

# Genetics of dementia

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**Many people with dementia are concerned that they have inherited the condition and that they may in turn pass it on to their children. Also, family members of people with dementia are sometimes concerned that they might be more likely to develop dementia themselves. Genes can play a role in the development of dementia, but their effects are complicated and patterns of inheritance vary considerably. This factsheet outlines the present state of knowledge about the genetics of dementia.**

## Genes and inheritance

Characteristics that we have inherited from our parents are passed down to us in the form of thousands of genes, the basic units of inheritance. Genes are made from DNA and are found packed within each cell of our bodies on structures called chromosomes. We have 23 pairs of chromosomes and we inherit two copies of each gene, one from each parent.

Genes provide the instructions needed to build our bodies. While many of our genes are identical for all of us, some genes have slight variations that account for the physical differences between people, and also underlie many diseases. Some of these variations between genes are common and are called genetic 'variants', while others are rare and are called 'mutations'.

Some of our physical characteristics are inherited in a relatively simple way, such as our blood group, which can be traced to a single gene. More often, our individual qualities (eg height) reflect the complicated effects of many different genes. Both simple

and complex (multi-gene) patterns of inheritance are seen in dementia.

Although genes are important in building our bodies, most of our physical characteristics and the diseases we may experience are also greatly influenced by our environment and lifestyle, which act to modify the effects of our genetic inheritance.

For more information see factsheet 450, Am I at risk of developing dementia?

## Genes and Alzheimer's disease

Alzheimer's disease is the most common form of dementia and, of all the main types of dementia, the genetics of Alzheimer's is the best understood. We can consider the disease to have two forms: the rare early onset Alzheimer's disease, where first symptoms appear before the age of 65; and the much more common late onset Alzheimer's disease, where typically the first symptoms develop after this age. These two types of Alzheimer's disease generally have different patterns of genetic inheritance.

### Early onset Alzheimer's disease

This form of Alzheimer's tends to cluster within families, sometimes with several generations affected, in which case it is called familial disease. In some of these cases, early onset Alzheimer's is caused by mutations in one of three genes. These three genes are the amyloid precursor protein gene (APP) and two presenilin genes (PSEN-1 and PSEN-2). People with any of these extremely rare mutations tend to develop Alzheimer's disease in their 30s or 40s.

The prevalence of the defective versions of these genes is as follows:

- More than 80 known families worldwide have a mutation in the APP gene on chromosome 21, which affects production of the protein amyloid. A build-up of amyloid in the brain has been linked to Alzheimer's disease.

- Nearly 400 known families worldwide carry a mutation in the PSEN-1 gene on chromosome 14. This causes up to half of all early onset familial Alzheimer's disease, with first symptoms from as early as 30 years of age.
- Only a few dozen known families (mainly resident in the United States) have a mutation in PSEN-2 on chromosome 1, causing early onset familial Alzheimer's disease that starts slightly later than for PSEN-1.

It is important to note that these mutations are extremely rare and account for fewer than one in 1,000 cases of Alzheimer's disease.

It is likely that all of those who inherit faulty versions of any of these three genes will develop Alzheimer's disease at a comparatively early age. On average, half of the children of a person with one of these rare genetic mutations will inherit the disease. People who do not inherit the mutation cannot pass it on.

If you have two or more close relatives (a close relative is defined as a parent, brother or sister) who developed Alzheimer's disease before the age of 60, your GP can advise you about genetic counselling and testing for these rare mutations, and refer you to a geneticist, if appropriate.

### **Late onset Alzheimer's disease**

Late onset Alzheimer's disease is much more common than early onset Alzheimer's disease and its inheritance follows a more complex pattern. This means that having a relative with this form of Alzheimer's increases your own chances of developing it, but not in a predictable way.

A small but growing number of genes have now been identified which affect – to different degrees – the chances of developing late onset Alzheimer's. The effects of these genes are subtle, with variations acting to increase or decrease the risk of developing Alzheimer's disease, but not directly to cause it.

The gene with the greatest known influence on the risk of developing late onset Alzheimer's disease is called apolipoprotein E (APOE). This gene is found on chromosome 19 and comes in three forms, which by convention are named with the Greek letter epsilon ( $\epsilon$ ):

- APOE  $\epsilon$ 2
- APOE  $\epsilon$ 3
- APOE  $\epsilon$ 4.

