HUMAN GENETICS

New Gene Found for Inherited Macular Degeneration

In a large Swedish family, geneticists have tracked a gene that could help reveal clues to what causes vision to fade in old age

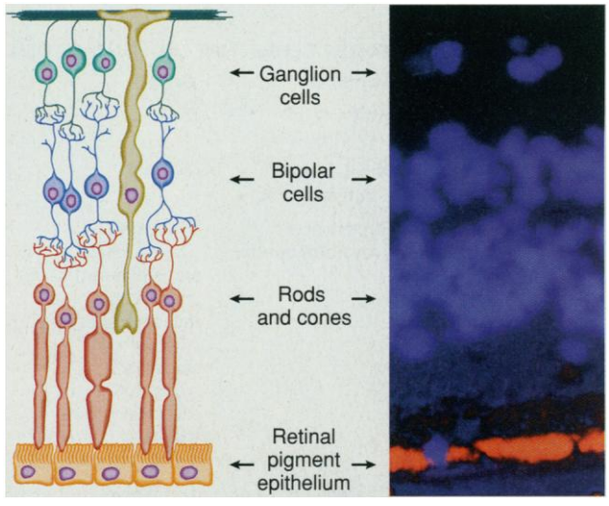
Gene-hunters dream of families like the one introduced to researchers almost 40 years ago by Yngve Barkman, an ophthalmologist in Falun, Sweden. Many of the family members, currently numbering more than 1000 individuals over 12 generations, either had or have an inherited disease called Best's macular dystrophy, which sometime during adulthood destroys the part of the retina responsible for the sharpest vision. Now, that heritage—a burden to family members—has proved a boon to geneticists, enabling them to track down the gene at fault.

In the July issue of *Nature Genetics*, Konstantin Petrukhin, a geneticist with Merck Research Laboratories in West Point, Pennsylvania, and his colleagues report that they have traced the mutation that causes Best's disease to a previously undiscovered gene, which they call *bestrophin*. The function of *bestrophin* is currently unknown. But its discovery, along with the earlier identification of the gene for Stargardt's disease, another inherited form of the condition, could help researchers track the roots of age-related macular degeneration, a common cause of vision loss in old age.

The new gene, like the Stargardt's gene, "now becomes a candidate" as the site of mutations causing the age-related eye problem, says Michael Dean, a molecular geneticist at the National Cancer Institute–Frederick Cancer Research and Development Center in Frederick, Maryland, who co-discovered the Stargardt's gene. Even if the genes are not involved directly, they might at least help researchers figure out what goes wrong in age-related macular degeneration. If so, these studies might lead to ways to prevent or treat the condition, which afflicts millions of people in the United States alone. In contrast, only about 1 person in every 30,000 has Best's disease.

When Barkman first came across this family in central Sweden, he didn't recognize that the macular degeneration that afflicted many of its members was due to Best's disease. That possibility also escaped Stefan Nordström, a medical geneticist at the University of Umeå in northern Sweden, who identified another family with macular degeneration in that part of the country. But as the two researchers became aware of each other's work, they began to wonder whether there was any connection between the families. They spent the next 2 years tracking down additional members of these families, aided by the extremely careful records churches in Sweden keep on their parishioners.

By 1976, the researchers had found the link. The family Nordström had identified was descended from a female member of Barkman's family in central Sweden who had moved north with her husband. Born in 1760, "she's the ancestor to all these cases," says Ola Sandgren, an ophthalmologist at the University of Umeå who now takes care of many of the current members with the disease. Barkman and Nordström had also recognized by then that their now-unified family suffered from Best's disease, which is diagnosed from the distinctive electrical potential that develops between the retina and cornea of the eye.



K. PETRUKHIN/MERCK

Crime scene. The faulty *bestrophin* gene (orange) is active where macular degeneration occurs in the retina.

More than a decade later, Claes Wadelius, a clinical geneticist at the University of Uppsala, realized that the linked populations gave researchers enough surviving family members to attempt to track down the faulty gene. His team pursued the gene by linkage analysis: seeing how often the condition was inherited together with markers at known locations on the chromosomes. Wadelius and his colleagues at Umeå were beaten by a couple of weeks in the first phase of the search, however. In 1992, Edwin Stone, an ophthalmologist and molecular biologist at the University of Iowa, Iowa City, used data from a large Iowa family that also has the disease to map the gene's approximate location on chromosome 11.

Further studies by Wadelius's team of DNA from 250 affected and unaffected family members narrowed the search to a million-base-pair section of the chromosome. At that point, the Swedish geneticists joined forces with Merck to home in on the gene. Once the combined team got to within 800,000 bases of it, the researchers searched computer databases for potential genes in that target region.

Both labs then looked for mutations in those genes in family members with the disease but not in people with normal vision. Petrukhin's group found that the mutations consistently appeared in the gene now called *bestrophin*. The researchers have since confirmed the finding in other families with Best's disease. "We now have looked at 25 independent families and have found [*bestrophin*] mutations in many, if not most, of those families in this gene," says Wadelius. "It's a wonderful piece of work," comments Stone, whose group has also been looking for the gene.

But the only sure thing about the bestrophin protein is where it's made: in the pigment cell layer of the retinal epithelium—"the exact place where you see the pathology," says Petrukhin. Over time, these cells accumulate debris that interferes with vision, particularly in the macula, the part of the retina that sees fine details. The big question now is how the *bestrophin* mutations bring about that pathology.

The next big question is whether people with age-related macular degeneration also have *bestrophin* mutations. Efforts to pin down a genetic link between the age-related condition and another inherited form for which the gene is known, Stargardt's disease, have been inconclusive.

But whether or not Petrukhin, Wadelius, Stone, and others succeed in finding abnormal *bestrophin* in elderly people with macular degeneration, study of how the protein triggers Best's disease could still shed light on the events that dim vision in old age. The cellular debris seen in Best's disease is more like what is seen in the age-related form than is the debris in Stargardt's disease, says Wadelius: "It's a most promising model for the age-related form."

–ELIZABETH PENNISI