HUMAN GENETICS

Gene Found for the Fading Eyesight of Old Age

For many people, retirement means more time to read, watch television, sew, play cards, or drive to places they have always longed to visit. Yet by the time they reach age 65, all too many retirees find they no longer have those options because they have lost much of their vision to age-related macular degeneration, a disease that destroys the macula, the part of the retina that sees fine details. Indeed, macular degeneration is the most common uncorrectable cause of vision loss in the elderly. Currently in the United States alone, 1.5 million people have seriously impaired vision, while another 10.5 million show early signs of the disease.

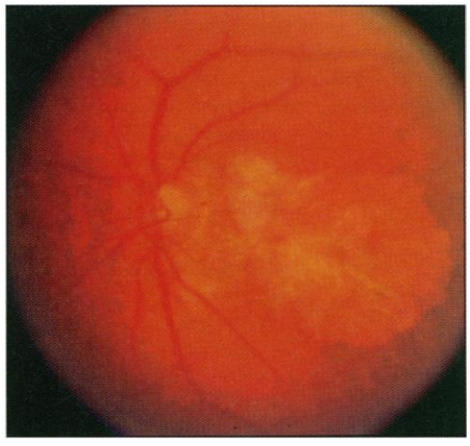
Now, on page 1805, a team led by molecular geneticist Michael Dean of the National Cancer Institute (NCI)–Frederick Cancer Research and Development Center in Frederick, Maryland, and Richard Lewis, an ophthalmologist at Baylor College of Medicine in Houston, reports a genetic cause for the disorder. Earlier this year, the same team had found that mutations in a gene called *ABCR* (ATP-binding cassette transporter-retina) cause Stargardt disease, a form of macular degeneration that develops early, usually leaving its victims blind by age 20. Now, the new work from Dean, Lewis, and their colleagues indicates that mutations in this gene, which codes for a protein thought to shuttle molecules across the membranes of certain retinal cells, could also account for 16% of the age-related cases.

Carl Kupfer, director of the National Eye Institute in Bethesda, Maryland, says the finding is "very exciting. This is the first demonstration of a causative role for a specific gene in age-related macular degeneration seen in the general population." By linking *ABCR* to age-related macular degeneration, Lewis and Dean's team has set the stage for researchers to identify the underlying mechanism of this gradual vision loss—and perhaps develop drugs that could halt it.

Moreover, if mutations in the gene are as common a cause of macular degeneration as it now appears, the work may lead to diagnostic tests that will enable ophthalmologists to pinpoint people at risk. "We then have decades to intervene to prevent or modulate this disorder," says Lewis. For example, people with *ABCR* mutations could be advised to avoid smoking and high-cholesterol foods, habits that increase the risk of macular degeneration.

Lewis began hunting for a gene involved in age-related macular degeneration in 1985. Like others in the field, he studied rare inherited diseases that lead to the destruction of the macula, thinking that one of the genes responsible for these diseases might also play a role in the age-related disorder. He and collaborators Mark Leppert of the University of Utah, Salt Lake City, and Baylor geneticist James Lupski concentrated on finding the gene for Stargardt disease, and by early 1996 they had mapped it to a particular spot on chromosome 1. At that point, Leppert got an unexpected phone call from Dean.

Dean said he had found an intriguing gene located in the same spot on chromosome 1. He had come across it as part of his efforts to learn more about a family of proteins known as ATP-binding cassette transporter proteins because they use ATP—the standard cellular energy source—to transport molecules into or out of cells. Mutations in these proteins had been linked to a variety of genetic diseases, including cystic fibrosis, adrenoleukodystrophy, and Zellweger syndrome, and Dean and NCI geneticist Rando Allikmets had been hunting for new ones by screening databases of human DNA for genes with related sequences. Of the 20 new candidates they and their colleagues had come across, they found *ABCR* the most interesting because it seemed to be expressed only in the eye. That hinted that it might play a role in eye diseases.



PAUL BERNSTEIN/UNIVERSITY OF UTAH

Shade of difference. This retina of a patient with an *ABCR* mutation shows changes (lighter orange) indicative of macular degeneration.

After Dean telephoned Leppert about the finding, the NCI, Baylor, and Utah groups joined forces to search for mutations in *ABCR* in patients with Stargardt disease. When they began finding them, "we knew we were on to something," Dean recalls. *ABCR* turned out to be the chromosome 1 gene at fault in that disorder, they reported in the March *Nature Genetics*.

