

# Research reveals biological mechanism of a leading cause of childhood blindness

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Konark Mukherjee led a research team that has unveiled the pathology underlying optic nerve hypoplasia, a leading cause of childhood blindness. Credit: David Hungate, Virginia Tech Carilion Research Institute

Scientists at the Virginia Tech Carilion Research Institute (VTCRI) have revealed the pathology of cells and structures stricken by optic nerve hypoplasia, a leading cause of childhood blindness in developed nations.

The discovery in a rodent model may provide insight into what happens in the visual systems of children born with a condition that prevents the [optic nerve](#) from fully developing. The condition is also associated with [autism spectrum disorder](#).

"Although clinicians have known about optic nerve hypoplasia for some time, the nature of the pathology was not clearly understood," said Konark Mukherjee, an assistant professor at the Virginia Tech Carilion Research Institute. "In people, the disorder is diagnosed using visualization of the retina within the patient's eye with ophthalmoscopy or imaging with a MRI scan. Those tests don't give us the details we need to understand the nature of the pathology at the cellular level, so we modeled the disease to perform a systematic analysis of the optic nerve, from its origin in the eyes to termination in the brain."

The researchers published their results in *Investigative Ophthalmology and Visual Science*, a journal of the Association for Research in Vision and Ophthalmology.

Optic nerve hypoplasia is closely related to optic nerve atrophy, in which the optic nerve develops normally initially, but later degenerates as its cells die off. The two disorders can be difficult to differentiate since the diagnosis is made after the onset of disease.

"The name of the disease depends on the time of diagnosis," said Mukherjee, who is also an assistant professor of biological sciences in Virginia Tech's College of Science. "There has always been this question of whether optic nerve hypoplasia occurred during development or if the visual system degenerated after the normal course of development. We can see the optic nerve is smaller than it should be, but did it start out normally and degrade or did it never develop properly in the first place? We had to develop a model to examine the optic nerve at different points in time."

In the clinic, a test is conducted to see a patient's entire retina, including the optic nerve. It appears as a small, lightly colored spot from which blood vessels spread around the eye's retina. The spot is called the [optic disc](#), and the size of it indicates health or disease - either optic nerve hypoplasia or atrophy.

Mukherjee, along with Michael Fox, an associate professor at the VTCRI and director of the VTCRI Developmental and Translational Neurobiology Center, engineered a mouse model missing a gene called CASK.

Relatively little is known about CASK, which is critical for brain growth during development and especially in early infancy. Children without the CASK gene develop microcephaly and intellectual disabilities. They also have severe visual impairment—the result of an underdeveloped optic nerve.

CASK helps provide architectural support and bridge the synapses that neurons need to communicate within the retina and brain. A healthy optic nerve has axons transmitting information from the eye to the brain along the nerve after considerable information processing and synaptic transmission between various cell types within the retina. An abnormal optic nerve is much smaller, limiting and sometimes completely eliminating the connections—and the transmission of information—between the eye and the brain.

"In a mouse, the optic nerve looks normal at birth, which is the equivalent of the third trimester of neonatal human development," said Fox. "The optic nerve starts to show a reduced diameter right before eye opening, which is right before birth in humans."

While the researchers caution that mice and humans are different, the mouse model indicates that optic nerve hypoplasia is related to the

CASK molecule.

"We looked at the optic [nerve](#) and saw normal myelination," Mukherjee said, referring to the fatty white sheathing wrapped around axons, the [nerve fibers](#) that allow information transmission over distances to proceed efficiently and rapidly.

If the axons had died off, there'd be decreased myelin, as well as lesions marking where axons had been. There weren't any lesions.

"That means something happens during development," Fox said. "We might be able to deliver CASK back into cells to prevent axonal loss, or maybe rescue what was already lost."

**More information:** Chen Liang et al, Optic Nerve Hypoplasia Is a Pervasive Subcortical Pathology of Visual System in Neonates, *Investigative Ophthalmology & Visual Science* (2017). [DOI: 10.1167/iovs.17-22399](#)

Provided by Virginia Tech

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