New Alzheimer's Gene Found

The new gene, which is located on chromosome 14, may cause up to 80% of early-onset familial Alzheimer's cases and may provide clues to what causes this devastating disorder

Among the hottest races in biology today are the contests to clone important disease-causing genes. One of these high-stakes races has just come to an end. This week, a large, multi-institutional research team announced the identification of a gene on chromosome 14 thought to be responsible for most early-onset familial Alzheimer's disease—an aggressive form of the devastating memory disorder that strikes in middle age.

Two other Alzheimer's genes had previously been discovered. But one of these is not a true disease gene in that it does not cause Alzheimer's in all who inherit it, although it does increase their risk of developing the more common, late-onset form of Alzheimer's. The other gene causes only about 2% to 3% of early-onset familial cases. In contrast, the new gene, described in this week's issue of *Nature* by Peter St. George-Hyslop of the University of Toronto and his colleagues, causes 70% to 80% of early-onset familial cases, which comprise up to 10% of all cases of the disease. That means the genetic defect could be responsible for as many as several hundred thousand current Alzheimer's cases in the United States alone. "It is a very exciting finding, because this [gene] is felt to be the most common molecular cause of early-onset Alzheimer's," says Harvard University Alzheimer's researcher Dennis Selkoe.

The discovery of the new gene may lead in the short term to diagnostic tests that can be offered to at-risk members of families that harbor the defective gene. But more important, an understanding of the gene's product, which seems to be a membrane protein of as-yet-unknown function, may provide important insights into the biochemical cause of Alzheimer's, which is still unknown.

That information could lead to new treatments that might benefit not just those Alzheimer's patients who carry this faulty gene, but all those with the disease. "Each time you find a gene like this, it gives you a whole new pathway to start exploring, and hopefully you will get some clues," says Gerard Schellenberg of the University of Washington, the leader of the team that in 1992 reported evidence that a gene causing a high percentage of familial Alzheimer's cases resides somewhere on chromosome 14.

It was that discovery that touched off a fast-paced race among at least four independent research teams. And like athletes unwilling to accept defeat, a week before the *Nature* paper's publication, several of the runners-up were still sprinting toward the finish line. "Many of us ... are still working very hard to find [the gene] independently," said Christine Van Broeckhoven of the University of Antwerp last week. Both Van Broeckhoven and another gene-hunter, John Hardy of the University of South Florida in Tampa, declined to hear any details about the new gene, lest it influence their own searches, which they planned to carry on until the Hyslop team's paper was out. "We want the satisfaction of finding it based on our own work," Hardy said.

Hyslop's team, like its competitors, began searching for the gene by collecting pedigrees of Alzheimer's-prone families in which the disease was linked to the chromosome 14 defect and then searching for DNA markers near the gene that would help narrow the search area. By early 1994, the Hyslop team had found two stretches of about a million base pairs each that seemed likely to carry the gene. They began sequencing genes in both regions, searching for any that were mutated specifically in family members with Alzheimer's.

Within a year they had found a gene—called *S182*—that fit the bill. In seven families they found five different mutations in the gene. And that suggests that more mutation sites will turn up as more families are examined, Hyslop says: "There are probably going to be mutations scattered all over the gene."

Having a full repertoire of possible mutation sites is essential for developing a reliable diagnostic test, and researchers working with chromosome-14 families are likely to begin searching for new mutations in *S182*. A diagnostic test would be of value to as many as a half-million people in the United States who are theoretically at risk for carrying a mutant *S182* gene, says Harvard Alzheimer's researcher Rudolph Tanzi, an author on the *Nature* paper.

But diagnostics are of limited value without a cure, and development of a cure depends on a better understanding of the disease. "The significance of this gene is not so much in its diagnostic potential," says Hyslop, "but in the fact that this is a piece of the molecular biological puzzle of Alzheimer's disease that we didn't previously have." A first step toward making sense of the new puzzle piece will be to pin down the gene's normal functions. So far, however, the clues are slim, but tantalizing.

