



# Genetics and dementia

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## Introduction

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.

## Genetics and disease

Genes are the unique set of instructions inside our bodies which make each of us an individual. There are many thousands of different genes, each carrying a different instruction.

We have two copies of each gene. One copy is inherited from each of our parents. When we

have children, we pass on only one copy of each of our genes.

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 our knowledge. There can be different versions of the same gene which may work differently or not as well. This can cause a genetic condition or disease, and some gene faults may lead to a person developing dementia.

Some diseases are caused by a genetic mutation, or permanent change, in one specific gene. If a person inherits from a parent a genetic mutation that is linked to a certain disease, then he or she will usually get the disease. Cystic fibrosis, muscular dystrophy, and Huntington's disease are examples of single-gene disorders.

In other diseases, a genetic variant, or a change in a gene, may occur, but it doesn't necessarily cause the person to develop the disease. More than one gene variant may be necessary to cause the disease, or the variant may increase a person's risk of developing the disease. When this happens, the changed gene is called a genetic risk factor.

## The genetic factors associated with dementia

It should be noted that 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 in itself is not evidence of a family link.

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 often 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

Early onset Alzheimer's disease is the term used when someone develops Alzheimer's disease under the age of 65. Most cases of early onset Alzheimer's disease are **not** inherited; however, a very small number of cases of early onset Alzheimer's are inherited.

The term Familial Alzheimer's disease is used for families where a genetic fault directly causes the disease. Familial Alzheimer's disease usually affects younger people (under the age of 65) rather than older people. These particular genetic faults can result in people developing Alzheimer's disease in their 30s and 40s.

On average, half of the children of a person with one of these rare familial Alzheimer's disease genetic faults inherit the faulty gene. Almost all those who inherit it develop Alzheimer's disease at a comparatively early age. People who do not inherit the faulty gene cannot pass it on to their children.

### Genetic factors for familial early onset Alzheimer's disease

- A small number of families worldwide have a genetic fault 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 in a gene called presenilin-1 leading to early onset familial Alzheimer's disease.
- A very small group of families has a fault in a gene called presenilin-2 causing early onset familial Alzheimer's disease.

### Late onset Alzheimer's disease

The vast majority of people with Alzheimer's disease are over 65. Late onset Alzheimer's disease 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. 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 Further reading section below for more information about risk factors and dementia.

### Genetic factors for late onset Alzheimer's disease

The best known genetic factor for late onset Alzheimer's disease is a gene called apolipoprotein E (ApoE) which was identified in the mid 1990s. It comes in three forms ApoE2, ApoE3 and ApoE4. We all have two copies of the gene, which may be the same version as each other or different.

The ApoE risk is different from how familial Alzheimer's disease is inherited.

Having one or two copies of ApoE4 increases the chance of developing the disease, but does not make it certain. Some people with one or two copies of ApoE4 never develop Alzheimer's

disease, and others who develop Alzheimer's disease do not have ApoE4.

One or two copies of ApoE3 are associated with an average risk, and the risk of developing Alzheimer's disease for people with two copies of ApoE2 is reduced. 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, causing people with ApoE4 to develop the disease before people with ApoE2.

A blood test is available that can identify which forms of ApoE a person has, but it is not yet possible to predict who will or will not develop Alzheimer's disease. Because ApoE testing cannot accurately predict who will develop the disease, it is generally not available to patients and their families except as part of a research study.

### **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.

### **Huntington's disease**

Huntington's disease is a progressive hereditary disease caused by a particular gene. The symptoms of Huntington's disease usually develop when people are 30-50 years old, although they can start much earlier or much later and can vary from person to person, even in the same family. The course of the disease also varies for each person and dementia can occur at any stage.

### **Other dementias**

Other forms of dementia can be inherited. Some people with fronto-temporal dementia or Pick's disease have a very strong family history. In some of these cases, a genetic change has been found in the Tau gene. These inherited forms of dementia are rare.