That work showed that both gene copies need to be mutated to produce the rapid macular degeneration of Stargardt disease. But the researchers wondered whether a single mutation might cause the slower degeneration that comes with age. To find out, Dean's team tested 167 people—96 from Utah and 71 identified in Boston by Harvard Medical School ophthalmologist Johanna Seddon—with age-related macular degeneration for *ABCR* mutations. Of those, 26 had an aberrant *ABCR* gene, the researchers report. Because this eye problem is considered to have multiple, albeit unknown, causes, the finding that 16% of the patients had problems in this one gene surprised even the researchers themselves. "That we found [mutated *ABCR*] in one person in six in the first 167 people we screened is mind-blowing," says Lewis.

What's more, *ABCR* mutations are especially frequent in patients with the most common form of age-related macular degeneration, the so-called dry type, which accounts for 80% of cases and apparently results from damage to the pigmented layer of cells in the retina. The damage causes bits of debris to accumulate, leading to gradual vision loss. Twenty-five of the 134 patients with dry-type macular degeneration had mutations in the gene. In contrast, the researchers found only one mutation in the 33 people with the wet form, which results when excess blood vessels grow into the eye and leak blood that apparently damages the retina.

Researchers do not yet know exactly what the protein made by *ABCR* does normally, or how it malfunctions to cause macular generation. But a major clue emerged soon after the *Nature Genetics* paper came out. Two groups independently showed that ABCR is actually the so-called rim protein, discovered 20 years ago in the rod cells, one of the two types of light-detecting cells in the retina. The rim protein gets its name because it is found along the outer edges of the membrane folds that make up the rod cells' light-sensitive ends. The discovery that it is actually a transporter protein suggests, says Dean, that it could be involved in the molecular recycling that goes on at the photoreceptive ends of rod cells. The cell ends are constantly being degraded, releasing pigments and other materials, and then reassembled. The retinal pigment epithelium, a cell layer that underlies the retina, takes up the materials released by the degradation, presumably for reuse.

If the ABCR protein helps transport these materials across the cell membranes, mutations that impede it could cause degraded material to build up and interfere with retinal cell function. Ultimately, Dean speculates,

not just the rod cells, but also the retinal pigment epithelium and the retina's other light detectors, the cone cells, could be damaged.

Or it may be that an altered ABCR protein does its job just fine, but is itself not recycled properly and so accumulates inappropriately. "So you are left with junk that may be toxic," suggests genetic epidemiologist Margaret Pericak-Vance of Duke University in Durham, North Carolina. "There are a number of possibilities."

To try and sort through them, several teams are knocking out the *ABCR* gene in mice to create animals that make no ABCR at all. By seeing what kind of defects result, they may be able to figure out what the protein does. Others are trying to find out what molecule the ABCR protein transports, if indeed that is what it does.

At the same time, there's a push to find out just how common *ABCR* mutations are among people with macular degeneration. "We have to look at large numbers of well-characterized patients and controls and really determine the prevalence of this gene in well-defined cases," says Kupfer. Moreover, Pericak-Vance points out that researchers also need to find out whether the age at which patients lose their vision depends on which mutations they carry. Answers to these questions will help determine whether screening for mutations in this gene is warranted.

But even if this gene proves to have a smaller role in age-related macular degeneration than this first result implies, it is a break in what had been an intractable case, says Dean: "This is the first chink in the armor of a disease that's been resistant to figuring out what's going on."

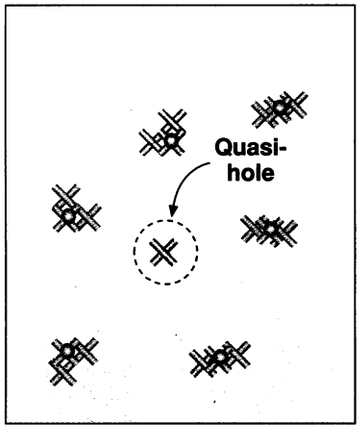
–Elizabeth Pennisi

PHYSICS

Slicing an Electron's Charge Into Three

As everyone learns in high school, electric charges come as multiples of an indivisible unit: the charge of an electron. But two groups of physicists have demonstrated an exception. As an Israeli team announced in last week's issue of *Nature* and a French team will report in the 29 September *Physical Review Letters*, charge in a thin layer of electrons subjected to a high magnetic field and chilled to nearly absolute zero can come in units of exactly a third of an electron.