From its sequence, the product of the *S182* gene appears to be a protein that is firmly embedded in one of the many membranes of the cell. The sequence also reveals that it bears some similarity to a membrane protein known as SPE-4 from the nematode worm *Caenorhabditis elegans*. Studies of worms in which SPE-4 is mutated show that this gene's product is needed for transporting proteins between cellular compartments during the formation of sperm, says Emory University biologist Steven L'Hernault, who discovered SPE-4. S182's resemblance to SPE-4 raises the possibility that it might also be involved in protein transport within cells.

That possibility is intriguing to some Alzheimer's researchers who feel that formation of β-amyloid—a protein fragment that makes up the so-called senile plaques found in the brains of Alzheimer's patients—is key to disease progression. β-amyloid is clipped off of a larger protein called amyloid precursor protein (APP). Support for β-amyloid as a cause for Alzheimer's came in 1991 with the discovery that 2% to 3% of early-onset

GENES LINKED TO ALZHEIMER'S DISEASE

Chromosomal Location	Gene Type	Age of Onset (Years)	% Cases Familial	% Cases All	Protein Product
14	Autosomal Dominant	30–60	70–80%	5–10%	S182 (Membrane protein)
19	Genetic Risk Factor	60+	——	40–50% (late onset)	ApoE4
21	Autosomal Dominant	45–65	2–3%	<1%	Amyloid precursor protein
?	Autosomal Dominant	40–70	approx. 20%	2–3%	?

familial Alzheimer's cases can be traced to a mutant APP gene.

Other research has shown that in normal brain cells most of the APP is transported by vesicles to the cell's plasma membrane, where it is clipped right in the middle of the β-amyloid sequence. That might explain why the β-amyloid fragment doesn't accumulate in normal brains. But even in normal cells, some APP winds up in other vesicles called lysosomes, where it is chopped up in a way that releases β-amyloid. Supporters of the amyloid hypothesis argue that a mutation in APP, or a change in how it travels through the cell, may tip the balance toward that second reaction, increasing β-amyloid deposition and touching off the disease (*Science*, 22 January 1993, p. 457).

If the S182 protein is indeed a player in protein transport, says Tanzi, it may be "involved with the packaging of APP in a vesicle and its delivery to portions of the neuron where it ... is going to be processed normally." Defects in the *S182* gene, he speculates, may cause a snag in APP's travel through the cell, possibly detaining it in a spot where it is more likely to be cleaved to β-amyloid.

But there are also other hypotheses about the development of Alzheimer's that view amyloid deposition as an effect, not a cause, of the disease. Selkoe, who studies amyloid, agrees that it is appealing to take a clue from SPE-4 and propose that mutations in *S182* disrupt APP transport in the cell. But he says that is "pure speculation" at this point and does not constitute further support for the amyloid hypothesis. "The [S182] finding is neutral as regards the amyloid hypothesis at this moment," he says.

Still, Selkoe notes that his lab and Steven Younkin's at Case Western Reserve University School of Medicine have found signs of increased β-amyloid secretion in cells from some chromosome-14 family members. "If this gene product turned out to have nothing to do with APP and [β-amyloid], then we would still have to find the reason why these patients have terrible amyloid deposition," he says.

That puzzle and others will spur the next phase of the research, as labs around the world pounce on the *S182* gene and begin racing to put it into cell lines, make knockout mice lacking the gene, and do anything else that may hint at its function. "There is a lot more work in figuring out what this gene is doing and what the relation is to Alzheimer's disease pathophysiology," says Van Broeckhoven. "Finding a gene is a good beginning, but it is definitely not the end." Although one heat of the Alzheimer's gene race is done, the starting gun for the next leg just went off.

