shiley Eye Institute at UC San Diego Health, has broadened and deepened understanding of how inherited retinal

dystrophies (IRDs) affect different populations of people, and in the process, have identified new gene variants that may cause the diseases.

The findings published in the October 18, 2021 issue of *PLOS Genetics*.

IRDs are a group of diseases, from retinitis pigmentosa to choroideremia , that result in progressive vision loss, even blindness. Each IRD is caused by at least one gene mutation, though mutations in the same gene may lead to different IRD diagnoses.

IRDs are rare, but they affect individuals of all ages, progressing at different rates, even within families afflicted with the same disease. Specific diagnosis depends on finding the genetic causative mutations.

The U.S. Food and Drug Administration has approved gene therapy for treating one form of IRD involving the gene RPE65, but for other IRDs caused by mutations in more than 280 different genes, there are no cures or treatments proven to slow disease progression.

The researchers conducted whole-genome sequences (WGS) of 409 persons from 108 unrelated family lineages, each with a previously diagnosed IRD. WGS is a process of determining the entirety, or near-entirety, of the DNA sequence of an individual. It provides a comprehensive portrait of the person's entire genome, including mutations and variants, which can be used for broad comparative purposes.

Study participants were recruited from three different geographic regions: Mexico, Pakistan and European Americans living in the United States. Genomic analyses were conducted from blood samples taken from all participants, which revealed causative variants in 62 of the 108 lineages. A total of 94 gene variants were found in the 62 families: 52 variants had previously been identified as causative and 42 had not.

Surprisingly, more than half of the new variants were not listed in the Genome Aggregation Database, an international compilation of genomic data.

Overall, causative variants were detected in 63 percent of Mexican participants, 60 percent of Pakistani, and 48 percent of European American.

The study also identified a large proportion of new IRD causative mutations specific to the populations studied and revealed the types of mutations contributing to inherited retinal dystrophies. Approximately 13 percent of the families displayed atypical or unexpected changes in the genome. Five of the family lineages had mutations in more than one gene in all affected individuals; one family carried mutations in different genes in different affected members and a de novo mutation was found in one patient that was not present in both parents.

An additional 8 percent of families had large changes in the structure of their genome causing the inherited retinal disease and the initial clinical diagnosis in four families was re-classified based on their genotype.

The authors said the new findings boost understanding of the distribution of IRD causative mutations in these three diverse populations, which will further understanding of disease variation and presentation. That, in turn, will help design more efficient genetic testing strategies and therapies applicable to global populations.

More information: Pooja Biswas et al, Deciphering the genetic architecture and ethnographic distribution of IRD in three ethnic populations by whole genome sequence analysis, *PLOS Genetics* (2021). DOI: 10.1371/journal.pgen.1009848