

# Genetics of dementia

People affected by dementia are often concerned about whether the condition can be inherited. The genetics of dementia are complex and not yet fully understood. This sheet discusses our current knowledge and the latest research on the role of genetics in Alzheimer's disease and other forms of dementia.

## What are genes and chromosomes?

Our bodies are made up of billions of cells. Most of these cells contain all our genetic material, packaged into structures called chromosomes. Each chromosome contains thousands of genes. Humans have 46 chromosomes, 23 inherited from our mother and 23 from our father. Genes and chromosomes are made of the chemical substance called DNA (deoxyribonucleic acid). The chromosomes are very long thin strands of DNA, coiled up like a ball of string. The genes are smaller segments of DNA within the long chromosome.

Because we have 23 pairs of chromosomes, we have two copies of every gene, one inherited from our mother and one from our father. The exception is the sex chromosomes, X and Y. While females have two X chromosomes, males have one X and one Y, so only have one copy of the genes on those chromosomes.

Genes contain instructions for making proteins and are therefore the blueprints for making our body and for all the functions it performs. They allow specific characteristics (e.g. hair colour, height, or the tendency to develop diabetes) to be passed from one generation to the next. Our genetic blueprint is 'read' by our cells in a background of our personal internal and external environments. This includes our diet, the chemicals that we are exposed to, our other genes and our age. Our environment plays a major role in how our bodies work by interacting with our genetic information.

Completed in 2003, the Human Genome Project identified the sequence of genes in our chromosomes. However, finding out what the information in each of our genes tells our bodies to do will take many more years.

Most genes come in a number of different forms, called variants or alleles. These normal variations are spread throughout the population and make us all

different. A mutation on the other hand, is a permanent change in a gene from its normal form that makes the gene faulty. It is a rearrangement of the DNA that changes the way the gene works and the proteins that it builds. If a person has a mutated gene, they may pass it on to their children. Because the person has two copies of the gene, one faulty and one normal, and only one is passed on, each child has a 50-50 chance of inheriting the faulty gene.

Gene mutations cause diseases in different ways. Some gene mutations cause diseases that you are born with, and are evident from birth. Some cause disease later in life, so that if a person inherits the mutated gene, they will develop the disease, provided they live to the age when it starts.

**Autosomal-dominant** genetic diseases occur when you inherit only one copy of the mutated gene and still develop the disease. This means that in each family the disease is caused by a mutation in a single gene, and that a single copy of the mutated gene, inherited from one parent, will cause the disease. However, even in people with a known autosomal dominant mutation, there is often a wide spectrum of disease age of onset and severity. This is termed **penetrance**, with some mutations being more penetrant than others. A well-known example of this type of genetic disease is Huntington's disease.

Some diseases are **autosomal recessive**, which means you need two copies of the gene to get the disease. The commonest autosomal recessive disease that people may have encountered is cystic fibrosis.

Other normal gene variations 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 it. Many susceptibility genes associated with an increased risk of dementia have been identified.

## What do we know about the genetics of Alzheimer's disease?

### Familial Alzheimer's disease

The vast majority of cases of dementia are not caused by an inherited genetic mutation. Dementia is so common that having several close relatives with dementia is not evidence of a genetic link.

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, provided they live to the age when it starts. Those who do not inherit the faulty gene cannot subsequently pass it on to their children.

Genetic testing can identify the presence of gene mutations that cause familial Alzheimer's disease. Genetic testing may help determine if a person with dementia has familial Alzheimer's, or 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. See below for more about the process of genetic testing.

Three major genes have been identified which, if mutated in certain ways, will cause familial Alzheimer's disease. These genes implicated in the production and breakdown of amyloid, an important protein deposited in the brain of people with Alzheimer's disease are called presenilin 1 (PSEN1) and presenilin 2 (PSEN2). There is also a mutation identified in the gene encoding the amyloid precursor protein (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 1% of all cases of Alzheimer's disease.

While mutations in these three genes predominantly cause younger onset Alzheimer's disease, recent research suggests they may be present in some cases of older onset Alzheimer's. There may also be additional gene mutations that cause familial Alzheimer's that have not yet been identified. Research is continuing that will lead to a more thorough understanding of the genetic causes of Alzheimer's disease.

The Dominantly Inherited Alzheimer's Network (DIAN) is an international research collaboration investigating familial Alzheimer's disease. Their research is helping discover how Alzheimer's disease starts and changes the brain over time, and what treatments could be used to stop disease progression before an affected person develops dementia. Two Australian centres are involved in DIAN: Neuroscience Research Australia in Sydney, and the Florey Institute for Neuroscience and Mental Health in Melbourne. For further information visit the DIAN website [dian-info.org](http://dian-info.org).

Genetic testing can identify the presence of gene mutations that cause familial Alzheimer's disease. Genetic testing may help determine if a person with dementia has familial Alzheimer's, or 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. See below for more about the process of genetic testing.

### Down syndrome and Alzheimer's disease

The genetic abnormality that causes Down syndrome is an extra chromosome 21. The APP gene is on chromosome 21, so people with Down syndrome produce more of this protein and more beta amyloid, which forms when APP breaks down and is the main component of the plaques in the brain that characterise Alzheimer's disease. People with Down syndrome therefore have a much higher chance of developing Alzheimer's disease, and at a much earlier age, compared to the general population.

