

Mutations In A2M Gene Linked With Late Onset Alzheimer's Disease

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Members of the DNA Bank research staff of the Medical College of Georgia, Institute of Molecular Medicine and Genetics, are continuing a study on mutations in the A2M gene. Teams of researchers from Canada, the US, Argentina, and Europe have been doing genome screens, looking for markers linked with late onset Alzheimer's disease.

Two previously published scientific papers reported findings of linkage of the disease with markers on chromosome 12. Shortly thereafter, two mutations in the gene for alpha 2-macroglobulin (A2M) were reported as being linked with Alzheimer's disease. The findings were from scientists at Harvard and from Europe. The gene for A2M is found on chromosome 12.

To find mutations in the A2M gene, investigators screened one set of 100 small families in which there were two affected siblings. DNA from these families was obtained from NIMH. The question now arises as to whether other families affected with the disease may also have these mutations in A2M.

Dr. Shirley E. Poduslo and staff screened large families as well as all the patients with confirmed Alzheimer's disease that have enrolled into the DNA Bank for the two mutations in the gene for A2M. This research involved screening 13 large families with two or three affected siblings (over 500 family members), more than 400 patients confirmed with Alzheimer's disease, and 200 spouses as controls.

In addition, researchers under Dr. Poduslo's direction looked at markers on chromosome 12 that surround the gene for A2M for linkage with the disease. They also analyzed whether there is any correlation of the presence of the mutations in A2M with the APOE or APOCI genotypes, with sex, or age of onset. Once the data has been collected, complex mathematical analysis can be done to determine whether there is any linkage of the disease with the A2M mutations in the families.

Dr. Poduslo explained, "The alpha 2-macroglobulin protein is quite interesting. It stops the cleavage (cutting) of other proteins by enzymes called proteinases. It does this by changing its shape and then trapping the proteinases in a so called 'bait' area." A2M binds to the same receptor that both ApoE and the amyloid precursor protein bind. A2M is found in the plaques that are the characteristic pathology of Alzheimer's brain at autopsy. (Fragments of the amyloid precursor protein [called the beta amyloid peptides] accumulate in the plaques. ApoE is a common protein that carries cholesterol in the blood. One form of the gene, APOE4, is increased in Alzheimer's disease.) A2M also binds tightly to the beta amyloid peptide and may help to carry it to a place where it will be degraded.

"So," Dr. Poduslo continued, "The A2M protein can be thought to be part of a crew that picks up potentially toxic peptides such as the beta amyloid peptide and takes them to the trash where they will be destroyed. This protects the neurons. When the A2M gene is mutated, it may not be able to do its job; then the beta amyloid peptide accumulates into plaques potentially toxic to neurons."

Produced by Oleta Toliver, Volunteer Coordinator