

Genetics and dementia

Many people with dementia are concerned that their disease may have been inherited and that they may pass it on to their children. Family members of people with dementia are also sometimes concerned that they might be more likely to develop dementia themselves. This information sheet outlines the present state of knowledge about the inherited risk of dementia.

Genes and dementia

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

It can be helpful to think of DNA as being the letters of the alphabet, genes as being the words that they form and chromosomes as being the sentences that convey the meaning.

We all inherit 23 pairs of chromosomes. One half of each pair comes from each parent. There are millions of combinations of genes that we could inherit, and the effect of each gene is not yet known, although scientists are rapidly expanding their knowledge. If you inherit a particular genetic defect from one of your parents, this increases your chance of developing dementia.

However, the vast majority of cases of dementia are not caused by an inherited genetic fault. Dementia is so common that having one or two close relatives with dementia is not evidence of a family link.

The genetic factors associated with dementia

The genetic factors associated with Alzheimer's disease and other forms of dementia can be summarised as follows:

- There is no single gene responsible for all cases of dementia
- Genetic factors only directly cause the disease in a very small number of families with dementia
- Among cases without a family link, there is a genetic component to the disease; however, inherited factors alone do not explain why some people develop it and others do not.

Early onset Alzheimer's disease

Alzheimer's disease where there is a family link, called familial Alzheimer's disease, usually affects younger people (under the age of 65) rather than older people. Only a very small number of families are affected, however. These particular genetic defects can result in people developing Alzheimer's disease in their 30s and 40s. However, it is important to remember that most cases of early onset Alzheimer's disease are not inherited.

On average, half of the children of a person with one of these rare genetic defects inherit the disease. Probably all those who inherit the genetic defect develop Alzheimer's disease at a comparatively early age. People who do not inherit the disease cannot pass it on.

If you have two or more close relatives (a close relative is defined as a parent or brother or sister) who developed Alzheimer's disease before the age of 60, your GP could advise you about genetic counselling and testing, and refer you to a geneticist if appropriate. You should think carefully before deciding to take a genetic test. The experience might be very difficult emotionally and it could also affect your ability to take out insurance in the future (see Genetic testing and counselling for people at risk of familial dementias below).

The genetic factors for early onset Alzheimer's disease

- A small number of families worldwide have a genetic fault on chromosome 21 in a gene called amyloid precursor protein (APP), which affects production of the protein amyloid. Amyloid build-up in the brain has been linked to Alzheimer's disease.
- A slightly larger number of families carry a fault on chromosome 14 ('presenilin-1') causing early onset familial Alzheimer's disease.
- A very small group of families (mainly in the US) has a fault on chromosome 1 ('presenilin-2') causing early onset familial Alzheimer's disease.

Late onset Alzheimer's disease

Late onset Alzheimer's disease (over 65) is not inherited in the same way as some cases of early onset Alzheimer's disease. Many factors combine to alter a person's risk of developing late onset Alzheimer's disease so that some develop it in later life and others do not. Genetic and environmental factors are both involved. Most of these factors are not fully understood but we do know that having a close family member with the condition increases risk - but only by a small amount. Other factors such as other illnesses, diet, levels of activity and random chance, are probably more significant in the development of Alzheimer's disease in later life.

See the Society's information sheet *Am I at risk of developing dementia?* for further information.

Genetic factors for late onset Alzheimer's disease

The genetic factor for late onset Alzheimer's disease is a gene called apolipoprotein E (ApoE), which we all have in our blood and brain. It comes in three forms: ApoE2, ApoE3 and ApoE4. We all 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. About a quarter of the population inherits one copy of the ApoE4 gene, which increases their risk of developing Alzheimer's disease by up to four times.
- Two per cent of the population get a 'double dose' of the ApoE4 gene, one from each parent. Their risk of developing Alzheimer's disease is increased by about ten times.
- Sixty per cent of the population have a 'double dose' of the ApoE3 gene and are at 'average risk'. About half of this group develop Alzheimer's disease by their late 80s.