Counterintuitive as it is, the result isn't a surprise to solid-state physicists. They have gotten over their shock during the 14 years since fractional charges were first predicted as part of a theory to explain a puzzling phenomenon called the fractional quantum Hall (FQH) effect. But actually observing a fractional charge—a manifestation of fractionally charged "quasi-particles" that take shape in the quantum-mechanical soup of electrons and magnetic field—is a thrill nonetheless. "It's exciting that the prediction has been confirmed," says Charles Kane of the University of Pennsylvania. "You can sort of imagine those quasi-particles going blip, blip, blip, and I think that makes it seem more real."



Quasi-particles. In a sea of electrons and magnetic field, each electron teams up with three vortices; extra vortices form positive "holes" carrying fractional charge.

The generic Hall effect has been part of physics since 1879, when Edwin H. Hall reported that a magnetic field applied perpendicular to a current-carrying wire creates a voltage across the wire's width. This Hall voltage develops, as physicists later realized, because the field causes electrons to pile up on one side of the wire. In the 1980s, physicists discovered a quantum variant of the effect: Under extreme conditions—when electrons were restricted to an ultrathin layer of a solid at very low temperatures and high magnetic fields—increasing the magnetic field caused the voltage to increase in discrete steps, rather than continuously.

Even more surprising, the plateaus in the Hall voltage appeared when the ratio of current along the layer to the voltage across it—known as the Hall conductance—reached multiples of a specific value. Physicists soon managed to explain the plateaus at integer multiples, known as the integer quantum Hall effect. But the FQH effect seen at higher magnetic fields, in which the plateaus correspond to fractional multiples such as 1/3, 2/3, 2/5, and 3/7, "was puzzling for quite a while," says physicist Rafi de-Picciotto of the Weizmann Institute of Science in Rehovot, Israel, a member of the Israeli team.

In 1983 Robert Laughlin, now at Stanford University, proposed an explanation for the FQH effect, and although the theory was widely accepted, it included a strange concept: fractional charges. Laughlin proposed that in the FQH effect the electrons in the layer form an exotic quantum-mechanical state in which they move collectively. In this state they coexist with vortices, pointlike objects resembling tiny whirlpools around which the electrons circulate. Electrons are fermions, particles that normally can't occupy the same quantum state, but when each electron teams up with an odd number of vortices, they form aggregates that can coexist in a single quantum state.

The number of vortices increases with magnetic field. At particular values of the field, there are just enough vortices for all of the electrons to form one of these stable arrangements, say, an arrangement in which each electron is "bound" to exactly three vortices. If another vortex is introduced, by increasing the magnetic field, for example, the electrons move away from it, to maintain the same ratio of electrons to vortices everywhere else. By doing so, they open a gap in the negative charge, and a positive charge corresponding to exactly a third of an electron's is left behind.

These fractionally charged quasi-particles can carry electric current in the FQH state. Meanwhile, because the background "sea" of electrons bound to vortices clings to stable configurations in the face of increasing magnetic field, the Hall conductance remains constant, as the FQH effect demonstrates.

Laughlin's picture has withstood every test since he proposed it, but physicists still had a hard time accustoming themselves to it. "It is very difficult to imagine that electrons will somehow divide, because they are really elementary particles," says de-Picciotto. "What [the physics community] wanted to see was a direct observation of the charge."

The two research teams—one led by Michael Reznikov of the Weizmann Institute and the other by D. Christian Glattli of the Commission of Atomic Energy in Saclay, France—set out to look for the fractional charges by measuring fluctuations in the current through an FQH system chilled to within a tenth of a degree of absolute zero. The method is like gauging the size of hailstones by listening to them hit a tin roof, Kane and Matthew Fisher of the University of California, Santa Barbara, explain in a commentary accompanying the *Nature* paper. By measuring a current so small that the size of the individual "hailstones" could be determined, the researchers found they corresponded to charges just one-third that of an electron.

De-Picciotto is delighted with the result, but he confesses to a little regret that it is so neat: "It would have been nice if we could identify something new which is not predicted by any theories, and then it would make people think even harder in order to try and explain it."

–David Ehrenstein