### Sporadic Alzheimer's disease

The vast majority of Alzheimer's disease cases are not caused by known gene mutations. Their genetic cause is unknown. Having close relatives with Alzheimer's disease is not evidence of a genetic link. Many genetic and environmental factors combine to alter a person's risk of developing Alzheimer's disease. 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. Ten susceptibility genes that increase the risk of Alzheimer's disease have now been identified. The most important of these is the apolipoprotein E (ApoE) gene. It comes in three forms – ApoE2, ApoE3 and ApoE4. We each 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.

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

ApoE3 is associated with an average risk of Alzheimer's disease, 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 not recommended and is generally not available except as part of a research study. Research is ongoing to determine how ApoE4 may interact with other genetic and environmental factors to influence the development of Alzheimer's disease.

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. Recent research has identified susceptibility genes that appear to be involved in cholesterol metabolism and inflammation. Untreated high cholesterol is a risk factor for Alzheimer's and inflammation in the brain is a feature of the disease. The discovery of these susceptibility genes may therefore open the door to potential new treatments or prevention of Alzheimer's disease.

### **What do we know about the genetics of frontotemporal dementia?**

Frontotemporal dementia is associated with degeneration of the frontal and/or temporal lobes of the brain. This manifests as changes in behaviour and/or language abilities. Some forms of frontotemporal dementia are inherited, caused by specific gene mutations. Three major autosomal dominant mutations have been identified: MAPT mutations, which is associated with abnormal tau protein deposition; the progranulin gene (PGRN), and the C9orf72 mutation, which is by far the commonest in Australians. These latter two are both associated with the deposition of a protein called TDP-43. Several other less common gene mutations have also been identified as causes of frontotemporal dementia.

On average, half of the children of a person with familial frontotemporal dementia will inherit the faulty gene and are therefore at risk of developing the disease. However, not everyone with the mutation necessarily gets FTD. For affected families, genetic testing is available. Familial frontotemporal dementia accounts for up to 30% of all cases. The majority of cases are sporadic. For further information visit the Frontier Research Group website: [ftdrg.org](http://ftdrg.org) or the Eastern Cognitive Disorders Clinic Toolkit, [ecdc.org.au](http://ecdc.org.au).

### **What do we know about the genetics of vascular dementia?**

The risk of developing vascular dementia is increased by conditions including high blood pressure, diabetes, high cholesterol and cardiovascular disease. Genetics can play a role in these conditions and their impact on brain health. The ApoE4 gene is also associated with increased risk of vascular dementia.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a rare inherited form of vascular dementia. It is thought to be rare, although may often be misdiagnosed so more cases may exist. It is caused by mutations in the NOTCH3 gene on chromosome 19. CADASIL is characterised by recurrent strokes, injury to the deep white matter of the brain visible on brain scans, migraines, psychiatric symptoms and progressive dementia. Symptoms and age of onset vary widely. There are also a few other very rare forms of inherited vascular dementia.

### **What do we know about the genetics of Lewy body disease?**

Most cases of dementia with Lewy bodies, one of the conditions in the spectrum of Lewy body disease, are sporadic with no known family history. Familial Lewy body disease is believed to be very rare, but mutations in a few genes that cause the disease have been identified. Mutations in the SCNA gene can cause Lewy body disease, which may manifest as dementia, Parkinson's disease or other related disorders. The SCNA gene is responsible for the protein alpha-synuclein, which is the main component of Lewy bodies, the abnormal bodies within brain cells that characterise the disease.

Susceptibility genes that increase the risk of Lewy body disease have also been identified. A variant of the glucocerebrosidase (GBA) gene is associated with increased risk of Lewy body disease, as is the ApoE4 variant.

### **Are there other genetic forms of dementia?**

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 huntingtin gene.

For all of the above familial dementias, children of an affected person have a 50-50 chance of inheriting the faulty gene.

## Is genetic testing available?

Many people with a family member affected by dementia wonder whether genetic testing is available to them, to determine whether or not they will also develop the condition. Because inherited forms of dementia are very rare, genetic testing is not relevant for most families affected by dementia. The dementia is not caused by a single gene, so no test can be performed that will establish whether the next generation will be affected by dementia or not.

For those affected by a familial dementia caused by a single gene however, genetic testing may be available. For a person with symptoms of dementia and a family history suggestive of an autosomal-dominant inheritance, genetic testing can help establish the diagnosis (diagnostic testing). 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 (predictive testing). However, interpreting the results of genetic tests for familial dementias is complicated and they do not always provide clear answers.

The decision to undergo genetic testing for familial dementia is very complex and the advantages and disadvantages must be carefully considered. Genetic counselling is an absolute requirement prior to any testing. Any person interested in seeking testing needs to be seen by a trained genetic counsellor, expert in the disease.

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 will usually include counselling regarding the purpose of the test, the meaning of positive or negative results, the implications of results for the person and their family, alternative options, and the potential benefits and risks. Genetic counselling can also help people understand the complexities of familial dementia and their own risk, even if they have no desire for genetic testing.

## Further Information

Genetic counselling and testing is available through state-based genetics services and your doctor can provide details and referrals. Services in Australia and New Zealand are also listed in the 'Genetics Services' section of the Centre for Genetics Education website [genetics.edu.au](http://genetics.edu.au).

## FURTHER INFORMATION

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



For language assistance phone the Translating and Interpreting Service on **131 450**

## 4 GENETICS OF DEMENTIA