Alzheimer's | SAN DIEGO

The Role of Genetics: *Will I get Alzheimer's disease?*

Scientists are still trying to determine the underlying causes of Alzheimer's disease. The hope is that one day we will be able to stop the disease from progressing or perhaps even prevent it altogether. To date, researchers have identified a few genes that play an important role in Alzheimer's. Some of these genes are simply risk factors for Alzheimer's disease. Other genes are hereditary and will cause (with nearly 100% certainty) Alzheimer's disease to develop.

There are two types of Alzheimer's disease: early-onset Alzheimer's disease and late-onset Alzheimer's disease. Early-onset Alzheimer's disease is rare, occurring in people age 60 and younger. This represents less than 5% of all people with Alzheimer's. One type of early-onset Alzheimer's disease is known as autosomal dominant Alzheimer's disease (ADAD) or early-onset familial Alzheimer's disease (FAD). This is even more uncommon, affecting less than 1% of all people with Alzheimer's. What makes this type of early-onset Alzheimer's disease so unusual is that it is caused by a hereditary genetic mutation to one of three genes – PSEN1, PSEN2, or APP.

If a child whose birth mother or father carries a genetic mutation on one of these three genes, then the child has a 50% chance of inheriting that mutation from the affected parent. People who inherit one of these genetic mutations will (with nearly 100% certainty) develop Alzheimer's disease, usually before the age of 60. The genetic mutation is usually passed down from generation to generation. About 50% of the family members will develop the disease before the age of 60.

In contrast, late-onset Alzheimer's disease, which occurs in people over the age of 60, is much more common. Unlike with early-onset Alzheimer's disease, there is no known genetic mutation that causes someone with nearly 100% certainty to develop the disease. Instead, there are some genes that increase a person's risk of developing Alzheimer's disease. However, just because you carry that particular form of the gene does NOT mean you will develop the disease.

APOE is the best known genetic risk factor (or susceptibility factor) for developing Alzheimer's in later life. APOE comes in 3 forms: e2, e3, e4. Each person inherits one APOE gene from their birth mother, the other from their birth father. As a result, there are 6 possible APOE combinations: e2/e2, e2/e3, e3/e3, e3/e4, e4/ e4. The e4 variant is associated with an increased risk of developing Alzheimer's in later-life. With each additional e4 type there is a higher risk of developing the disease at a younger age (but still after age 60). The e2 type is associated with a slightly reduced risk of developing the disease. Although other genes have been identified that are associated with an increased risk of developing Alzheimer's, APOE is the greatest risk. Efforts are underway to determine if there is one or more combination of genes that increases risk of the disease. This is particularly important in people without

any copies of the e4 type of APOE. In addition, researchers are also busy looking for genes that may protect against Alzheimer's disease. For example, a very rare genetic mutation on the APP gene is associated with people living longer without Alzheimer's disease.

A recent study examined data from 4 large, observational studies of adults ages 60 and older. The study reported the association between various APOE genotypes and the risk of developing mild cognitive impairment (MCI) or dementia due to Alzheimer's by age 85 as follows:

- The e3/e3 APOE genotype is associated with a 10-15% risk of developing MCI dementia due to Alzheimer's disease by age 85.
- The e3/e4 APOE genotype is associated with a 20-25% risk of developing MCI or dementia due to Alzheimer's disease by age 85.
- The e4/e4 APOE genotype is associated with a 30-55% risk of developing MCI or dementia due to Alzheimer's disease by age 85.
- The e2 form of APOE is rare, so we have less information available about individuals with this form. As a result, we estimate it may be slightly lower or higher than the e3/e3 risk of 10-15% by age 85.

It is important to keep in mind that just because a person has 1 or 2 copies of the e4 type of APOE does not mean that they will develop dementia due to Alzheimer's disease. Likewise, just because a person has no copies of the e4 type of APOE does not mean they will not develop the disease.

There are other factors that can increase or decrease a person's risk of developing Alzheimer's disease. This is also true for people with 2 copies of the e4 type of APOE. For example, age is the biggest non-genetic risk factor for developing Alzheimer's disease. Therefore everyone is at risk for developing the disease as they age.

Factors that may <u>decrease</u> a person's risk of developing dementia due to Alzheimer's include: no family history of dementia, being male, more years of education, good cardiovascular health.

Factors that may <u>increase</u> a person's risk of developing Alzheimer's include: having a family history of Alzheimer's, older age, being female, fewer years of education, cardiovascular disease and conditions such as diabetes and high blood pressure.

In the past few years academic researchers, have partnered with the National Institutes of Health (NIH) and pharmaceutical companies to launch several important Alzheimer's prevention trials. These trials

are focused on healthy people with different genetic risk factors for Alzheimer's disease. The studies will determine if they can remove amyloid from the brain or stop its production, thereby slowing or stopping the disease. Hopefully this will prevent memory and thinking problems from occurring. If one of the treatments studied in any of these trials is found to delay the onset of cognitive decline associated with Alzheimer's or delay the onset of the disease itself, it opens the door to the possibility of testing the treatment's effectiveness in other at-risk groups. This also includes those without the genetic risk factors. Examples of these trials include:

- The Alzheimer's Prevention Initiative's Autosomal Dominant Alzheimer's Disease (ADAD) Trial is a study led by Banner Alzheimer's Institute and Genentech/ Roche of approximately 300 members of the world's largest extended family of ADAD carriers is taking place in Colombia, South America.

- The Dominantly Inherited Alzheimer's Network (DIAN) Trial's Unit program is a study in people from families with a known ADAD mutation , taking place in the United States, Canada, Europe and Australia.

- The Alzheimer's Prevention Initiative's Generation Study 1 is a trial led by Banner Alzheimer's Institute, Novartis, and Amgen taking place the United States, Canada, Europe and Australia in approximately 1300 people with 2 copies of the e4 type of APOE.

Other trials are in various stages of planning to launch later in 2017, 2018 and beyond. For more information about local research and clinical trials, contact Alzheimer's San Diego at 858-492-4400.

In summary, the role of genetics is playing an important role in not only understanding Alzheimer's disease but testing new therapies that may one day lead to a world without Alzheimer's.

Adapted from Banner Alzheimer's Institute, July 2017