

Could Alpha 2-Macroglobulin Be Linked With Late Onset Alzheimer's Disease?

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Medical College of Georgia DNA Bank researchers are joining other scientists around the world in studies to determine whether alpha 2-macroglobulin is linked with late onset Alzheimer's disease. Mutations in the gene may be an additional risk factor for the disease.

Last summer there was a report from scientists in Boston who had found a gene that, when mutated, may increase the risk of Alzheimer's disease. They suggested that this mutation might affect persons developing symptoms later in life. The gene is called alpha 2-macroglobulin (A2M). The protein encoded by the gene was thought to act by cleaning up any toxins that may be found adjacent to nerve cells in the brain. The mutations in the gene make the protein less efficient in doing its job. Interestingly, they found that patients who do not carry the APOE4 variant had a higher frequency for the mutation. (As a reminder, about 40 percent of Alzheimer's patients have the APOE4 variant. The A2M mutation affects the 60 percent who do not have APOE4.) To analyze the data from the families for the mutations, they used complicated mathematical formulations, which compared affected patients with unaffected siblings. The families were obtained from a consortium obtained through 3 sites in the U.S. (These families are called the NIMH data set).

Then last fall a group of scientists from Boston and Europe found a second mutation in A2M that may also be increased in Alzheimer's patients. However, the increase in the frequency of this second mutation is modest.

Since that time, there have been a number of studies by researchers trying to duplicate these findings. Last fall a group of scientists from England using families from England did not find an increased risk in the first mutation in alpha 2-macroglobulin. A second group of scientists used families from Wales, France, London, and the U.S.; they also did not find an increased risk with this mutation. A third group of scientists used families from Canada, Belgium, Italy and the U.S. and did not find the increased risk. However, a group of scientists from Finland used a large number of families and controls from Finland. They found an association with the second mutation in their families, which was stronger in the absence of the APOE4 variant.

Dr. Poduslo explained, "We decided to analyze our Alzheimer's families from Texas that are enrolled into the DNA Bank for the two mutations found in the gene for alpha2macroglobulin. We assessed 422 patients and 237 spouse controls. We did not find an increased frequency for either mutation in the patients when compared with the control spouses. Complicated mathematical formulations were used in the original study by the group from Boston in which affected patients are compared with unaffected siblings. Here 89 families with 276 sibs (130 affected and 146 unaffected siblings) were analyzed. We found that neither mutation was significant when the total sample was analyzed.

However, when the samples were divided according to age of onset of clinical symptoms, the results were interesting. We found that the first mutation in the alpha 2-macroglobulin gene was significant for patients that developed symptoms before the age of 65 years. Neither mutation was significant for any age group with clinical symptoms occurring after the age of 65 years. Our data must still be analyzed for the effect of the APOE 4 variant."

Samples from the NIMH group of families were analyzed. We found that with 17 families with 71 sibs (51 affected and 20 unaffected siblings), both mutations were significant. These results confirm the original findings of the

Boston group and indicate that in the NIMH families, mutations in the alpha 2-macroglobulin gene are risk factors for the disease.

The gene for alpha 2-macroglobulin is on chromosome 12. The DNA Bank staff analyzed markers on chromosome 12 surrounding the gene for linkage with the disease in our group of 13 large extended families. We did find that the disease in several of these families is linked with markers that are further downstream from the alpha 2-macroglobulin gene. We believe that there may be another gene near the alpha 2-macroglobulin gene that may be mutated and may be causing the disease in several of our families. We are in the process of identifying this gene.

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