Hearing Gene

Sounding out the heredity of deafness

By CAROL EZZELL

"The nature of the bond of correlation is very frequently quite obscure .... certain malconformations [occur together] very frequently, and... others rarely coexist, without our being able to assign any reason. What can be more singular than the relation between blue eyes and deafness in cats ... ?"

— Charles Darwin, *On the Origin of Species*

Nineteenth-century naturalist Charles Darwin was probably not the first person to observe that many blue-eyed cats are also born deaf, although he might have been the first to record the observation. Over the years, farmers and city folk alike have noticed that some blue-eyed, all-white cats are poor mousers and tend to get mauled in fights — good tip-offs that they can hear neither prey nor predator. Generations of pet owners have also noted that these cats usually startle easily and never learn to respond to their names.

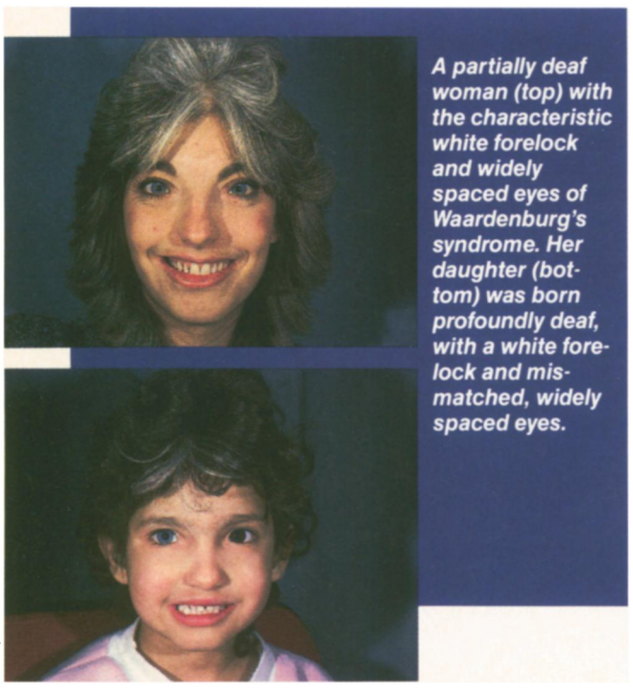
Geneticists studying the inherited causes of deafness have now uncovered an explanation for why blue eyes and white hair go hand in hand with deafness in species as disparate as cats, mice, mink, horses and humans.

Two independent groups of researchers have found that people with a pigmentation and hearing disorder called Waardenburg's syndrome bear mutations in a gene thought to direct a critical phase of early embryonic development. The researchers suspect that defects in an extremely similar gene cause a comparable syndrome in most mammals — including the common white house cat and a pedigreed domestic feline called the Turkish Van.

Waardenburg's syndrome accounts for 2 to 3 percent of the 1 million cases of congenital deafness in the United States, according to the National Institute on Deafness and Other Communication Disorders in Bethesda, Md. But many researchers studying the syndrome believe it is responsible for a much larger proportion of cases.

"I think it's very, very underdiagnosed," says Aubrey Milunsky of the Boston University School of Medicine, who led one of the two groups reporting the new findings. "It's so variable; the manifestations can be very mild."

Waardenburg's syndrome — first described in 1951 by Dutch physician Petrus J. Waardenburg — has several hallmarks, including widely spaced eyes that are pinched at the inner corners, deafness, light blue or mismatched eye color, fused eyebrows, and a white forelock of hair. The syndrome is a dominant genetic disorder, which means that a defect in only one of the two copies of a necessary gene causes it.



Asher/J. Med. Genetics

A partially deaf woman (top) with the characteristic white forelock and widely spaced eyes of Waardenburg's syndrome. Her daughter (bottom) was born profoundly deaf, with a white forelock and mismatched, widely spaced eyes.

However, because of genetic phenomena known as incomplete penetrance and variable expressivity, most Waardenburg's patients do not exhibit all of the syndrome's characteristic traits. A hearing mother with the Waardenburg's traits of a white forelock and widely spaced eyes, for example, can have a deaf son with widely spaced eyes and fused eyebrows, but no white forelock.

For the past few years, geneticists at six laboratories in three countries have sought the gene responsible for Waardenburg's. Many have studied so-called "Splotch" mice, named for the white splotches that appear on the animals' bellies, heads and tails.

Splotch mice have several Waardenburg's traits, including white forelocks and small, widely spaced eyes. A group led by Douglas J. Epstein of McGill University in Montreal reported in the Nov. 15, 1991 Cell that Splotch mice have a defect in one copy of a gene named *Pax-3*, which prods the ectoderm of the embryo to develop into the skin and nervous system. The chemical structure of *Pax-3* resembles that of another gene family, the homeobox genes, which play a role in overall body development in the early embryos of everything from mice and fruitflies to humans (SN: 4/20/91, p.255).

