Genetic error linked to rare disease that causes chronic respiratory infections

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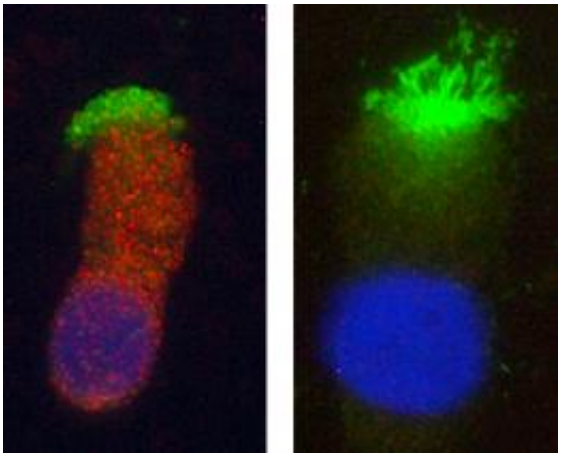

A newly identified mutation in the HEATR2 gene causes a rare disease, primary ciliary dyskinesia, in some patients. The gene makes a protein that powers hair-like structures called cilia to beat, removing pollutants and bacteria from the lungs, nose and ears. In cells lining the nose, the HEATR2 protein (red, at left) is present in a healthy person. But in a patient with the disorder, HEATR2 is missing and cilia (green) can't beat, leading to chronic infections. Credit: Washington University in St. Louis

(Medical Xpress)—Scanning the DNA of two people with a rare disease has led scientists to identify the precise genetic error responsible for their disorder, primary ciliary dyskinesia.

The condition affects the tiny hair-like structures, called cilia, that extend from various cells in the body, and causes a range of symptoms:

persistent lung, sinus and ear infections, male infertility, and sometimes a reversed orientation of major organs in the body.

The new discovery, by a team at Washington University School of Medicine in St. Louis, is reported online in the American Journal of Human Genetics.

The research highlights the potential for using DNA sequencing technology to quickly identify genes responsible for rare diseases, an approach that likely will improve diagnosis.

"Primary ciliary dyskinesia is difficult to diagnose and requires a high degree of suspicion," says senior author Thomas Ferkol, MD, director of the division of allergy, immunology and pulmonary medicine and a pediatric specialist at St. Louis Children's Hospital. "Because it is inherited, we should be able to diagnose the disease using genetic tests, so we can identify and treat affected children earlier and hopefully avoid the most severe chronic infections."

The researchers found the error in a gene, HEATR2, which had never been linked to primary ciliary dyskinesia or to cilia. It brings the number of genes associated with the disorder to 15, but they are still thought to account for fewer than half of all cases of the disorder.

Ferkol, along with first author Amjad Horani, MD, a fellow in pediatric pulmonology, identified the mutation by sequencing the genes from two people with primary ciliary dyskinesia and, as a comparison, the genes from both sets of their parents, who did not have the disease. The family members came from two related Amish families that now live in Missouri, Arkansas and Wisconsin. Nine of them have the disorder, and the researchers can now attribute their cases to the HEATR2 mutation.

About 1 in every 20,000 babies is born with primary ciliary dyskinesia.

Because the disease is rare and symptoms like chronic respiratory and sinus infections don't always raise a red flag, making a diagnosis can be difficult.

Typically, newborns with the disorder have respiratory distress shortly after birth and may need the help of a ventilator to breathe. As they grow, the children develop persistent cough. Runny or stuffy noses and respiratory infections are common year round.

The wide-ranging symptoms can be traced to defects in cilia that sit atop cells lining the respiratory tract, from the nose to the airsacs of the lungs. Cilia normally beat rapidly – roughly 10 times a second – to clear inhaled pollutants and bacteria from the lungs, nose and middle ear.

Early in development, cilia also move fluid across the embryo's surface and detect signals that indicate where the heart, lungs, spleen and other internal organs should be placed. Sperm sport similar structures, called flagella, that propels their movement.

But in patients with primary ciliary dyskinesia, the cilia don't beat effectively if at all. In many patients, the cilia clearly look defective under an electron microscope. However, cilia can appear normal in some patients. The newly identified mutation in HEATR2 changes the structure of cilia and affects the microscopic motors that power them to beat.

"In these patients, the cilia motors are not assembled properly, and they just sputter," Ferkol says. "Without the motor, cilia don't beat."

In the lab, the researchers confirmed their discovery by silencing the HEATR2 gene in normal, healthy cells that line the respiratory tract and in a simple model system, a single-celled green algae called Chlamydomonas. This caused the same defect in the motors that the

scientists observed in the family members with primary ciliary dyskinesia.

While the new discovery will help scientists unravel the disparate genetic origins of primary ciliary dyskinesia, it also could help them identify biological similarities between this rare disease and more common ailments.

"Many young children without primary ciliary dyskinesia experience chronic or repeated sinus or ear infections," Ferkol explains. "It is possible that a more subtle error in one or more genes linked to this rare disorder may be at the root of these common conditions."

The research is an unusual collaboration that brought together Washington University physicians and scientists in diverse fields. Ferkol and Horani, both pediatric pulmonologists, teamed with Steven Brody, MD, a specialist in pulmonary medicine, Susan Dutcher, PhD, a geneticist who studies green algae, and Philip Bayly, PhD, an engineer who investigates the mechanics of beating cilia. Funding for the project came from the National Institutes of Health (NIH) and the Children's Discovery Institute, a partnership between St. Louis Children's Hospital and Washington University School of Medicine.

"Ultimately, we want to identify all the mutations responsible for primary ciliary dyskinesia," Ferkol says. "In our dreams, we hope that one day we can correct ciliary defects that lead to respiratory disease. But in the short term, a more complete understanding of the genetics of primary ciliary dyskinesia will be a huge step forward toward improving diagnosis and allow us to better connect particular mutations with specific symptoms."

More information: Horani, A, Druley TE, Bayly PV, Brody SL, Dutcher SK, Ferkol TW et al. Whole-exome capture and sequencing

identifies HEATR2 Mutation as a Cause of Primary Ciliary Dyskinesia. *American Journal of Human Genetics*. Oct. 5, 2012.

Provided by Washington University School of Medicine in St. Louis