

Genetics and Alzheimer's disease

Many people become concerned that they may have inherited the gene for Alzheimer's disease and that they may pass it on to their children. This information sheet outlines the present state of knowledge about inherited risk.

Genetic Factors

The genetic factors associated with Alzheimer's disease can be summarized as follows:

- There is no single gene for Alzheimer's disease.
- Genetic factors are responsible for the disease in a small number of families.
- In the wider community there is a genetic component to the disease, but inherited factors alone do not explain why some people develop it while others do not.

Genes and inheritance

The basic material of inheritance, DNA, is passed on in the form of genes, and delivered in packages called chromosomes, which are long chains of genetic instructions.

We each inherit 23 pairs of chromosomes, one half of each pair from our mother and the other from our father. There are literally millions of combinations of genes we can inherit, and the effect of each gene is not yet known, although scientists worldwide are rapidly expanding our knowledge.

Alzheimer's disease genes

Alzheimer's disease runs in a small number of families, where up to half of the family members are at risk. Alzheimer's disease is common amongst elderly people, so having one close relative with the disease is not evidence of a family link. Even where there are two close relatives with the disease it is likely to have occurred by chance.

Early Onset

If you have three or more close relatives who developed Alzheimer's disease at an early age, then your doctor will be able to counsel you about genetic testing for 'familial Alzheimer's disease' and refer you to a geneticist where appropriate.

- About 15 families in the world have a genetic fault on chromosome 21 in a gene called amyloid precursor protein, or APP which affects production of a protein called amyloid. This protein has been associated with Alzheimer's when it builds up in the brain.

- A larger number of families carry a fault on chromosome 14 ('presenilin-1') which could be responsible for the majority of the early onset cases of familial Alzheimer's, sometimes below the age of 40.
- A smaller group of families (mainly in the United States) has a fault on chromosome 1, which has been named 'presenilin-2'.

All these genetic faults are associated with early onset of Alzheimer's disease, usually between the ages of 35 and 60. On average half the children of someone with one of these genetic defects inherits it, and probably all those who inherit the gene develop the disease. Those who do not inherit cannot pass on the genetic faults. They do not skip a generation.

Some other forms of dementia can be inherited in the same way. Some people with frontal lobe dementia (such as Pick's disease) and some people with Creutzfeldt-Jakob disease (CJD) and similar diseases have a very strong family history of the same disease and in some of these cases the gene has been found. For example, faults in the tau protein can cause inherited frontal lobe dementia and faults in the prion gene can cause CJD. These inherited forms are quite uncommon – the majority of people with frontal lobe Dementia do not have an inheritable form.

Later onset

Most cases of Alzheimer's develop later in life. Below the age of 65 the risk is approximately one in 1000. Over the age of 65 it affects one person in 20. The risk rises to one person in five by the age of 80. There is also a genetic link with many later cases, weaker than the link described above but not confined to a few families.

The link is with a protein called apolipo-protein E (ApoE), which we all have in the blood and the brain. It comes in three forms, known as ApoE2, ApoE3 and ApoE4, which are all found in the general population. We each have two copies of the gene, which may be the same as each other or different.

ApoE4 is associated with a higher risk of Alzheimer's disease. About a quarter of the population inherits one copy of the ApoE4 gene and this increases the risk of developing Alzheimer's disease by up to four times.

Two per cent of the population gets a 'double dose' of the ApoE4 gene, one from each parent. The risk of Alzheimer's disease is increased by about ten times in this group, but it is still not inevitable that the disease will develop.

Sixty per cent of the population have a double dose of the ApoE3 gene and are at 'average risk'. About half develop Alzheimer's by their late 80s. ApoE2 is the gene least associated with Alzheimer's disease, but only one in six people carry it. People who have one ApoE2 gene and

one ApoE3 gene (11 per cent of the population) have to live into their late 90s before the risk of Alzheimer's disease reaches 50 per cent.

One in 200 people inherit two copies of the ApoE2 gene and are at lower risk.

The ApoE risk is very different from familial Alzheimer's. ApoE4 increases the chances of the disease, but does not make it certain. Some other factor, not yet understood, must also contribute.

Indeed, some researcher's think that ApoE4 does not affect whether a person will get the disease but more when they might get it, with people with ApoE4 developing the disease before those with ApoE2.

Scientists often think they have found a gene that might contribute to late onset Alzheimer's disease. However, after the initial finding, it can take many years before they are certain. So far scientists are only agreed on ApoE. It is likely that other genes will be found that contribute to Alzheimer's disease but the degree of risk involved is likely to be quite small.

What are the pros and cons of genetic testing?

A genetic test for Alzheimer's could:

- Identify people who might benefit from new drugs to delay symptoms in the early stages of Alzheimer's disease.
- Help genetic researchers understand the disease better and so lead to better treatment
- Help some people plan for the future

However, population-wide screening would create problems for individuals and for society as a whole.

A genetic defect cannot be repaired, and effective treatment is not yet generally available, so a test could raise anxiety without offering a clear course of action.

A genetic test for ApoE4 cannot accurately predict who will develop the disease: testing positive does not mean you will get it; testing negative does not guarantee you will not.

People tested 'positive' could face discrimination, which could damage their ability to buy a house, obtain insurance or plan financially for their old age.

If you have three or more close family members with early onset of Dementia, you may want to be referred to a specialist centre for genetic testing. Your GP will counsel you and help to assess your risk. You should discuss the issues carefully before making a decision.