Encouraged by the Canadian finding, Milunsky's group and a separate team of European researchers led by Andrew P. Read of St. Mary's Hospital in Manchester, England, began looking for similar mutations among families with Waardenburg's. Working independently, the two groups found mutations in the human equivalent of the *Pax-3* gene in four families. Each of the families has a different mutation in the same gene, the researchers report in back-to-back papers in the Feb. 13 Nature. They named the new human gene *HuP2*.

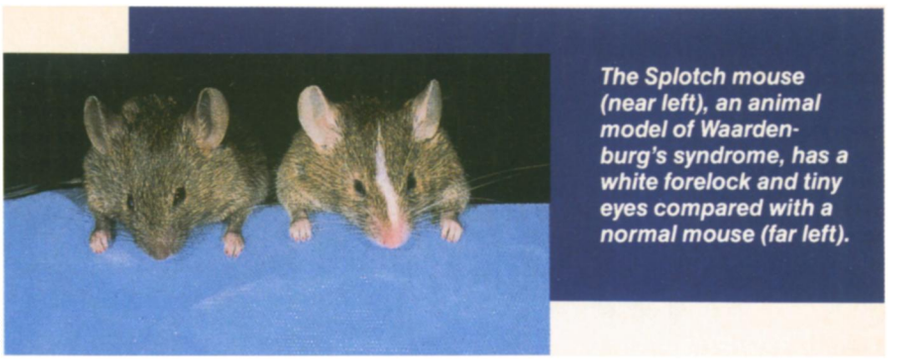
Both Milunsky and Read speculate that the *HuP2* gene directs the production of a protein that attaches to other genes involved in later stages of embryonic development, turning those genes on or off. In particular, they think *HuP2* might control the development or migration of melanocytes, the pigmented cells that produce skin, eye and hair color.

Melanocytes play an important role in the inner ear of mammals. They make up a tiny, dark stripe that winds through the cochlea, the spiral-shaped organ that contains the so-called hair cells that sense sound waves. By regulating the concentrations of charged potassium and sodium atoms in

the special fluid within the cochlea, melanocytes allow the hair cells to generate electrical signals that convey sound to the brain. If these melanocytes fail to grow or move to their appropriate places in the developing embryo, Milunsky and Read assert, deafness and pigmentation anomalies could result.

Karen Steel, a biologist at the Medical Research Council's Institute of Hearing Research in Nottingham, England, has been studying the hearing and inner-ear structure of Splotch mice to determine whether this scenario might occur in people with Waardenburg's. Although her initial experiments suggest that Splotch mice are not deaf, she says the mice may still be good animal models of Waardenburg's syndrome.

"Really, nobody knows what the pathology is in the inner ear of Waardenburg's syndrome," Steel says. "It may be that it's a lack of melanocytes, but it may be abnormal growth of the whole inner ear." She adds that Splotch mice with mutations in both copies of the *Pax-3* gene have severe neurological defects — such as a tiny or partially formed brain or spina bifida, in which the vertebrae fail to enfold and protect the spinal cord.



Asher

The Splotch mouse (near left), an animal model of Waardenburg's syndrome, has a white forelock and tiny eyes compared with a normal mouse (far left).

Because people with two copies of the mutant Waardenburg's gene might also face such dire neurological problems, developmental geneticist James H. Asher Jr. of Michigan State University in East Lansing is trying to develop a genetic screening test for Waardenburg's. He hopes to offer such screening to deaf couples, who he calculates have a 1 in 2,500 chance of both having Waardenburg's.

Asher says that even though many deaf couples would prefer to have deaf children, if both parents carry the same mutation in the *HuP2* gene, "one-quarter of their children would have severe developmental defects or be born dead." He says he knows of one marriage between two individuals with Waardenburg's syndrome, and their children have severe optic defects and pigmentary problems, including extremely fair skin.

"Knowing more about the molecular genetics of hearing impairment improves diagnosis and genetic counseling," says James B. Snow Jr., director of the National Institute on Deafness and Other Communication Disorders. "I think that individuals in the deaf community are very interested in the genetics of hearing impairment."

Snow, Read and Milunsky are optimistic that genetic counseling will not be the only benefit of the *HuP2* discovery. They hope eventually to use the knowledge to correct Waardenburg's syndrome through gene therapy or medicinal strategies to stimulate the biochemical function lost in the disorder.

"It opens up for the first time a molecular understanding of the genetics of deafness," asserts Milunsky. "There is at least the theoretical possibility that for the first time in history, a treatment or intervention to prevent or avoid deafness might be possible." □