We all have two copies of the APOE gene, and these may be the same as each other or different. Hence we each have one of the six possible combinations:  $\epsilon$ 2/ $\epsilon$ 2,  $\epsilon$ 2/ $\epsilon$ 3,  $\epsilon$ 3/ $\epsilon$ 3,  $\epsilon$ 2/ $\epsilon$ 4,  $\epsilon$ 3/ $\epsilon$ 4 or  $\epsilon$ 4/ $\epsilon$ 4.

- APOE  $\epsilon$ 4 is associated with a higher risk of Alzheimer's. About a quarter of the general population inherits one copy of the APOE  $\epsilon$ 4 gene. This increases their lifetime risk of developing Alzheimer's disease by up to four times.
- About 2 per cent of the population gets a 'double dose' of the APOE  $\epsilon$ 4 gene – one from each parent. This increases their risk of developing Alzheimer's disease by about 10 times or more. However, even then, they are not certain to develop Alzheimer's.
- About 60 per cent of the population has a 'double dose' of the APOE  $\epsilon$ 3 gene and is at 'average' risk. Up to half of this group develops Alzheimer's disease by their late 80s.
- The APOE  $\epsilon$ 2 form of the gene is mildly protective against Alzheimer's: people with it are slightly less likely to develop the disease. In the general population, 11 per cent has one copy of APOE  $\epsilon$ 2 together with a copy of APOE  $\epsilon$ 3, and one in 200 (0.5 per cent) has two copies of APOE  $\epsilon$ 2.

Some researchers think that APOE  $\epsilon$ 4 does not affect whether a person will get Alzheimer's disease but the age at which they get it. This suggests that people with APOE  $\epsilon$ 4 are likely to develop the disease before people with APOE  $\epsilon$ 2.

Until recently, APOE was the only gene to be consistently linked to the risk of late onset Alzheimer's disease. Recent scientific developments have allowed researchers to test many more genes to see whether there are additional links with Alzheimer's disease. This approach has revealed further genes which are linked to increased risk, called CLU, PICALM, CR1, BIN1, ABCA7, MS4A, CD33, EPHA1 and CD2AP. Variants in these genes are linked to significant differences in risk of Alzheimer's, but their effects are much smaller than for APOE.

Research to find further risk and protective genes is ongoing. In particular, several teams from Europe and the USA have now joined forces to create the International Genomics of Alzheimer's Project. These researchers hope to carry out the largest genetics study of Alzheimer's disease to date, and to provide further insights into the inheritance of the condition.

It is natural for someone whose relative has been diagnosed with Alzheimer's disease to wonder whether they are at increased risk. For someone with a close relative (parent or sibling) who is diagnosed with late onset Alzheimer's disease, the evidence is that their own risk of developing Alzheimer's is increased – on average, about doubled – over their lifetime. However, this does not mean that Alzheimer's is inevitable for them, and everyone can reduce their overall risk by adopting a healthy lifestyle.

## Vascular dementia

Vascular dementia is the second most common form of dementia. There are no established direct genetic causes for the more common forms of vascular dementia, but researchers are looking for risk genes for the disease.

Some studies have reported links between APOE (see above) and vascular dementia, but others have not. The most recent findings suggest that APOE  $\epsilon$ 4 is a risk factor for vascular dementia, but with weaker effects than for Alzheimer's disease. There are also known genes that contribute to some of the underlying risk factors for vascular dementia, such as high cholesterol levels, high blood pressure

and diabetes. Overall, the role of genes in the development of the more common forms of vascular dementia seems to be less significant than in late onset Alzheimer's disease.

By contrast, some very rare forms of vascular dementia are caused by known simple genetic defects. For example, mutations in a gene called NOTCH3 cause a rare form of vascular dementia known as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). CADASIL is inherited in a simple, single-gene pattern similar to early onset familial Alzheimer's disease.

## Fronto-temporal dementia

Fronto-temporal dementia (FTD) often runs in families: about one third of people with it have a strong family history, with at least two or three relatives affected. In some of these cases FTD is inherited as a mutation in a single gene, most notably in the genes for the proteins tau (MAPT) and progranulin (GRN). On average, half of the children of someone with such a mutation will inherit the gene and develop FTD. Families with known mutations will be offered referral to specialist genetics services and counselling.

