Genetic variants found in two types of strabismus, sparking hope for future treatment of eye condition

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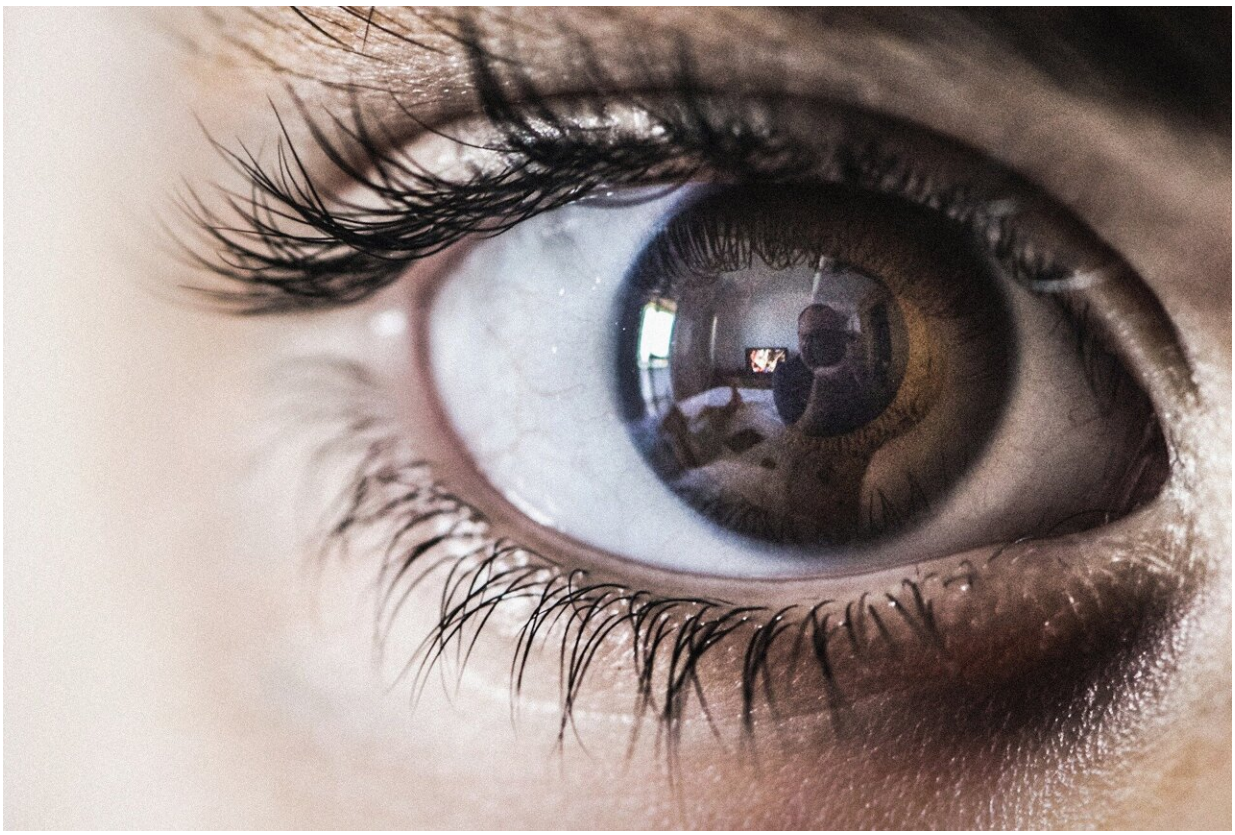

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Determining how genetics contribute to common forms of strabismus has been a challenge for researchers. Small discoveries are considered

meaningful progress.

Boston Children's researchers believe they've helped move the needle. They discovered that two types of strabismus—esotropia and exotropia—may have shared genetic risk factors. Duplications on the second, fourth, and tenth chromosomes that were present in patients with esotropia were also found in patients with exotropia.

"Our long-term goal is to identify the underlying pathophysiology so that we can develop treatments that address strabismus," says Mary Whitman, MD, Ph.D., a Boston Children's ophthalmologist and the principal investigator of the study. "This finding implies that those treatments might work for both esotropia and exotropia, if they share underlying causes."

Chromosomal duplications for esotropia also found in exotropia

Strabismus affects as much as 4% of the population. Several environmental risk factors—including prematurity, low birth weight, smoking during pregnancy—have been connected to common horizontal strabismus: eyes turning inward (esotropia) or outward (exotropia). Still, even after considering those environmental factors, genetics play a substantial role, Whitman says.

To get a better understanding of that role, Whitman and researchers from Boston Children's departments of Ophthalmology and Neurology and Howard Hughes Medical Institute worked off a previous Boston Children's study that had identified three recurrent genetic duplications that increased the risk of esotropia in white patients. They wanted to see if the variants in those three chromosomes were specifically associated with esotropia or if they connected more broadly to strabismus.

They studied genetic samples from 234 patients who had been recruited for research over an 18-year span. The patients had exotropia, while their family members either had or didn't have strabismus. Also, unlike the previous study, participants self-identified across a wide range of race and ethnicity categories. The researchers presented their findings about the possibility of shared genetic risk factors in an article published in *JAMA Ophthalmology*.

There are still unanswered questions: It is possible that esotropia or exotropia develop by other shared genetic variants or independent ones? What is the role of environmental factors? But the new findings nonetheless give ophthalmologists hope they're moving in the right direction.

"When we started looking at this, we thought maybe we'd find a specific gene is deleted and that will tell us the gene is important," Whitman recalls. "But that's not what we found. We found these regions that are duplicated, and we think it probably affects gene regulation."

Now, work begins to understand contributions to strabismus

Whitman and the researchers have since introduced the chromosomal variants into pluripotent stem cells. They're differentiating those cells into neurons and looking for changes in neuronal structure and function, as well as gene expression and chromatin rearrangement, to understand how the variants contribute to strabismus.

The study's findings aren't enough to yet help in the creation of specific treatments for strabismus, but they have researchers thinking about possibilities, Whitman says. "The benefit of genetics is we may be able to someday identify people at risk before they develop strabismus. We

could potentially even prevent it, if we knew who to target and were able to give them a treatment."

More information: Mayra Martinez Sanchez et al, Presence of Copy Number Variants Associated With Esotropia in Patients With Exotropia, *JAMA Ophthalmology* (2024). DOI: 10.1001/jamaophthalmol.2023.6782

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