–Marcia Barinaga

CHEMISTRY

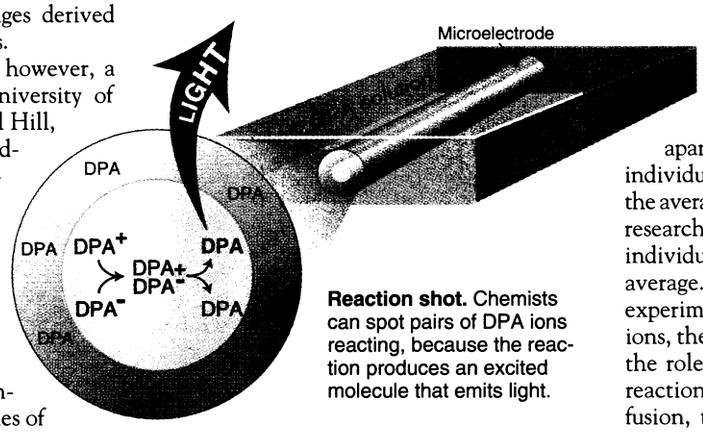
Getting a Reaction in Close-up

Chemists have long been curious about the time it takes for two molecules to react to produce a product. That timing varies, even among pairs of the same molecules in a solution, and researchers don't really know why. The difficulty of tracking individual molecules in solution has forced scientists to content themselves with averages derived from large numbers of molecules.

On page 1883 of this issue, however, a group of researchers at the University of North Carolina (UNC), Chapel Hill, report catching a series of individual reactions in the act, by narrowing their viewing window to a tiny volume of solution—thus narrowing down the number of molecules observed—and detecting faint flashes of light given off when pairs of reacting molecules collide. Although they were still unable to measure the reaction times of these pairs directly, the scientists were able to clock the interval between light pulses and statistically crunch these numbers to show how individual reaction rates were distributed about the average.

"It's really wonderful work," says Jonathan Sweedler, a chemist at the University of Illinois, Urbana, as the ability to see the distribution of individual reaction times adds a new level of sensitivity in monitoring chemical reactions. That, adds UNC team leader R. Mark Wightman, may eventually help researchers refine their knowledge of reaction dynamics, such how different rates of electron transfer between colliding molecules can slow or speed up reactions between pairs of the same type of molecule.

Wightman and Maryanne Collinson studied a reaction between oppositely charged ions of 9,10-diphenylanthracene, or DPA. When these ions collide and react, one of the partners briefly jumps into an excited state, then gives off a photon of light. To track these flashes, the researchers began by placing DPA molecules in an organic solvent and then rapidly reversing a potential in an electrode to first create a burst of positive ions followed by another of negative ions in the solution. The electrode had to be extremely small, a mere 10 microns in diameter. A device this small ionizes far fewer DPA molecules than would a larger variety, reducing the likelihood of overlapping photon bursts that would make it hard to discern the finishing times of the reactions.



Reaction shot. Chemists can spot pairs of DPA ions reacting, because the reaction produces an excited molecule that emits light.

ILLUSTRATION: K. SUTLIFF

It's even harder, however, to discern the starting times. Because the electrode generates ions continuously when charged at one potential, it was impossible to gauge the starting time for any particular ion. Nevertheless, from previous electrochemical experiments, the researchers knew that the positive ions were being added to the solution at a constant average rate, which the scientists used to derive an average start time for the reactions.

The key to the work was determining a series of specific finishing times. The UNC team was able to use a sensitive photon detector to clock the precise time each photon emerged. When the researchers looked at the finishing times of these photons, "we found that some occurred very close together in time and others occurred much farther apart in time," says Wightman. These individual photo finishes were compared to the average reaction time, and for the first time researchers were able to get a sense of how far individual reaction times departed from the average. By manipulating variables in future experiments, such as the concentration of ions, the researchers hope to get a handle on the role that diffusion plays in varying the reaction times. And after accounting for diffusion, the remaining variation can be ascribed to changes in electron transfer rates at the moment of molecular interaction.

This technique may also find a practical use, such as detecting trace numbers of molecules such as antibodies, says Allen Bard, a chemist at the University of Texas, Austin. Techniques already exist for tracking antibodies by tagging them with one ion of an electrochemiluminescent pair and then adding a batch of oppositely charged ions to the solution, triggering a photon burst that reveals the tagged molecule. But they require hundreds of luminescent molecules to generate a signal. If the UNC technique can do more with less, says Bard, it would also be an above-average achievement.

–Robert F. Service