



Gene for Successful Aging Without Cognitive Decline Identified by Poduslo's Research Lab in Georgia

Study Continues With TRPC4AP

In the previous newsletter, Dr. Poduslo announced that her research lab had identified a gene on chromosome 20 that was the cause of late-onset Alzheimer's disease in two large extended families with many siblings who were affected with the disease. The gene is the TRPC4AP gene and its protein is involved with the regulation of calcium in the brain. Further studies have now shown that 36 percent of Alzheimer's patients have the same pattern of sequences as found in the two families.

That compares with 26 percent of the spouse controls. The spouse controls at time of entry into the study did not have Alzheimer's disease. However, it is not known whether the spouse controls may have developed the disease since that time. Thus some of the 26 percent of the spouse controls may now have Alzheimer's disease which suggests that the number of controls with the same pattern of sequences as in the Alzheimer's families may be quite lower.

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Dr. Shirley E. Poduslo and her assistant, Rong Huang, have identified a gene involved with successful aging without cognitive decline. Dr. Poduslo went into the community to recruit seniors who were age 85 years or older, had normal mental status tests, and did not have any major illnesses, such as cancer, diabetes, heart or vascular disease, or obesity. They also did not have any immediate relatives with dementia or Alzheimer's disease. The seniors who qualified for participation in the study signed consent forms and donated blood samples. DNA was purified from the blood samples for the study.

Dr. Poduslo used a technique which looked at all of the genes (a genome-wide scan) in these seniors and compared the results with the DNA from Alzheimer's patients. The researchers were searching for differences between the successful aging without cognitive decline seniors and those with severe cognitive decline (Alzheimer's). Several very significant changes were noted in the DNA. The study was extended to examine additional sequences in a particular area of DNA. It was found that the seniors had a pattern of sequences in one gene that was different from that of Alzheimer's patients.

The gene is called the low density lipoprotein receptor-related protein 1B (LRP1B) which is located on chromosome 2q21.2. The gene is very large, 1,906,000,000 basepairs (similar to a word having 1,906,000,000 letters). The gene product is found in all brains at high levels. The LRP1B protein interacts with the beta-amyloid precursor protein which is the protein that is cut to form the Abeta42 peptide found in the plaques in the Alzheimer's brain. The LRP1B protein binds the beta-amyloid precursor protein and slows the process of its being cut. Therefore, there is decreased production of the Abeta42 peptide and potentially decreased production of plaques in the successful aging subjects.

The next step will be to identify the exact changes that protect the seniors from developing Alzheimer's disease. DNA samples from the seniors and from Alzheimer's patients are being sequenced to determine the variations which are protective for the successful aging subjects.

Dr. Poduslo is excited by the findings as it suggests that there is a genetic variation that protects from developing Alzheimer's disease. The protein product may be a new form of therapeutic treatment.

Study Continues With TRPC4AP Gene. . .

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We also did a cluster analysis to determine the clinical phenotype (characteristic) of the patients. It was found that the Alzheimer's patients with this pattern of sequences had more behavioral changes and psychiatric issues, such as hallucinations. They also developed the disease at a somewhat later time with the range of age-of-onset being 66 to 80 years of age.

We are still sequencing this large gene to identify the variations that are the cause of the disease.

Meetings and Honors

Dr. Poduslo presented the research findings on TRPC4AP at the International Conference of Alzheimer's Disease in Chicago, at the American Society of Human Genetics in Philadelphia, and at the Society for Neuroscience in Washington, DC.

Dr. Poduslo was recently honored with the Horizon award from the Georgia chapter of the Alzheimer's Association. The award honors outstanding volunteers who support the association's missions of research, enhanced care and increased public awareness of Alzheimer's disease.

Dr. Poduslo has recently become the President of the Faculty Senate at the Medical College of Georgia. Her colleague, Dr. Suzanne Smith, the neurologist who is the Director of the Memory Disorders Clinic, received the Patient Care award at this ceremony.

Dr. Eleanor Fennell will receive her Ph.D. at graduation from the School of Nursing and the School of Graduate studies in the Medical College of Georgia. Dr. Fennell worked closely with Dr. Poduslo to identify the clinical phenotype of one of the extended families with late-onset Alzheimer's disease. Dr. Fennell is very appreciative of this family's willingness to talk with her about the affected siblings and the progression of the disease.

Retirement

Dr. Poduslo has decided to retire. This will be the last newsletter. Dr. Poduslo would like to thank all of the participants in the DNA Bank. They are all heroes for being part of the studies described. The DNA samples in the DNA Bank are the property of the Medical College of Georgia. Special thanks go to Oleta and Coke Toliver for producing the newsletter and for their continued support.

Visit our web site: <http://www.mcg.edu/alzres/>

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