# Families Shed Light on Likely Causative Gene for Alzheimer's

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Dr. Shirley E. Poduslo, neuroscientist in the Medical College of Georgia Schools of Medicine and Graduate Studies. Credit: Phil Jones

The genetic profile of two large Georgia families with high rates of late-onset Alzheimer's disease points to a gene that may cause the disease, researchers say.

Genetic variations called single nucleotide polymorphisms, or SNPs, are common in DNA, but this pattern of SNPs shows up in nine out of 10 affected family members, says Dr. Shirley E. Poduslo, neuroscientist in the Medical College of Georgia Schools of Medicine and Graduate Studies and the Charlie Norwood Veterans Affairs Medical Center in

Augusta.

The 10th family member had half the distinctive pattern. The SNPs also were found in the DNA of 36 percent of 200 other late-onset patients stored in the Alzheimers' DNA Bank.

"We were shocked; we had never seen anything like this before," Dr. Poduslo says of findings published online in the American Journal of Medical Genetics. "If we looked at unaffected spouses, their SNPs were all different. The variants consistently found in affected siblings are suggesting there is something in this gene. Now we have to go back and find what is in this gene that is making it so unique for Alzheimer's patients."

The variation was in the TRPC4AP gene, part of a large family of genes that is not well-studied but is believed to regulate calcium. Calcium is needed throughout the body but its dysregulation can result in inflammation, nerve cell death and possibly plaque formation as well, she says.

The finding provides new directions for research and possibly new treatment targets, Dr. Poduslo says. It also shows the important role large families affected by a disease can have in determining the cause of the disease.

The specific genetic mutation responsible still must be identified and will require sequencing the very large gene, or determining the order of the base pairs that form the rungs of the ladder-like DNA, Dr. Poduslo says. An SNP represents a change in either side of a rung. "The mutation could be a deletion of some of the nucleotides, could be an insertion, or something in the promoter gene that turns the gene off so it's never transcribed. It could be a wide variety of things, and that is what our next step is to identify the mutation." She'll work with The Scripps Research

Institute in Jupiter, Fla., to expedite the required high-throughput analysis.

One of the families that provided the sentinel genetic information had 15 members, including five with Alzheimer's that started in their 60s and 70s; the second family had 14 members, six of whom had the disease. The disease incidence itself was notable and the incidence of the pattern of SNPs was equally so. "This to me is very, very striking. Genetics and lifestyle either could be the biggest risk factors," says Dr. Poduslo. "We looked at these families very, very carefully to see what in their background may make them different and we couldn't come up with anything. They were farmers living fairly healthy lifestyles."

Families donate to the Alzheimer's DNA bank to help others at this point and don't get feedback from findings generated by their genetic material, Dr. Poduslo says. "Right now, we have no way of treating it, so it's not going to help them. When we come up with new drugs so we can treat this disease, then it becomes important to identify it early and get treatment."

Source: Medical College of Georgia