The same researchers who identified the link with the Tau gene have also identified granulin as a second gene mutation involved in fronto-temporal dementia.

There are other very rare causes of inherited dementia with changes in different genes, such as the PRP gene in inherited Creutzfeldt-Jakob disease (CJD) and the NOTCH3 gene in a rare disorder called CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). A few families worldwide have an inherited dementia, the cause of which has yet to be discovered.

### **Recent findings on genetic risk factors**

Dementia researchers across the world are constantly searching for other risk-factor genes. Identifying these risk factors may open the way for scientists to develop ways to modify these genes to prevent disease developing, or help them develop treatments.

Two of the newly found genes, CLU, which produces Clusterin, and CR1, have been shown to be involved in the clearance of amyloid beta peptide, a major component of the "plaques" that form in the brains of people with Alzheimer's disease. Defective versions of these genes could fail to clear out these peptides effectively from the brain.

As well as helping rid the brain of potentially destructive amyloid protein, Clusterin also dampens down damaging inflammation caused by an overactive immune response — a function it shares with CR1. Previously, the inflammation detected in the brains of people

with Alzheimer's disease was thought to be caused by the disease and the build of plaques of amyloid protein. This new research suggests that the inflammation is the cause of the cell damage.

Another identified gene, called PICALM, is involved in the connections between brain cells, one of the key parts of the brain for memory.

In 2009, American researchers announced the discovery of particular variant of a gene called PCDH11X which appeared to be closely linked to a higher risk of Alzheimer's disease, but mainly in women with two copies of this genetic variant. PCDH11X controls production of a protein called a protocadherin, part of a family of molecules that help cells in the central nervous system to communicate with each other.

### **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 close 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 but for most families this will not be the case.

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 available to people with Huntington's disease in the family, for example. Before having 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 Alzheimer's drugs
- Help people plan for the future
- Help genetic researchers understand the disease better and so lead to improved treatment.

However, it may also:

- Lead to problems getting a mortgage or life insurance in the future, although there is a moratorium on the use of genetic information by the Association of British Insurers until 2017. This means you do not currently have to disclose the result of any genetic test for dementia when applying for life insurance or if you have a genetic test after you have taken out life insurance. The only exception to this is for people with a family history of Huntington's disease who want to take out substantial life insurance
- Raise anxiety without offering any useful treatment.

Testing for genes which are risk factors, like ApoE4, but not predictive as in familial Alzheimer's disease, is not done. This sort of test is not helpful because a higher risk does not necessarily mean someone will develop the illness and a lower risk does not mean they won't, and there is no treatment to offer someone at high risk.

### Further reading

Alzheimer Scotland (2006). Dementia – how to reduce your risk. Free information leaflet.

Alzheimer Scotland (2006). Good for You Good for Your Brain: the evidence on risk reduction and dementia. Free.

Available from Alzheimer Scotland, 22 Drumsheugh Gardens, Edinburgh EH3 7RN. Tel: 0131 243 1453 or visit [www.alzscot.org](http://www.alzscot.org)

### Acknowledgements

We are grateful to the Alzheimer's Society for permission to reproduce, with amendments, the text of their factsheet *Genetics and dementia*.

### Feedback

Alzheimer Scotland actively seeks the views of people with dementia and their carers. If you have any comments or suggestions about this information sheet please send them to:

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E-mail: [alzheimerscot@alzscot.org](mailto:alzheimerscot@alzscot.org)

This information can be found on-line at [www.alzscot.org/pages/info/geneticsanddementia.htm](http://www.alzscot.org/pages/info/geneticsanddementia.htm)

It is also available as a pdf and as a large-print version.



The logo for the Dementia Helpline 24 Hour service. It features a circular icon with a person and a telephone handset. The text reads: "Dementia Helpline 24 HOUR" in large, bold letters. Below this, it says "Alzheimer Scotland Action on Dementia". At the bottom, it provides the freephone number "0808 808 3000" and the email address "helpline@alzscot.org".

### Alzheimer Scotland

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