Missing Alzheimer's Gene Found

Researchers find the gene that causes Alzheimer's disease in "Volga German" families. It shows a remarkable similarity to another recently discovered Alzheimer's gene

This summer, research on Alzheimer's disease, the memory-loss disorder that affects 17 million to 20 million people worldwide, has sizzled as much as the weather. Less than 2 months ago, researchers reported the discovery of a gene on chromosome 14 that is responsible for 80% of the cases of familial Alzheimer's disease, a particularly virulent form of the disorder that can strike as early as age 40.

Now, a collaborative team led by molecular geneticists Gerard Schellenberg of the Veterans Affairs Medical Center and the University of Washington, Seattle, and Rudolph Tanzi of Massachusetts General Hospital in Boston reports on pages 970 and 973 the discovery of a gene on chromosome 1 that may account for most of the remaining familial Alzheimer's cases. Even more remarkable, the new gene is closely related to the chromosome 14 gene, known as *S182*.

"It's ... a striking development coming so close on the heels of the chromosome 14 gene discovery," says Alzheimer's researcher Dennis Selkoe of Harvard Medical School. "It is very important that the new gene on chromosome 1 has high homology to *S182*," he adds. The similarity between the two genes may mean that the proteins they encode have similar functions. According to Selkoe, the resemblance "suggests that something about this type of ... protein is very important for the biology of Alzheimer's disease."

Just what that something is will take time to figure out, as researchers know little about the functions of the genes. But Alzheimer's researchers agree that these back-to-back discoveries will fuel basic research that is bound to produce a better understanding of the causes of Alzheimer's disease, including not only the early onset form, but also the much more common sporadic form that strikes people over age 65. "You cannot overemphasize how seminal these discoveries are," says Alzheimer's researcher Steven Younkin of the Mayo Clinic in Jacksonville, Florida. "They will enable all kinds of work."

The Schellenberg team has been on the trail of the new gene since 1987, a time when no Alzheimer's-causing genes had yet been identified. The first of those wasn't found until 1991, when John Hardy, then at St. Mary's Hospital Medical School in London, and his colleagues showed that mutations in the gene for the amyloid precursor protein (APP), located on chromosome 21, cause Alzheimer's disease in some families. That discovery was provocative because it provided a direct link to a characteristic feature of Alzheimer's pathology: APP is the source of a peptide called β-amyloid that is found in the abnormal "senile plaques" that stud Alzheimer's patients' brains. But mutant APP genes turned out to account for only 2% to 3% of familial Alzheimer's cases.

About a year later, several teams, including Schellenberg's, showed that many more cases of familial Alzheimer's are caused by an unknown defective gene on chromosome 14. That gene was identified earlier this year by a team led by Peter St. George-Hyslop of the University of Toronto; the results were reported in the 29 June issue of *Nature*.

Intriguing as these discoveries were, they left untouched one handful of Alzheimer's-carrying families, which had been identified by Thomas Bird at the Veterans Affairs Medical Center in Seattle: the so-called Volga Germans, who were all descended from a colony of ethnic Germans living in the Volga valley of Russia in the 18th and 19th centuries. Schellenberg's group had shown that the mutation in these families (which are a very small subset of those who trace their ancestry to the Volga Germans) was on neither chromosome 14 nor chromosome 21. That meant there was at least one other Alzheimer's gene. The Schellenberg group's efforts to pinpoint that gene initially met with failure, but earlier this year, with the help of better genetic markers and more sophisticated statistical analysis methods developed by team member Ellen Wijsman, the researchers finally localized the gene to chromosome 1 and submitted a paper describing their finding to *Science* in early June.

At the time, the team hadn't found the gene itself, but the discovery of *S182* provided an unexpected clue that led them right to it. Wilma Wasco of Massachusetts General Hospital and Tanzi, both of whom were part of the team that found *S182*, compared the *S182* sequence to a collection of expressed sequence tagged (EST) sequences, short DNA sequences known to come from active genes. Wasco found an EST with a sequence similar to *S182*, Tanzi recalls, and said, "maybe this is the Volga German gene."

