NEWS

Gene therapy for genetic blindness proves safe and effective in clinical trial

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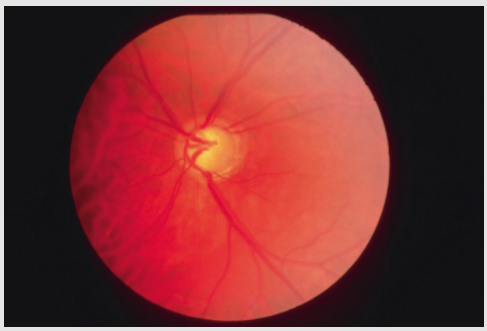
The genetic eye disease known as Leber congenital amaurosis (LCA) is a group of conditions that lead to childhood blindness. Variants in more than 25 genes lead to LCA. Clinical trials for two subtypes have shown that gene-based therapies are safe and effective. However, clinical trial results for a third remaining subtype have not yet been reported. Variants in *GUCY2D*, a gene that encodes for retinal guanylyl cyclase isoenzyme-1 (RetGC1), result in the third subtype. *GUCY2D*-LCA variants lead to an insufficient rate of cyclic guanosine 3′,5′-cyclic monophosphate (cGMP) production that is incapable of maintaining normal photocurrent in rods and cones. In a study recently published in the journal *iScience* (https://doi.org/10.1016/j.isci.2021.102409), Jacobson and colleagues report early results from the first-in-human clinical trial of gene therapy for *GUCY2D*-LCA. As part of an ongoing nonrandomized phase I/II single center, open-label safety and efficacy trial (ClinicalTrials.gov Identifier: NCT03920007), the researchers administered uniocular subretinal injections of a recombinant adeno-associated virus serotype 5-*GUCY2D* (rAAV5-*GUCY2D*) gene therapy vector in three LCA patients with biallelic *GUCY2D* variants. All patients received the lowest dose planned for the trial and are compound heterozygotes for disease-causing *GUCY2D* variants. Before receiving treatment, patients had poor visual acuity and reduced rod photoreceptor–mediated sensitivities, but intact retinal structure. In vitro analyses revealed that *GUCY2D* variant alleles in two patients encoded inactive enzymes, whereas trace guanylyl cyclase activity was detectable in the third patient. Patients were monitored for 9 months following therapy administration. Following treatment, patients showed no change from baseline on physical examination and the researchers did not detect routine clinical laboratory abnormalities. Patients experienced ocular adverse events from the injection surgery, such as discomfort and reduced intraocular pressure, but all resolved. Although all patients showed abnormally reduced field stimulus test sensitivities in treated eyes directly after surgery, patients 1 and 2 regained baseline levels within 30 to 60 days and patient 3 showed improvement beyond baseline. Rod photoreceptor–mediated vision improved in the treated eye over the course of study for patients 1 and 2, while patient 3 showed cone photoreceptor–mediated improvement as well as a bump in visual acuity. Altogether, the researchers conclude that the results demonstrate both safety and preliminary evidence of rod-and-cone-mediated efficacy for subretinal *GUCY2D*-LCA gene therapy. —*V. L. Dengler, News Editor*

CYP39A1 variants associated with exfoliation syndrome, a leading cause of glaucoma



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More than 3 million Americans likely have glaucoma, although only half know it. The disease is the second leading cause of blindness worldwide, and many cases are the result of exfoliation syndrome (XFS), a systemic condition wherein abnormal fibrillar protein aggregates progressively accumulate in the anterior chamber of the eye. The aggregates block drainage of the aqueous humor and cause intraocular pressure to increase, leading to glaucoma. In a recent study published in the *Journal of the American Medical Association* (https://doi.org/10.1001/jama.2021.0507), the Genetics of Exfoliation Syndrome Partnership assessed whether rare, coding-sequence variants are related to XFS pathogenesis. The researchers conducted a case–control, exome sequencing study that included more than 20,000 participants from 14 countries. The team enrolled about 9,500 participants in a discovery cohort, around 4,000 of whom had XFS. Sequencing analysis identified nearly 416,000 rare variants predicted to impair protein function across more than 18,000 genes. Two genes —*LOXL1* and *CYP39A1*—were significantly associated with XFS. Rare variants that bestowed protection against XFS drove the association with *LOXL1*, whereas participants with XFS were significantly more likely to carry damaging *CYP39A1* variants than participants without the condition. The researchers then repeated the analysis in two independent validation cohorts comprising about 5,000 participants each and found that individuals with XFS were again more likely to carry damaging *CYP39A1* variants than those without XFS. Confirmatory sequencing of the 130 *CYP39A1* rare variant carriers displayed complete concordance with the rare variant calls from the exome sequencing analysis. CYP39A1 is an enzyme that metabolizes 24(S)-hydroxycholesterol. Deficient CYP39A1 may lead to excess cholesterol accumulation in extracellular aggregates, a hallmark of XFS. Post hoc analysis of all study participants identified nearly 500 individuals carrying 42 unique *CYP39A1* rare variants predicted to be damaging. Biochemical analyses revealed that 34 of the 42 damaging *CYP39A1* variants substantially reduced enzymatic activity compared with wild type. Follow up experiments showed consistent downregulation of *CYP39A1* gene expression across affected versus unaffected eye tissues. Immunohistochemical analysis corroborated these results by exhibiting reduced CYP39A1 immunostaining in the ciliary epithelium and retina of XFS syndrome patients compared with those without XFS. The authors conclude that XFS is significantly associated with sequence variants leading to functionally deficient *CYP39A1*. They suggest that restoring impaired *CYP39A1* function could be a viable approach to treatment. —*V. L. Dengler, News Editor*

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