

# New Alzheimer's Gene Is Pinpointed

Wall Street Journal – By Shirley S. Wang  
July 13, 2009

New research has pinpointed a gene that could improve predictions of who will develop Alzheimer's and at what age.

Allen Roses, director of Duke University's Deane Drug Discovery Institute, said that if other researchers get the same findings, it could mean a drastic improvement in the accuracy of predictions about the disease as well as the approximate age within a five-to-seven-year window when individuals might begin noticing symptoms. And if drugs to slow the course of Alzheimer's become available, the gene could help identify who should begin taking those drugs earlier.

In 1993, Dr. Roses reported that people who have a variant of the ApoE gene have an unusually high risk of developing Alzheimer's. Despite facing initial skepticism, his findings have since been replicated by a number of independent scientists. Testing for the gene variant, called ApoE4, has become accepted as a way of identifying individuals at high genetic risk for Alzheimer's.

But investigators haven't found drugs that slow the disease in these ApoE4-positive individuals; they have only been able to identify their risk of getting the disease. Also, the ApoE4 findings don't explain why many people with the most common version of the gene, ApoE3, also get the disease.

In research presented Sunday at the International Conference on Alzheimer's Disease in Vienna, Dr. Roses and his team looked at the area of DNA surrounding the ApoE gene. They found that a gene linked to ApoE called TOMM40 had mutations that involved a small number of extra copies of a particular building block of DNA in some individuals and a large number of extra copies in others.

Individuals with the large number of extra copies -- known as the "long repeat" version of TOMM40 -- coupled with ApoE3 develop Alzheimer's an average of seven years earlier -- about age 70 -- compared with ApoE3 individuals with a "short repeat" version of TOMM40.

"What you need is the information on the repeat in order to make sense of what type [of ApoE3] you have," said Dr. Roses, who started a company, Zinfandel Pharmaceuticals, to help fund the research.

The researchers used several pools of people with and without Alzheimer's to identify and confirm the genetic findings, including a small group who agreed to have their brain autopsied upon their deaths.

Some scientists urged caution about the new findings. "Before I get too excited about it, I'd like to see it confirmed in more patient populations," said William Thies, president of the Alzheimer's Association, which is sponsoring the conference. With any single study, it is important to make sure the results aren't a result of "statistical anomaly," Dr. Thies said.

The TOMM40 gene is related to how easily molecules can get into and out of the surface of the mitochondria, the energy center of cells. Some researchers propose that this permeability is part of

Alzheimer's disease, according to Dr. Thies. One experimental drug called Dimebon, which is being studied by [Medivation Inc.](#) and its partner [Pfizer Inc.](#), may be a therapy that acts through that mechanism, Dr. Thies said.

Zaven Khachaturian -- the former director of Alzheimer's research at the National Institutes of Health who currently runs Khachaturian Radebaugh & Associates Inc., an international consulting group on Alzheimer's and aging -- called the findings "quite significant."

"I do get excited about the possibility of having a good genetic marker that's going to tell us with greater precision who's going to get it and within a time window," Dr. Khachaturian said. "I also have skepticism that we need to validate with larger numbers before we go public."