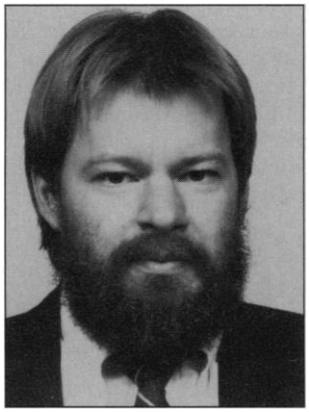
Familial Alzheimer's Linked To Chromosome 14 Gene

Five years ago, researchers trying to identify the gene defect that causes hereditary Alzheimer's got a rude jolt. They found that the disease was genetically heterogeneous—caused by two or more genes located on different chromosomes. That posed a problem because it vastly complicated the job of looking for patterns of inheritance to nail down the genes' locations, and the techniques then were not up to the task.

But the Human Genome Project is now providing researchers with a wealth of new "markers" for mapping the chromosomal locations of disease genes that show more variation, and can therefore provide more information about inheritance patterns, than the old ones. One of the first fruits of those markers can be savored on page 668, where a team led by Gerard Schellenberg of the University of Washington School of Medicine in Seattle reports locating on chromosome 14 a genetic defect linked to an inherited form of Alzheimer's that develops unusually early, at about 45 years of age. Their finding is buttressed by unpublished results from two additional groups that have found linkage between early onset, familial Alzheimer's and a chromosome 14 gene.



Gene hunter. University of Washington's Gerard Schellenberg.

None of these groups has yet pinned down the identity of the chromosome 14 gene, but once they do, having the gene should lead them to the biochemical defect that gives rise to the brain degeneration in the affected families. And finding that mechanism, they hope, will point the way to understanding the molecular mechanisms underlying all Alzheimer's cases.

In particular, the discovery of the new gene could shed light on what may well be the burning issue in Alzheimer's research: the β-amyloid question. β-amyloid is a small protein found in the cores of "senile plaques" that are a characteristic pathological feature of Alzheimer's brains. Researchers have long been arguing over whether β-amyloid deposition is a cause, or merely a consequence, of the disease. The idea that the deposition is a culprit got a big boost 2 years ago when John Hardy's group, then at St. Mary's Hospital Medical School in London, found that patients in some Alzheimer's families have mutations in the gene on chromosome 21 that encodes β-amyloid. It was clear from the first, however, that mutations in the β-amyloid gene are relatively rare. What's more, an earlier genetic study by the Schellenberg group itself had shown that chromosome 21 couldn't be the only site of an Alzheimer's gene, indicating that a gene unrelated to β-amyloid might cause the disease.

Naturally, researchers wanted to know the locations of other genes that might be involved in early onset Alz–heimer's, and whether they have anything to do with β-amyloid deposition. And that's where the new work comes in. "It's extremely interesting," says neurogeneticist Rudy Tanzi of Harvard's Massachusetts General Hospital, "because it would appear from the data that the chromosome 14 locus would account for the majority of early onset Alz–heimer's cases."

To identify the chromosome 14 site, Schellenberg and his colleagues, who include Ellen Wijsman and Tom Bird of Seattle and Harry Orr and June White of the University of Minnesota, made use of the growing number of chromosome "markers," DNA sequences that show a lot of variation in the population and whose chromosomal locations are known. To get an idea of where a particular disease gene might be situated in the genome, researchers compare the inheritance pattern of a selection of markers with the inheritance pattern of the disease itself. If a particular marker variant is consistently inherited with the disease, then the disease gene must be located near the marker.

When the Schellenberg group first surveyed the inheritance of 64 markers (including at least one from every chromosome) in their early onset families, two chromosome 14 markers seemed to be linked to the disease, although the association was not statistically significant. The researchers then checked out two additional markers from different chromosome 14 sites, and with one of them (designated D14S43) hit paydirt.

Seven of the nine families studied showed clear linkage to D14S43, which is located three-quarters of the way down the long arm of chromosome 14. "The fact that so many families map to the same location is our best dream come true," Schellenberg says. Similar results have also been obtained by Mike Mullan, John Hardy, and their colleagues at the University of South Florida in Tampa and by a team led by Peter St. George-Hyslop of the University of Toronto.

But while the researchers have narrowed down the location of the chromosome 14 gene, they are still a long way from actually finding the gene. They now have to sort through 10 million base pairs of DNA, which may contain hundreds of genes. "It can be done," says Schellenberg, "but it's tough." It will be worth the effort, though, especially if it resolves the vexing β-amyloid question as researchers hope. "This is going to be the acid test of the amyloid hypothesis," says Mullan. "If the amyloid thing is right, then this gene should have some effect on amyloid processing."

Mullan was referring to the fact that β-amyloid is made as part of a much larger protein called the amyloid precursor protein (APP). To accumulate in Alzheimer's plaques, β-amyloid apparently has to be released from APP by protein-splitting enzymes. Recent evidence from several groups has been building a case that in Alzheimer's disease this APP "processing" somehow goes awry, leading to excessive β-amyloid deposition.

So researchers will be looking to see whether the protein encoded by the chromosome 14 gene can be connected to APP synthesis or processing. And there are a couple of candidate genes in the region containing the gene that might fit the bill. One is the *fos* gene, which makes a transcription factor that might increase the activity of the APP gene, thereby making more of the protein. Another encodes a heat shock protein that might be involved in the cell's protein-processing pathways. But even if the chromosome 14 gene has nothing at all do with β-amyloid formation, it should nevertheless provide some clue to Alzheimer's. As Schellenberg points out: "Whatever gene is defective here, it's got to be in the pathway causing the disease."

It's also clear that the gene won't be the last to be linked to familial Alzheimer's. The disease in a group of U.S. families with hereditary Alzheimer's, who are known as the "Volga Germans" because they are descended from Germans who settled along the Volga River in the 18th century, shows no linkage to either chromosome 14 or 21—nor for that matter, Schellenberg says, to chromosome 19, the site of a gene that has been linked to some cases of late onset Alzheimer's, occurring after the age of 60.

That indicates that at least four genes can cause the disease. When they are all isolated, researchers should have a wealth of clues to Alzheimer's etiology. And as the number of genes increases, the disease's genetic heterogeneity, far from being the obstacle it was once thought to be, may well turn out to be a major boon for researchers.

–Jean Marx