Medical Xpress

Researchers discover elusive gene that causes Leber congenital amaurosis

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Researchers from the Massachusetts Eye and Ear Infirmary, The Children's Hospital of Philadelphia, Loyola University Chicago Health Sciences Division and their collaborators have isolated an elusive human gene that causes a common form of Leber congenital amaurosis (LCA), a relatively rare but devastating form of early-onset blindness. The new LCA gene is called NMNAT1. Finding the specific gene mutated in patients with LCA is the first step towards developing sight-saving gene therapy.

LCA is an inherited retinal degenerative disease characterized by reduced vision in infancy. Within the first few months of life, parents usually notice a lack of visual responsiveness and unusual roving eye movements known as nystagmus. LCA typically involves only vision problems, but can be accompanied by disease in other organ systems in a minority of patients. LCA is a common reason children are enrolled in schools for the blind.

"The immediate benefit of this discovery is that affected patients with mutations in this new LCA gene now know the cause of their condition," said Eric Pierce, M.D., Ph.D., co-senior author and director of the Ocular Genomics Institute at Mass. Eye and Ear. "Scientists now have another piece to the puzzle as to why some children are born with LCA and decreased vision. The long-term goal of our research is to develop therapies to limit or prevent vision loss from these disorders."

NMNAT1 is the 18th identified LCA gene. The gene resides in a region

that was known to harbor an LCA gene since 2003, but the specific disease gene has been undiscovered until now. These findings will be published on July 29 in the online edition of Nature Genetics.

To identify NMNAT1, scientists performed whole exome sequencing of the family of two siblings who initially presented for evaluation of LCA but who had no mutations in any of the known LCA genes. Being seen by a multi-disciplinary team that took the case from careful clinical characterization to genetic testing to the research laboratory was an essential ingredient for success.

"By using whole exome sequencing, we found a mutation in a gene that no one could have predicted would be associated with LCA," said Dr. Pierce.

"Whereas most of the known LCA genes involve dysfunction of retinal ciliary proteins necessary for light detection in the eye, NMNAT1 is uniquely distinguished by being the first metabolic enzyme linked to LCA," said Marni J. Falk, M.D., co-first author and Clinical Geneticist at The Children's Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine.

Having found a mutation in NMNAT1 in this one family, the investigators next asked if mutations in NMNAT1 also cause disease in other patients with LCA. Screening of 284 unrelated patients with LCA from the United States, England, France and India allowed them to identify 13 other patients with mutations in NMNAT1 as the cause of their disease.

Drs. Falk, Pierce and colleagues also studied how the identified mutations in NMNAT1 affect the function of the NMNAT1 protein, and thus may cause dysfunction and death of the light sensitive photoreceptor cells in the retina. Working together with Eiko Nakamaru-

Ogiso, Ph.D., in the Department of Biochemistry and Biophysics at The University of Pennsylvania, they found that mutations in NMNAT1 appear to decrease the ability of the NMNAT1 protein to produce NAD+, a key mediator of cellular signaling and energetics.

Early treatment for patients with NMNAT1-related LCA could be especially beneficial.

Researchers found that all but the youngest patient with NMNAT1 mutations had damage to the macula, the center of the retina that is needed for central vision. "This 4-year-old girl who doesn't have central vision loss yet can possibly benefit substantially if we can devise a therapy for her NMNAT1-mediated LCA that prevents her from developing severe central vision loss," Dr. Pierce said.

This study is an example of the multidisciplinary collaboration among the three institutions, using exome sequencing to discover genes involved in inherited diseases caused by mutations of a single gene. "With the robust database and pipeline that we have developed, we have analyzed more than 300 whole exomes of patients and families with single-gene diseases," said Dr. Xiaowu Gai, co-senior author and director of the Center for Biomedical Informatics at Loyola University Chicago Stritch School of Medicine. "We are following up on a number of strong candidate genes. We are sequencing many new samples and expect similar exciting discoveries for other diseases."

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