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Genomics transforming diagnosis of inherited eye disorders

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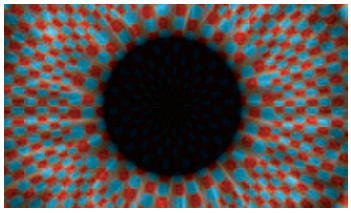

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Until recently, clinicians faced with a difficult case of suspected congenital eye disease had limited diagnostic options. Visual-field testing can document progressive photoreceptor loss, but an understanding of the underlying cause of vision loss remained elusive. Today, modern genomics offers a panoply of individual genetic tests and broader genomic panels that provide many more diagnostic options for clinicians and patients. Indeed, few medical specialties have benefited more directly from the recent revolution in genomic technology than ophthalmology. Massively parallel sequencing has now been demonstrated to be a potent tool for diagnosing inherited eye disease, and the delineation of mutations that underlie diagnosis is becoming even more relevant owing to dramatic advances in gene therapy for such disorders.

In this themed issue, we present a cross-section of studies across a range of research in ophthalmic genetics. A review by Kristy Lee and Seema Garg of the University of North Carolina, Chapel Hill, provides a guide to navigating current clinical genetic testing options for detecting inherited retinal dystrophies. Over the past 25 years, more than 200 genes contributing to inherited retinal dystrophies have been identified, as the authors point out. One of the most widely distributed of these related disorders, retinitis pigmentosa (RP), represents not one but a group of inherited disorders of the eye's photoreceptors, each of which can lead to progressive vision loss. RP affects 1 in 4,000 people worldwide. Numerous genomic regions can harbor genes linked to RP, and the pattern of inheritance may be autosomal dominant, autosomal recessive, or X linked, making it difficult to pinpoint a genetic cause. However, next-generation genomic panels can now provide an accurate diagnosis in many more cases. Commercially available panels include more than 100 genes known to be associated with syndromic and nonsyndromic retinal dystrophies. As the authors state, the advent of genomic testing for retinal disorders offers information to allow risk assessment for patients and their family members and to determine eligibility for inclusion in gene-based clinical trials.

Topics addressed by original research articles in this issue include unexpected diagnostic revisions made after comprehensive genomic analysis of patients with Stargardt macular dystrophy, the reproducibility of panel-based diagnostic testing for inherited eye diseases, and novel variants identified by whole-mitochondrial genome sequencing in primary open-angle glaucoma.

—Jim Evans, Editor-in-Chief, and Karyn Hede, News Editor

NEWS BRIEFS

Genomic cause of mysterious syndrome identified

An online crowdfunding effort has finally answered a family's pleas for help in determining why their young child has succumbed to a mysterious degenerative neurological syndrome involving involuntary eye movements, microcephaly, involuntary muscle contraction, developmental delay, and progressive neurological decline. The affected three-year-old girl and her parents underwent whole-exome sequencing to identify the genetic cause of the disease after other medical tests provided no answers. The genomic testing revealed a novel mutation in the tubulin β4A class IVa gene (*TUBB4A*) that causes mental retardation and severe developmental delays. The research team, led by Noam Shomron of Tel Aviv University, Israel, describes the novel crowdfunding mechanism used to support the research in a research article published in the *Journal of Genetics and Genomics*. Shomron is among many investigators worldwide who have set up a funding mechanism for families interested in pursuing personalized research projects for rare genetic diseases through the Rare Genomics Institute (http://www.raregenomics.org). "Crowdfunding provides the means for economically disadvantaged patients to pursue a genetic diagnosis for their ailment," stated Shomron in a news release issued by Tel Aviv University. "Our project reached its financial goal of $5,000 within 50 days. We were pleased, to say the least. Crowdfunding is a simple and efficient solution for families with rare genetic diseases who lack private or outside funding sources." *—Karyn Hede, News Editor*

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Another novel gene mutation found for RP

A genomic study involving an extended six-generation Louisiana family with impaired vision has revealed a new gene mutation that can lead to retinitis pigmentosa (RP), the underlying cause of progressive vision loss in millions of people worldwide. The recent study, published in the journal *Investigative Ophthalmology & Visual Science*, found that a mutation in the gene hexokinase 1 (*HK1*) leads to the condition and is inherited through an autosomal dominant mechanism. One family member was found to carry two copies of the mutant gene and had a severe form of RP. Lead author Stephen Daiger, a member of the Human Genetics Center at The University of Texas Health Science Center at Houston, used a combination of strategies, including

NEWS BRIEFS *(continued)*

candidate-gene screening, genome-wide linkage mapping, and whole-genome sequencing to identify the coding mutation, an amino acid change, Glu847Lys. The HK1 protein normally acts as an enzyme, converting the sugar glucose to a modified form. The researchers suggest that the effect of this mutation is limited to the retina, as patients exhibit no other physical abnormalities. Further study revealed that the mutation is also present in four other families, from the United States, Canada, and Italy. They speculate that the mutation arose in a common ancestor who lived centuries ago. *—Karyn Hede, News Editor*