- ApoE2 is least associated with Alzheimer's disease. One in six people carry it. People with one ApoE2 gene and one ApoE3 gene (11 per cent of the population) have a 50 per cent chance of getting Alzheimer's disease when they reach their late 90s.
- One in 200 people inherit two copies of the ApoE2 gene and are at a lower risk of developing Alzheimer's disease.

The ApoE risk is different from familial Alzheimer's disease. ApoE4 increases the chance of developing the disease, but does not make it certain. Some other factor, not yet understood, must also contribute. Some researchers think that ApoE4 does not affect whether a person will get the disease but, rather, when they get it, making people with ApoE4 develop the disease before people with ApoE2.

Scientists often discover genes that they think might contribute to late onset Alzheimer's disease. However, after the initial finding, it can take many years to be certain. So far, scientists are only agreed on the significance of ApoE. Other genes may be found that contribute to Alzheimer's disease but the degree of risk involved is likely to be small.

Vascular dementia

There are no established direct genetic causes for vascular dementia but the ApoE gene described above is a risk factor for vascular dementia as well as Alzheimer's disease. There are known genes that contribute to some of the risk factors for vascular dementia, such as high cholesterol levels, high blood pressure and diabetes.

Down's syndrome

People with Down's syndrome are at particular risk of developing Alzheimer's disease. Different studies have suggested different rates of dementia among people with Down's syndrome, but it could be as high as 50 per cent of people with Down's syndrome in their 60s. See the Society's information sheet *Learning disabilities and dementia*.

Huntington's disease

Huntington's disease is a progressive hereditary disease caused by a particular gene. The course of the disease varies for each person and dementia can occur at any stage. See the Society's information sheet *Rarer causes of dementia*.

Other dementias

Some other forms of dementia can be inherited. Some people with fronto-temporal dementia (such as Pick's disease) or with CJD and similar diseases have a very strong family history of the disease. In some of these cases, the genetic link has been found; some families with inherited fronto-temporal dementia have one of a number of faults on the TAU gene, for example. These inherited forms of dementia are rare. See the Society's information sheets *What is Creutzfeldt-Jakob disease (CJD)?* and *What is fronto-temporal dementia (including Pick's disease)?*

There are other very rare causes of inherited dementia with known faults in different genes, such as the PRP gene in inherited CJD and the NOTCH gene in a rare disorder called CADASIL. A few families worldwide have an inherited dementia the cause of which has yet to be discovered.

Genetic testing and counselling for people at risk of familial dementias

Anyone who is worried about inheriting a form of dementia and who has a relative with the condition should speak first to their GP. Although scientists are discovering more about the genetics of late onset Alzheimer's disease there are no approved tests for this condition. However, if you have more than one family member affected by early onset dementia, and particularly if your family members first showed signs of the disease between the ages of 30 and 50, you may be referred to a regional clinical genetics department. Here you will be given more information and an opportunity to discuss the risk to yourself and other family members. For a few families it may be possible to identify a gene change that is responsible for the disease in that family. Most people with a dementia affecting a family member do not have such a gene change. However, if such a change is found in your family this raises the possibility of testing to see if you too have the change. This sort of testing is called predictive testing and is currently offered to people with Huntington's disease in the family, for example. Before having such a predictive test you will be offered extensive counselling to make sure it is the right decision for you.

The pros and cons of genetic testing

A genetic test might:

- Identify people who might benefit from the new Alzheimer's drugs
- Help genetic researchers understand the disease better and so lead to improved treatment
- Help people plan for the future.

However, genetic testing - either for family members or for whole populations - could create problems:

- A genetic defect cannot be repaired, and effective treatment is not yet generally available, so a test might raise anxiety without offering a clear course of action.
- The genetic test for a higher risk of late onset Alzheimer's disease (ApoE4) cannot accurately predict who will develop the disease; testing positive does not mean a person will definitely develop the disease and testing negative does not guarantee that they will not.
- People testing positive could face discrimination affecting their ability to buy property, get insurance or plan financially for their old age.
- In November 2001 the government announced a five-year moratorium on the use of genetic information by insurance companies.

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