After the *S182* sequence was published, Tanzi and Wasco told Schellenberg about Wasco's idea. "Having seen a zillion candidates [for the Volga German gene] come and go, I wasn't excited," Schellenberg recalls. But Ephrat Levy-Lahad, in his lab group, went ahead and checked. She found that the new gene was not only on chromosome 1, but was in the very stretch of DNA that she had pinpointed as the likely site of the Alzheimer's gene. "That was like a sledgehammer to the forehead," says Schellenberg. "It went from being a ho-hum project to ... saying 'oh my God this is the gene.' "

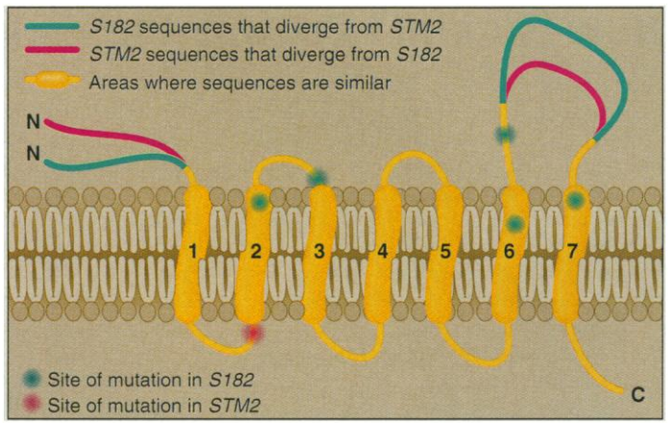

ILLUSTRATION: K. SUTLIFF

Family resemblance. Mutations in the similar proteins made by the genes *S182* and *STM2* cluster around the membrane-spanning regions.

Within a few days, the team sequenced the gene from Volga German family members, with help from David Galas and his colleagues at Darwin Molecular, a biotech firm in Bothell, Washington. They found that family members with Alzheimer's all had the very same mutation in the gene, while unaffected family members did not. Finding just one mutation makes sense, says Schellenberg. The families trace their ancestry to two neighboring villages in Russia; the mutation probably originated in a common ancestor.

Because of their years of collecting and studying Volga German families with Alzheimer's, the Schellenberg group was perfectly positioned to link the new gene to the Volga Germans. But multiple other groups were hot on their trail, having also found the

gene by scanning the EST database. The findings of these other groups, which include the teams of Samuel Sisodia at Johns Hopkins University Medical School; Hardy, now at the University of South Florida, Tampa; Alison Goate at Washington University in St. Louis; and Hyslop, are still unpublished.

As these groups focus their attention on the new gene, it is likely to emerge as the cause of Alzheimer's in other families besides the Volga Germans. Some Alzheimer's families have as-yet-unidentified mutations, and researchers can now test these families to find out whether they have defects in the chromosome 1 gene. That will indicate whether the three known genes are responsible for all familial Alzheimer's cases, or whether other genes are still at large.

The sequence of the new gene is useful not only for screening families, but also for comparing the gene to *S182*. The two genes' sequences reveal that both of their protein products contain roughly 450 amino acids and weave through the cell membrane, apparently crossing it seven times. That led the Tanzi-Schellenberg team to name the new gene *STM2* (for the second seven-transmembrane gene associated with Alzheimer's). Overall, the protein sequences are 67% identical, with the membrane segments showing the greatest similarities. This pattern suggests the proteins have similar, although not identical, functions.

But the proteins have provided very few hints about what their normal functions might be, or how their mutant forms cause Alzheimer's. Perhaps the most promising clue so far is the observation by Younkin and Selkoe that cells from patients with a defect in the *S182* gene make abnormally high amounts of β-amyloid. That finding suggests that the mutation in *S182* increases β-amyloid production, which may in turn trigger the disease. Based on the similarity of *STM2* to *S182*, Younkin suspects mutations in the new gene may also elevate β-amyloid. "It makes sense that a similar protein would wind up causing a similar effect," says Younkin. He and Selkoe, Tanzi's group, and likely others as well are testing that hypothesis.

That experiment is only one of the many that will soon be under way. Researchers in many labs will be putting the new genes into cultured cells in an attempt to understand their cellular effects that may lead to the disease. The mutant genes will also be introduced into mice in hopes of creating new animal models of Alzheimer's. Such models could be used to explore how Alzheimer's develops and to test therapies. "You can expect to see a real flurry of activity in the Alzheimer's disease [research] community," says Younkin. And that activity promises to heat up Alzheimer's research long after the hot summer of '95 has passed.

