Whole DNA sequencing reveals mutations, new gene for blinding disease

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Retinitis pigmentosa (RP) is a genetic disease that causes progressive loss of vision and is caused by mutations in more than 50 genes. Conventional methods for identification of both RP mutations and novel RP genes involve the screening of DNA coding sequences.

In a paper in the *Proceedings of the National Academy of Sciences*, researchers from the Massachusetts Eye and Ear, Harvard Medical School, the University of Lausanne, Switzerland, and others tested DNA with the use of whole genome sequencing, a technique that takes into account all variants from both the coding and noncoding regions of the human genome. With this approach the authors report a number of unique RP mutations, a previously undescribed disease gene called NEK2 that involves the retinal photoreceptors, and structural DNA rearrangements originating in introns.

This paper supports the advantages of the use of whole genome sequencing to search for mutations in patients with RP.

The researchers performed whole genome sequencing in 16 unrelated patients with autosomal recessive retinitis pigmentosa (ARRP), a disease characterized by progressive retinal degeneration and caused by mutations in over 50 genes, in search of pathogenic DNA variants, the authors wrote. Eight patients were from North America, whereas eight were Japanese, a population for which ARRP seems to have different genetic drivers.

Using a specific work flow, they assessed both the coding and noncoding regions of the human genome, including the evaluation of highly polymorphic SNPs, structural and copy number variations, as well as 69 control genomes sequenced by the same procedures. They detected homozygous or compound het erozygous mutations in 7 genes associated with ARRP (USH2A, RDH12, CNGB1, EYS, PDE6B, DFNB31, and CERKL) in eight patients, three Japanese and five Americans. Fourteen of the 16 mutant alleles identified were previously unknown. Among these, there was a 2.3-kb deletion in USH2A and an inverted duplication of 446 kb in EYS, which would have likely escaped conventional screening techniques or exome sequencing.

Moreover, in another Japanese patient, they identified a homozygous frameshift (p.L206fs), absent in more than 2,500 chromosomes from ethnically matched controls, in the ciliary gene NEK2, encoding a serine/threonine-protein kinase. Inactivation of this gene in zebrafish induced retinal photoreceptor defects that were rescued by human NEK2mRNA.

In addition to identifying a previously undescribed ARRP gene, the study highlights the importance of rare structural DNA variations in Mendelian diseases and advocates the need for screening approaches that transcend the analysis of the coding sequences of the human genome.

More information: Whole genome sequencing in patients with retinitis pigmentosa reveals pathogenic DNA structural changes and NEK2 as a new disease gene, www.pnas.org/cgi/doi/10.1073/pnas.1308243110

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