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Why Scientists Are Blaming Cilia for Human Disease

Hairlike structures on cells may play a role in a host of genetic disorders, including kidney degeneration, vision impairment and even some cancers
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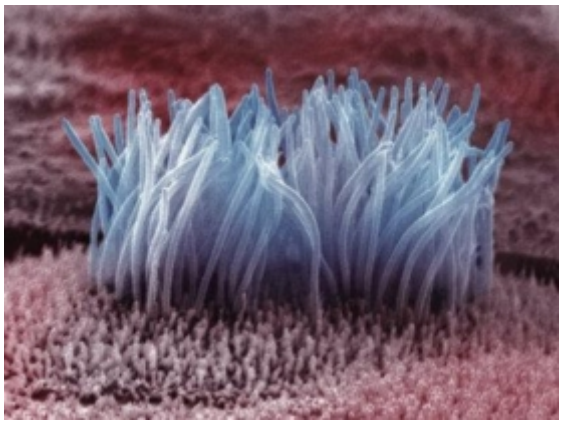

Hairlike cilia may be at the roots of of several genetic disorders.
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Scientists now believe that a number of genetic disorders, from polycystic kidney disease to some forms of retinal degeneration, can ultimately be traced back to cilia—bristly, hairlike structures that dot cell surfaces.

In a review article published in the December 1 *BioScience,* George B. Witman, a cellular biologist at the University of Massachusetts Medical School, highlighted the growing body of evidence that **abnormal or absent cilia can cause a wide range of human disorders, dubbed "ciliopathies.**"

"Kidney disease and blindness, multiple digits, shortened bones or extremities, obesity—all of these things, it turns out, are due to defects in cilia," he says. Experts add that the discovery of a common thread between these disparate disorders may eventually help researchers develop gene-based therapies to combat those conditions.

At first blush, cilia seem relatively innocuous. As they beat back and forth outside the cell, coordinated brushes of so-called motile cilia regulate fluid flow nearby. But almost **all human cells also have one primary, or nonmotile, cilium that functions more like a molecular antenna**. The primary cilium is an internally dynamic structure, packed with proteins that detect and *convey important messages to its cell about the local environment.* "The signaling machinery is concentrated in the cilia," Witman says. "All in this very tightly controlled, constrained space."

Effective cellular communication is especially important for a developing embryo. If faulty molecular antennae cut off or warp a signal in these early stages, the resulting miscommunication can disrupt organ formation. For that reason, **"when you have defects in these cilia, you get a lot of congenital diseases,"** Witman says.

The **most common ciliopathy is polycystic kidney disease (PKD),** which affects about 12.5 million people worldwide. Almost all patients face renal failure as multiple fluid-filled sacs (cysts) clog their kidneys and prevent blood purification. In 2000 Witman was part of the team that identified a gene responsible for cilia growth in green algae and noticed that it was nearly identical to a mouse gene that, when defective, caused polycystic kidney disease.

Scientists later learned that defects in that same gene cause malformed or absent cilia, which contribute to the formation of dangerous cysts in human kidneys. As urine flows through the channels and chambers of the kidney it bends the primary cilia, which act like sensors for fluid flow. *"If you don't have those cilia, you get these cysts* that come up in the kidney," says Ketan Badani, director of the Comprehensive Kidney Cancer Program at Mount Sinai Hospital in New York City.

Although scientists had known about the existence of primary cilia since the late 1800s, Witman's study prompted researchers to revisit the structures that they had once assumed served minimal purpose. "Suddenly there was this idea that the primary cilium was a signaling system and that you had to put specific receptors into the primary cilium to prevent a pathology—in this case, polycystic kidney disease," says Peter Satir, professor of anatomy and structural biology at Albert Einstein College of Medicine who was not involved in the research. "But then it turned out that that wasn't the only pathology related to receptors in the primary cilium."

The **next major ciliopathy to emerge** was a broad class of diseases related to the Hedgehog signaling pathway, a cascade of specific molecular interactions that occurs during embryonic development. Researchers found that the receptors and other proteins that mediate this essential signaling pathway are concentrated in the primary cilium—when these cilia do not form properly, the Hedgehog pathway malfunctions and the messages that it conveys end up distorted. *"The whole nervous system depends on Hedgehog signaling," Satir says. "If it's wrong, you get things like the brain developing outside of the head and other serious deformations."*

Later, more ciliopathies emerged. Babies born with Bardet–Biedl Syndrome face blindness, obesity and intellectual disabilities. People with situs inversis, in which many of the major organs form in reverse—their hearts are often on the right side of their chests—have malformed cilia to thank for their condition. And scientists suspect that some forms of retinal degeneration, which can cause blindness, *stem from malfunctioning ciliary genes, too, because "the photoreceptors of the eye are in fact just modified cilia," Satir says.*

One still speculative idea is that even some cancers may be linked to cilia. “There’s a whole series of reports that primary cilia are lost in a variety of cancers,” Satir says. “It’s possible that some cancers will turn out to be ciliopathies.”

At least for polycystic kidney disease, Badani is optimistic that further study of primary cilia could lay the groundwork for eventual gene-based therapies. Conventional treatments for PKD rarely work, Badani says, so attacking kidney disease at its source may be the best option for future treatments. “Right now, everyone with kidney disease is going to have renal compromise,” he says. “If you can prevent kidney failure by targeting the mechanism that causes polycystic kidney disease, maybe you can prevent ultimate death from this disease.”

Witman, likewise, sees a future for cilia-based gene therapies that could stop retinal degeneration before it causes blindness. “I think we could probably use it therapeutically, to restore function in these defective photoreceptor cells,” he says.

It may be some time before we start seeing gene therapies that target cilia. But a better understanding of the basic science behind ciliopathies could ultimately have clinical payoffs. “You don’t just all of the sudden say, hey, we figured it out,” Badani says. “Basic science is a long process—it takes time.”