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## Research on Inherited Eye Disorders Uncovers New Information About Blood-Vessel Formation

Researchers have discovered that genetic mutations underlying two inherited eye disorders arise in different components of a single intracellular signaling pathway that is responsible for development of blood vessels in the eye.

Understanding more about how this pathway functions could provide useful information for the development of drugs to treat the two diseases. That information might also aid in understanding retinal blood vessel disorders associated with diabetes, macular degeneration, and premature birth.

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— **Jeremy Nathans**

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Howard Hughes Medical Institute (HHMI) investigator Jeremy Nathans at The Johns Hopkins University School of Medicine led the research team, which published its findings in the March 19, 2004, issue of the journal *Cell*. Co-lead authors of the article were HHMI associate Qiang Xu and HHMI research specialist Yanshu Wang. Other authors are from the National Institute on Deafness and Other Communication Disorders, the University of Utah, and the Wills Eye Hospital in Philadelphia.

The researchers studied two inherited disorders, Norrie disease and familial exudative vitreoretinopathy (FEVR), whose underlying genetic defects were already known, but whose mechanistic relationship was not. Norrie disease, caused by a defect in the gene for the protein Norrin, produces congenital blindness and a progressive deafness due to blood vessel malformation in the inner ear. "Almost certainly the sequence of events within the eye is that there is a problem in vascular development, a compensatory growth of blood vessels, and a leakiness in those blood vessels that leads to scarring and ultimately blindness," said Nathans. The function of the Norrin protein was unknown before this new work, he said.

The second disorder the researchers studied, FEVR, “tends to be milder and with a range of severity all the way from a modest abnormality of vasculature that does not impair vision at all to a severity of scarring that eliminates vision completely,” said Nathans. FEVR is known to arise from defects in a gene known as *Frizzled-4*, which codes for a protein receptor (Fz4). Although Nathans and his colleagues had studied the *Frizzled-4* gene and the Fz4 protein, they did not know what that external signal was, he said.

The first hints that the two diseases might be functionally related came when the researchers observed intriguing similarities in the blood vessel defects in the two disorders in mice lacking the responsible genes. These vessel pathologies occurred in both the eye and the inner ear.

“While there was a clinical similarity, the two diseases were far from identical, because FEVR patients have a much milder version of the problem,” said Nathans. Also, he said, people with Norrie disease show progressive deafness, while those with FEVR do not. “In speculating about how the pieces of the puzzle of the two diseases might fit together, we thought the idea of a direct relationship seemed kind of crazy—but not too crazy. So, we decided to try a few experiments that might reveal that link. Within a month we had the answer.”

The researchers conducted cell culture experiments using techniques to trace the interaction of the proteins, which revealed that together the Norrin and Fz4 proteins activate a key development pathway called the Wnt pathway. The two components also required a third co-receptor called Lrp5, which is known to be key to Wnt signaling, said Nathans.

The cell culture experiments also revealed that the Norrin protein was a key trigger for the Fz4 receptor, selectively binding to it and activating it. “Importantly, we found this to be very high-affinity, highly specific binding,” noted Nathans.

Further, the researchers studied two human forms of FEVR, finding that in patients with the disorder, mutations in the *Frizzled-4* gene interfered with Norrin-dependent signaling.

If reduced activity of the Norrin signaling pathway is in fact the underlying cause of the two disorders, Nathans said, a drug that increases that activity could be helpful. Such a drug might also be effective in treating diseases that occur later in life in which the Norrin-Fz4 system might play some role, such as diabetes and age-related macular degeneration, Nathans added. Similarly, a condition known as retinopathy of prematurity, in which premature infants treated with high oxygen levels because of their undeveloped lungs subsequently suffer abnormal retinal vascular development, might also be benefited.

Since the Norrin-Fz4 pathway is specific to the eye, a drug that manipulates that system might be able to treat these disorders without many side effects, a significant improvement over drugs that more generally affect vascular growth, Nathans said.

However, emphasized Nathans, far more work needs to be done to understand the role of the Norrin-Fz4 pathway in vascular development. “We're not sure how much this pathway generalizes,” he said. “In fact, we don't know very much about vascular development in general. It's a fascinating and provocative question of why nature went to the trouble of evolving a specific pathway just to build these vessels in the eye and the inner ear. It hints that there may be other specialized vascular development systems in other tissues and organs.”