–Marcia Barinaga

HUMAN ORIGINS

New Hominid Crowds the Field

The base of the hominid family tree is getting crowded. For 2 decades, a 3.5-million-year-old creature nicknamed Lucy and her kin were its sole occupants, but Lucy's solitary reign ended last year, with the discovery of a primitive, 4.4-million-year-old hominid called *Ardipithecus ramidus*. This week a third ancient hominid entered the picture, with the announcement by Meave Leakey and her colleagues of a new species, perhaps Lucy's direct ancestor, that walked the forests of Kenya 4 million years ago.

The new species, *Australopithecus anamensis*, is an anthropologist's delight because its age and features make it an excellent intermediate between *ramidus* and the younger *Australopithecus afarensis*—Lucy's species. "This is what creationists don't want to hear," says Tim White of the University of California, Berkeley, who described *Ardipithecus* last year. But anthropologists aren't certain yet whether these three species represent a single line of descent. Says Alan Walker of Pennsylvania State University, who helped lead the work on the new fossils, "Now you could connect the dots, from *ramidus* to *anamensis* to *afarensis*. But my opinion is that ... we'll soon have too many dots to connect in a simple way."

Leakey, Walker, and their colleagues—Craig Feibel of the National Museums of Kenya and Ian McDougall of the Australian National University in Canberra—identified the new species on the basis of fossils collected over a period of years from two sites called Kanapoi and Allia Bay. Because both sites are located near Kenya's Lake Turkana, they named the new species *anamensis*, after *anam*, the word for lake in the Turkana language. At Allia Bay the fossils were mostly isolated teeth. But they could be dated precisely to 3.9 million years ago, because they were embedded in or beneath volcanic tuff, which is ideal for argon dating.

At Kanapoi the fossils are more complete, including a humerus found back in 1965 and a shinbone found last year. Two new-found jaws clinched the fact that these fossils belong to a new species, says Leakey. But at Kanapoi, some fossils were not embedded in datable rocks, so the researchers had to rely on the ages of nearby tuffs and other rocks to arrive at an estimate of 3.9 million to 4.2 million years.

KENNETH GARRETT/NATIONAL GEOGRAPHIC SOCIETY

Long in the tooth. Jaws of the ancient hominid have primitive features, including large canines.

As the researchers report in this week's issue of *Nature*, these fossils create a picture of a creature that weighed perhaps 55 kilograms and displayed a mixture of primitive and advanced features. *Australopithecus anamensis* has a primitive jaw with a shallow palate and large canines. It also has small ear openings like today's African apes and *Ardipithecus*. But the new species' shinbone and arm bones resemble those of the younger species, *A. afarensis*—and even of early *Homo*.

Details such as the shape of the shinbone where it articulates with the knee show that *A. anamensis* walked upright, although it may also have foraged in the trees, says Walker. "This is just what the lower part of a bipedal knee joint ought to look like," agrees Bernard Wood of the University of Liverpool. Until now the oldest direct evidence of upright walking has been 3.6- to 3.7-million-year-old footprints at Laetoli in Tanzania, presumably left by *A. afarensis*, so the telltale shinbone may be the oldest evidence of bipedalism.

White, for one, thinks *A. anamensis* is so nicely poised between *Ardipithecus* and *afarensis* that all three must lie on the same lineage. "I think there's little doubt that *anamensis* arose from *ramidus*," he says. "This is very strong confirmation of what seems to be a [single] rapidly evolving lineage."

But Leakey and colleagues hypothesize that about 4 million years ago, the novel adaptation of bipedalism spurred hominids to radiate into several different species—and only one led to humans. The anatomical similarities between the new species and fossils of *A. afarensis* at Laetoli suggest that *A. anamensis* may have led to *A. afarensis*, Leakey says. But she doesn't rule out the possibility that *Ardipithecus* may be a closely related dead end rather than a direct human ancestor. And to Peter Andrews of the Natural History Museum in London, the human-like shinbone and humerus raise a heretical notion: Perhaps *A. anamensis*, not Lucy, lies closest to the lineage leading to *Homo*.

It will take more early hominid fossils before researchers can begin to choose among these theories. For now, paleoanthropologists can take pleasure in a new glimpse of Lucy's heritage—and our own.

–Elizabeth Culotta