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Gene Mutation Exacerbates Eye Defect in Inherited Glaucoma

While studying mice with a mutant gene whose counterpart causes inherited glaucoma in humans, researchers have discovered a second gene mutation that worsens the structural eye defect that causes this type of glaucoma.

The newly discovered gene mutation affects production of L-DOPA. The researchers suggest that it might be feasible to prevent glaucoma by administering L-DOPA, which is used in treating Parkinson's disease.

The researchers, led by Howard Hughes Medical Institute investigator [Simon W. M. John](#) at The Jackson Laboratory, reported their findings in the March 7, 2003, issue of the journal *Science*. John's colleagues included Richard Libby and Richard Smith of The Jackson Laboratory, and Frank Gonzalez of the National Cancer Institute.

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- **Simon W. M. John**

In their studies in mice, the researchers explored how the absence of the gene that encodes the protein Cyp1b1—the same defect that occurs in humans with primary congenital glaucoma (PCG)—affects development of glaucoma. In examining the mice, the scientists found malformations of ocular drainage structures that normally control pressure as the liquid aqueous humor flows out of the eyeball. These eye abnormalities are known as anterior segment dysgenesis.

According to Smith, who has treated patients with PCG, the ability to pinpoint the abnormalities in mice will most likely advance understanding of how the disease develops in humans. "The frustrating thing about attempting to understand human PCG is that there have been very few cases reported in which the patients haven't already had glaucoma for many years and been

subjected to surgery and multiple medications,” said Smith. “So, by the time we can examine the human tissue, the anatomic defect is very difficult to determine.”

According to John, these anatomic abnormalities are an underlying cause of the severe glaucoma that affects people with PCG. Although the disorder is relatively uncommon—occurring in about one in 10,000 births in the United States—it can cause devastating consequences, he said.

“If you have abnormalities or decreased functioning of the drainage structures, the input of aqueous humor can result in increased intraocular pressure and the very nasty glaucoma that human infants suffer,” he said. “This can be a painful condition with pressures high enough to tear the cornea and risk loss of vision.”

One puzzle confronting researchers, said John, is that some infants with the inherited condition can suffer serious glaucoma, while others either show delayed effects or none at all. “So, although it is not widely accepted, we believed that there could be multiple genetic and/or environmental factors that could affect the course of the disease,” he said. Such factors could interact with one another to compromise the intricate drainage structures to a greater degree in some cases than in others, said John.

A clue to one possible genetic factor arose from observations that albino mice lacking *Cyp1b1* appeared to show worse pathology than pigmented mice. A series of genetic crosses of various mice by Libby and his colleagues produced strains of mice whose only difference was the presence or absence of pigmentation. The researchers ultimately pinpointed the key modifier of severity of glaucoma, showing that in the *Cyp1b1*-negative mice it hinged on the status of the gene that encodes the enzyme tyrosinase. The tyrosinase enzyme is involved in the pigmentation process as a key catalyst for converting the amino acid tyrosine to a precursor pigment molecule, L-DOPA.

The researchers also explored how mutations in the gene for tyrosinase affected mice lacking the *FOXC1* gene, which also causes PCG and other forms of glaucoma in humans. They found that the tyrosinase-deficient *FOXC1* mice also showed more severe abnormalities in their ocular drainage system.

To determine whether administering L-DOPA might alleviate these defects, the researchers administered the chemical to the drinking water of pregnant mice lacking both *Cyp1b1* and tyrosinase. They found that the treatment prevented the severe abnormalities in pups born to the mice who had been fed L-DOPA.

John noted that another enzyme, tyrosine hydroxylase, is also involved in L-DOPA production, suggesting yet another biochemical pathway affecting anterior segment development in the eye and severity of PCG.

“Together, these findings open a new avenue for investigating the role of L-DOPA in anterior segment development and glaucoma caused by various genes,” said John. “Furthermore, identifying L-DOPA as a key molecule may link the functions of many of the known genes that cause anterior segment dysgenesis and glaucoma,” he said. “Most of these known genes can affect tyrosine hydroxylase in the neural crest cells, from which the relevant anterior segment structures derive. Therefore, our work provides a conceptual linkage for anterior segment developmental disorders caused by different genes, and it provides an important framework for future experiments.”

While the researchers note that L-DOPA is already used to treat symptoms of Parkinson's disease, they are cautious about recommending its use in treating glaucoma. “L-DOPA is a molecule that affects the nervous system, and we need to proceed very carefully with further animal and human studies before we will know whether such a treatment can become a clinical reality,” said John.

It may be the case, said John, that drugs that enhance the enzyme tyrosinase itself—and not administration of L-DOPA—that will be more useful as therapeutics. “We are very excited because these findings open up a new avenue for research on these disorders,” he said.