

# Pendred syndrome

# Research

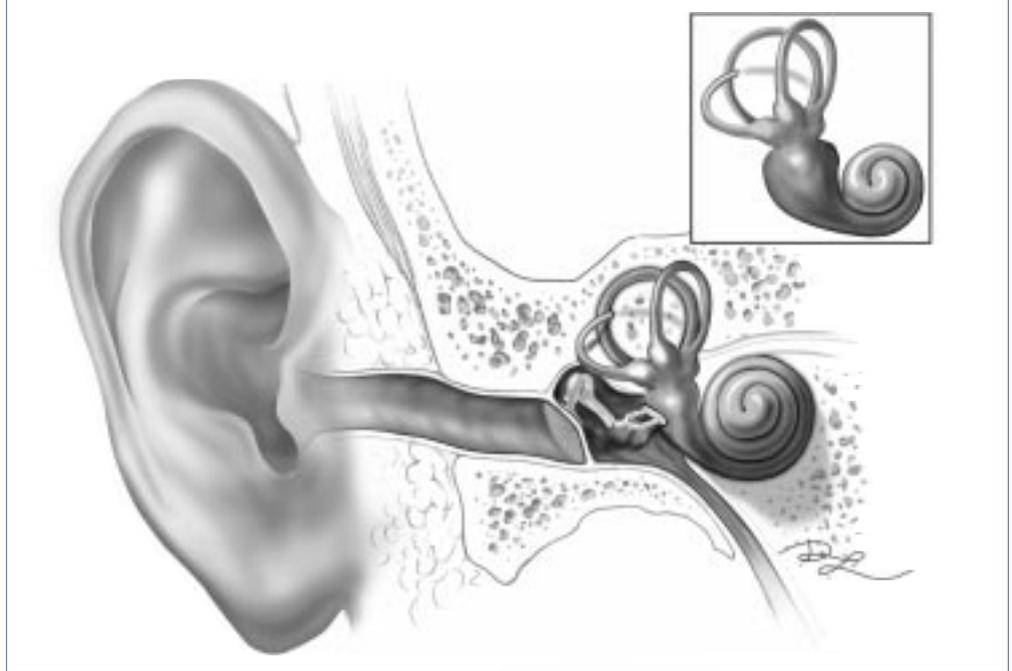
**W**hat's the point of mapping human chromosomes? A satisfying answer to that question can be found in the DIR's Genome Technology Branch.

The laboratory of Eric Green, Chief of the Branch, completed a physical map of chromosome 7, which accounts for about 5% of the human genome, in 1997. In the meantime, researchers studying a genetic disease known as Pendred syndrome, which is thought to account for 5–10% of hereditary deafness, discovered that the defective gene resided on chromosome 7, so they teamed up with Green's lab to isolate the gene.

Pendred syndrome is noteworthy because, in addition to deafness, its other hallmark feature is goiter, an enlargement of the thyroid gland. The question that fascinates researchers is: How can one defective gene cause these two dramatically different abnormalities?

At the end of last year, post-doctoral fellow Lorraine Everett, working in Green's lab, identified the Pendred syndrome gene. In the few months since, the lab's scientists and collaborators have already made progress toward understanding the mutant gene's disruptive effects.

All Pendred syndrome patients examined so far have a mutation in the identified gene. A couple of mutations seem to account for a significant portion of cases, but numerous other mutations have also been uncovered.



The human auditory system. Boxed is a cochlea of a Pendred syndrome patient with fewer turns in the "spiral" as well as other structural differences.

"As with many other genetic diseases, we are finding common mutations and very rare ones," says Green.

The scientists have also identified at least one mutation that causes deafness only, with no thyroid disease. "That implies certain defects in the gene can result in deafness alone," says Green. "This observation makes untangling the function of the gene even more interesting." Green expects that identifying additional mutations and correlating them to specific abnormalities in patients will provide insight about the function of the encoded protein in the ear and thyroid.

The Pendred syndrome studies involve collaborations with research groups around the world and at NIH itself. Green's laboratory is now working with the National Institute on Deafness and Other Communication

Disorders to study the deafness component of the disease and with the National Institute of Diabetes and Digestive and Kidney Diseases to examine the role of the encoded protein in the thyroid.

Green's lab is now enlisting the help of the laboratory mouse. The scientists have already sequenced the corresponding mouse gene and verified that it is very similar to the human Pendred syndrome gene. They have also studied where and when the gene is turned on, discovering that it is expressed in a very limited way within the mouse embryo—for example within certain cells of the developing cochlea in the inner ear. In humans, the syndrome's deafness is accompanied by a distinctive malformation of the cochlea.

"Right now we're in the process of making a knockout mouse, that will carry defective

copies of the Pendred syndrome gene," says Green. "Our prediction is that such a mouse will likely have an abnormally developed cochlea and perhaps goiter."

Green points out that in the past, his lab's strengths have been in genome mapping and sequencing, not in making mouse models of human disease, screening patients for mutations, characterizing proteins, or understanding ion transport across membranes. "But because we built a strong infrastructure for studying genes on chromosome 7, we were able to identify the Pendred syndrome gene in just over a year. And then in the past few months, thanks to the remarkable strengths which exist in a variety of disciplines at NHGRI, we have been able to launch ourselves into whole new areas of research." •

<http://www.nhgri.nih.gov/NEWS/Pendred/>

May, 1995

Collaboration with Howard University to investigate susceptibility to non-insulin dependent diabetes mellitus and hereditary prostate cancer in African-Americans began.

June, 1995

Gene and its related mutations that cause ataxia-telangiectasia isolated.

June, 1995

Mutations in Fas gene found to cause ALPS.

July, 1995

Mutated gene that causes hypochondroplasia isolated.

July, 1995

Clinical genetics training program admits first student. Clinical genetics residency begins.