For information about this type of dementia, see factsheet 404, What is frontotemporal dementia?

## Dementia with Lewy bodies

The genetics of dementia with Lewy bodies (DLB) is not well understood, although – as for most other common forms of dementia – there are both rare familial cases and more common cases not linked to family history.

The symptoms of DLB overlap with those of both Alzheimer's disease and Parkinson's disease with dementia, and there is evidence that some of the risk genes for DLB are also known risk genes for these other dementias. Whether these overlapping risk genes include APOE (see above) is not yet clear.

For information about this type of dementia, see factsheet 403, What is dementia with Lewy bodies (DLB)?

## **Down's syndrome**

People with Down's syndrome are at particular risk of developing dementia. This is typically Alzheimer's disease, which can affect as many as 50 per cent of people with Down's syndrome who live into their 60s. This increased risk may be present because people with Down's have an extra copy of chromosome 21, and hence an extra copy of the amyloid precursor protein gene (APP) which is found on that chromosome. APP has been linked to Alzheimer's disease.

For more information on Down's syndrome and dementia, see factsheet 430, Learning disabilities and dementia.

## **Huntington's disease**

Huntington's disease is a rare progressive hereditary condition caused by a mutation in a particular gene (Huntingtin). The course of the disease varies for each person, and dementia can occur at any stage. Huntington's is inherited in a simple single-gene pattern. Someone with Huntington's disease therefore has a 50 per cent chance of passing it on to each child, and affected families are routinely offered genetic counselling (see 'Genetic testing and counselling' below).

## **Genetic testing and counselling**

Anyone who is worried about inheriting a form of dementia and who has a relative with the condition should speak to their GP. Although scientists are discovering more and 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 Alzheimer's, 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 genetics clinic. Here you will

be given more information and an opportunity to discuss the risk to yourself and other family members.

For some families with early onset familial Alzheimer's disease it may be possible to identify a specific genetic mutation that is responsible for the disease in that family. If such a mutation is found in your family this raises the possibility of testing to see if you too have the mutation. This sort of testing is called 'predictive testing', and is currently offered to people with genetic diseases with predictable inheritance patterns, such as Huntington's disease. 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**

Genetic testing for the rare single-gene causes of dementia is available through referral to genetics services. Testing for risk genes such as APOE is not generally recommended but is still commercially available.

Genetic testing is not a straightforward issue and individuals need to think very carefully before deciding to take such a test. The experience might be very difficult emotionally, may not provide conclusive results either way, and may cause practical difficulties.

On the positive side, genetic testing might:

- help genetic researchers understand the disease better and so lead to improved treatment
- encourage someone to adopt a healthier lifestyle
- help people to plan for the future.

However, genetic testing may create problems, for the following reasons:

- A genetic defect cannot be repaired, and effective treatment to slow the disease is not yet generally available. A gene test

might therefore raise anxiety without offering a clear course of action.

- In the case of genetic testing for APOE variants there is a risk of reading too much into the test results. Testing positive for one or two copies of APOE ε4 does not mean a person will definitely develop late onset Alzheimer's disease. Testing negative for APOE 4 does not guarantee that they will be free from Alzheimer's.
- People testing positive for any genetic test could face discrimination affecting their ability to buy property, get insurance or plan financially for their old age, although there is a moratorium (delay or suspension of an activity or law) on the use of genetic information by UK insurance companies until 2017. This means that the companies cannot use this information at the moment.

For details of Alzheimer's Society services in your area, visit [alzheimers.org.uk/localinfo](http://alzheimers.org.uk/localinfo)

For information about a wide range of dementia-related topics, visit [alzheimers.org.uk/factsheets](http://alzheimers.org.uk/factsheets)

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This factsheet has also been reviewed by people affected by dementia. A list of sources is available on request.



## Alzheimer's Society National Dementia Helpline

England, Wales and Northern Ireland:  
**0300 222 11 22**

9am–5pm Monday–Friday  
10am–4pm Saturday–Sunday

[alzheimers.org.uk](http://alzheimers.org.uk)

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