News of the Week continued from p.103

Higher risk of Alzheimer's linked to gene

Scientists have identified a gene whose presence warns of increased risk of late-onset Alzheimer's disease. The finding opens up new avenues of research into an illness that afflicts some 4 million Americans.

Alzheimer's leads to declining memory and cognitive functions, usually after the sixth decade of life. In the final stages, patients with the condition progressively lose their ability to speak, to walk, to sit up, to smile, and to hold up the head. No definitive diagnostic tests, treatments, or cures exist.

Most Alzheimer's patients have the late-onset form of the disease. Less than 5 percent of patients have the early-onset form, which may begin in a person's 40s. Although the early-onset form has been linked to genes on chromosomes 21 and 14, this is the first genetic link for late-onset Alzheimer's.

The molecular culprit is a version of the gene that codes for a common protein, called apolipoprotein E, or apoE. The protein, which normally helps transport cholesterol in the blood, has three different forms. One of these, apoE-4, is abundant in the autopsied brains of deceased late-onset Alzheimer's patients. The version of the gene now linked to Alzheimer's disease, called APOE-4, is located on chromosome 19 and codes for the apoE-4 protein. The two other versions, or alleles, of the gene are not linked to Alzheimer's disease, although one of them is associated with coronary artery disease.

A person may have no, one, or two copies of the APOE-4 allele, and the more copies, the higher the risk of getting Alzheimer's, according to a report in the Aug. 13 SCIENCE. Elizabeth H. Corder, a genetic epidemiologist at Duke University Medical Center in Durham, N. C., and her colleagues analyzed 42 families with late-onset Alzheimer's disease. The researchers found that having just one APOE-4 allele increased a person's risk of developing the disease about fourfold. Those with two APOE-4 alleles were eight times as likely to be affected as those with none. Having two APOE-4 genes "is virtually sufficient to cause Alzheimer's disease by the age of 80," says study coauthor Warren J. Strittmatter, a neurologist at Duke.

Furthermore, the more APOE-4 alleles, the earlier in life individuals are affected. The study found that patients who had no APOE-4 alleles came down with the disease, on average, at about 84 years of age. Those with one APOE-4 allele were affected by age 75, and those with two of the alleles by age 68.

"This is the first really critical susceptibility marker for late-onset Alzheimer's disease," says Richard Mayeux, a neurologist at Columbia University in New York. And it is very common. "Fifteen percent of the overall population has one APOE-4 allele, and 1 percent of the population has two of the alleles," he says.

Others caution that Alzheimer's is a complex disease with multiple causes. "Not everyone with APOE-4 will develop Alzheimer's disease," says Blas Frangione, a molecular biologist at New York University Medical Center.

Scientists are unraveling the biological role of the protein produced by the APOE-4 allele. Strittmatter has found that the protein binds tightly to a substance in the plaques found in brains of Alzheimer's patients. And Frangione has shown that, in cell culture, the protein speeds the formation of similar plaques. He speculates that an imbalance between different kinds of apoE proteins may cause plaque formation, and he notes that a similar imbalance between two apoE proteins causes heart disease.

If Alzheimer's is related to a protein imbalance, the finding may have therapeutic value. "Then we can alter diet or lower the protein that is too high," Frangione says. — *B. Wuethrich*