

# GENETICS OF DEMENTIA

This Help Sheet discusses the role of genetics in Alzheimer's disease and other forms of dementia and whether the condition can be inherited

## Understanding genes

The genetic material that we each inherit from our parents is packaged into structures called chromosomes. Each chromosome contains thousands of genes. Genes contain instructions for making proteins – they are the blueprints for making a person. They allow specific characteristics (e.g. hair colour, height, the tendency to develop diabetes) to be passed from one generation to the next. We have two copies of every gene, one inherited from our mother and one from our father.

A mutation is a permanent change in a gene from its normal form. Some gene mutations cause disease, so that if a person inherits a mutated gene for a certain disease, they will definitely develop that illness in life. The vast majority of cases of dementia are not caused by an inherited genetic mutation. Dementia is so common that having one or two close relatives with dementia is not evidence of a genetic link.

Other genes are so called susceptibility or risk genes – they do not inevitably lead to a person developing the illness, but they increase the risk of developing the illness. Susceptibility genes associated with an increased risk of dementia have been identified.

## Genetics of Alzheimer's disease

### Familial Alzheimer's disease

The term familial Alzheimer's disease is used for the small number of families who carry a genetic mutation that directly causes the disease. Familial Alzheimer's disease usually affects younger people (under the age of 65), some as young as their 30s and 40s. On average, half of the children of a person with familial Alzheimer's disease will inherit the faulty gene. All those who inherit it will develop Alzheimer's disease. People who do not inherit the faulty gene cannot pass it on to their children.

Three genes have been identified which, if mutated in certain ways, will cause familial Alzheimer's disease. These are called presenilin 1, presenilin 2 and the amyloid precursor protein gene (APP). The result of these mutations is increased production of the beta amyloid plaques that damage the brain in Alzheimer's disease. Mutations in these genes are rare, and account for less than 5% of all cases of Alzheimer's disease.

Genetic testing can identify the presence of gene mutations that cause familial Alzheimer's disease. This test can tell if a person has familial Alzheimer's and if a child has inherited the changed gene from a parent and will develop the disease in the future. It cannot determine when the symptoms will begin. Usually though, the age of onset is similar to that of the parent.

### Sporadic Alzheimer's disease

The vast majority of Alzheimer's disease cases are not caused by known gene mutations; their cause is unknown. Having a close relative with Alzheimer's disease is not evidence of a genetic link. Many factors combine to alter a person's risk of developing Alzheimer's. Genetic and environmental factors are both involved. We do know that having a close family member with the condition increases risk – but only by a small amount.

Susceptibility genes only partly explain this increased risk. About 10 susceptibility genes that increase the risk of Alzheimer's disease have been identified. The most important of these is the apolipoprotein E (ApoE) gene. It comes in three forms – ApoE2, ApoE3 and ApoE4. We have two copies of the gene, which may be the same form as each other or different. Having one or two copies of ApoE4 increases the chance of developing Alzheimer's disease, but does not make it certain. Some people with ApoE4 never develop Alzheimer's, and others who develop Alzheimer's do not have ApoE4.

ApoE3 is associated with an average risk, and ApoE2 with a reduced risk. A blood test can identify which forms of ApoE a person has, but it is not possible to predict who will or will not develop Alzheimer's disease. ApoE testing is therefore generally not available except as part of a research study.

Other susceptibility genes are also associated with increased Alzheimer's risk. They increase the risk by very small amounts, so don't play as large a role in the risk of Alzheimer's as ApoE4.

Carrying ApoE4 has also been associated with increased risk for cardiovascular disease and vascular dementia.

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### Genetics of frontotemporal dementia

Frontotemporal dementia is associated with degeneration of the frontal and/or temporal lobes of the brain and changes in behaviour and/or language abilities. Some forms of frontotemporal dementia are inherited, caused by specific gene mutations. Of these familial forms, two genes account for around 50% of cases – the MAPT or tau gene and the progranulin gene. Several other less common gene mutations have also been identified as causing frontotemporal dementia.

On average, half of the children of a person with familial frontotemporal dementia will inherit the faulty gene and develop the disease. For affected families, genetic testing is available. Familial frontotemporal dementia accounts for only around 10-15% of all cases. The majority of cases are sporadic. For further information visit the Frontier research group website [ftdrg.org](http://ftdrg.org).

### Other genetic forms of dementia

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a rare inherited form of vascular dementia. It is caused by mutations in the NOTCH3 gene on chromosome 19. CADASIL is characterised by recurrent strokes, lesions in the deep white matter of the brain, migraines, psychiatric symptoms and progressive dementia.

Familial Lewy body disease is very rare, but a few gene mutations causing the disease have been identified. Mutations in the SCNA gene cause Lewy body disease, which may manifest as dementia, Parkinson's disease or other related disorders.

There are familial forms of Creutzfeldt-Jakob disease, which causes a rapidly progressing dementia. Mutations of the PRNP gene account for 5-10% of Creutzfeldt-Jakob disease cases.

Huntington's disease is an inherited condition causing motor, psychiatric and cognitive symptoms, and in most cases dementia. It is caused by mutations in the Huntington's gene.

For all of the above familial dementias, children of an affected person have a 50% chance of inheriting the gene and developing the disease.

### Genetic testing

Because inherited forms of dementia are very rare, genetic testing is not relevant for most families affected by dementia. For those affected by a familial dementia, genetic testing is available. For a person with symptoms of dementia and a family history suggestive of a genetic cause, genetic testing can help establish the diagnosis. For family members, especially children, of a person with a known genetic mutation, genetic testing can predict the development of the disease in the future.

The decision to undergo genetic testing for familial dementia is very complex and the advantages and disadvantages must be carefully considered. The test can only be completed with the informed consent of the person being tested. No one should ever be pressured to have such a test. Knowing that you are carrying the gene may help some people plan for the future. It enables them to consider future lifestyle and reproductive choices. However, given that no cure is available an individual has to consider whether they want to know that they will develop dementia at some time in the future.

For those concerned about passing on a faulty gene to future children, in some cases prenatal genetic testing or IVF procedures are now available that provide additional choices for dealing with this difficult issue.

To help people consider the issues for themselves and their family, specialised genetic counselling is essential. This is available through state-based genetics services and your doctor can provide details and referrals.

The Centre for Genetics Education provides current genetics information for people affected by genetic conditions. Visit [genetics.edu.au](http://genetics.edu.au)

### FURTHER INFORMATION

Alzheimer's Australia offers support, information, education and counselling. Contact the National Dementia Helpline on **1800 100 500**, or visit our website at [fightdementia.org.au](http://fightdementia.org.au)



Interpreter

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