MedicalXpress

A first step toward cracking the genetics of strabismus

September 6 2018

Strabismus is a common condition in which the eyes do not align properly, turning inward, outward, upward or downward. Two to four percent of children have some form of it. Some cases can be treated with glasses or eye patching; other cases require eye muscle surgery. But the treatments don't address the root causes of strabismus, which experts believe is neurologic.

For decades, Elizabeth Engle, MD, in Boston Children's Hospital's F.M. Kirby Neurobiology Center, has been studying rare forms of strabismus, such as Duane syndrome, in which strabismus is caused by limited eye movements. Her lab has identified a variety of genes that, when mutated, disrupt the development of cranial nerves that innervate the eye muscles. These genetic findings have led to many insights about motor neurons and how they develop and grow.

More recently, with postdoctoral research fellow Sherin Shabaan, MD, Ph.D., Engle's lab has been gathering families with common, non-paralytic strabismus, in which both eyes have a full, normal range of motion yet do not line up properly in any gaze direction.

Such "garden variety" forms of strabismus have been much harder to pin down genetically. While they clearly run in families, they don't follow predictable Mendelian dominant or recessive patterns of inheritance. Instead, they likely result from variations in multiple genes acting together.

Focusing on esotropia

Engle, Shabaan and colleagues decided to look specifically at esotropia, in which the eyes turn inward, making children appear cross-eyed. They enrolled about 1,200 U.S. patients of white European ancestry, most seen at Boston Children's. But even with careful exams of patients and their parents, it was difficult to establish clear inheritance patterns.

"Even within a family, a mom can have esotropia, and the child has exotropia [in which the eyes turn outward]," says Mary Whitman, MD, Ph.D., an ophthalmologist who joined the project. "Or grandma can have exotropia and the kid has esotropia. Or the mom remembers that 'there was something wrong with grandma's eyes.' Or you may have had eye surgery when you were 3 years old, but don't remember why."

Ultimately, the researchers further narrowed their investigation to 826 patients with "non-accommodative" esotropia, which cannot be corrected with glasses.

"Despite being so common in the general population, the causes of non-accommodative forms of strabismus remain undefined," notes Engle.

They decided to conduct a genome-wide association study (GWAS) - the first ever used to investigate esotropia.

GWAS, a technique that emerged about 15 years ago, searches across the genomes of large populations, using known genetic markers known as SNPs. It can be helpful in finding genetic variants that influence common, multi-gene traits like height, obesity, diabetes and hypertension. The identified genes can offer clues about the biology of the trait or disorder.

"We did not achieve the large number of participants that you typically

need for a successful GWAS," says Engle. "But we had a very well-phenotyped cohort, so we decided to move forward."

Scratching the surface

Their findings, published last month in *Investigative Ophthalmology & Visual Science*, were interesting but—not surprisingly, given the small number of participants—a little disappointing.

"Normally with GWAS, you get tens to hundreds of hits," says Whitman. "We got one."

Their "hit," validated in a second cohort of 689 patients from the U.K. and Australia, was in an intron of a gene called WRB—a non-coding bit of DNA that alters WRB's level of expression, or how frequently it's turned on.

Notably, WRB is an "imprinted" gene, meaning that its expression varies depending on which parent it came from. In the study, patients with strabismus were more likely to have inherited the genetic variant from their father. Also, WRB is on chromosome 21, and children with trisomy 21 (commonly known as Down syndrome) have a higher incidence of strabismus, an intriguing connection.

The bigger disappointment was that the discovery didn't shed any immediate light on how strabismus develops. WRB is known to be involved in the processing of proteins, a "housekeeping" job critical to the function of all cells. While many of the genes Engle found in the past act in specific brain regions, WRB is expressed pretty much throughout the body.

"It remains difficult to say how it's contributing to strabismus," says Engle.

Collaborator David Hunter, MD, Ph.D., chief of ophthalmology at Boston Children's, has a different take on the results. "These findings represent more than 10 years of hard work rounding up families, conducting careful examinations and collecting samples," he says. "At long last we have an established a genetic association with strabismus more definitive than anyone has ever been able to demonstrate. We may be poised to learn something very unexpected and very important about the elusive cause of this common condition."

The search continues

To extend their findings, Engle and her colleagues are reaching out internationally, hoping to identify new cohorts of strabismus patients. This would increase the statistical power of GWAS analyses and hopefully yield further genetic associations.

"This study is a stake in the ground," says Engle. "Eventually, we hope to be able to sculpt a picture of pathways that may influence your susceptibility to strabismus."

"Considering how common strabismus is, it's surprising that we know nothing about it genetically," adds Whitman. "If we find genetic causes, we can compare how people with different genetic causes respond to different treatments. Surgery is successful in about 85 percent of patients, but some patients require multiple surgeries. If we figured out what was causing the strabismus, it could open up new options for treating it."

More information: Sherin Shaaban et al, Genome-Wide Association Study Identifies a Susceptibility Locus for Comitant Esotropia and Suggests a Parent-of-Origin Effect, *Investigative Opthalmology & Visual Science* (2018). DOI: 10.1167/iovs.18-24082

Provided by Children's Hospital Boston

Citation: A first step toward cracking the genetics of strabismus (2018, September 6) retrieved 23 May 2024 from https://medicalxpress.com/news/2018-09-genetics-strabismus.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.