Many people will be concerned about whether dementia can be inherited – that is, passed down from an affected relative. People with dementia might be worried that they have inherited it and may pass it on to their children. Family members of people with dementia, such as brothers and sisters, may also be worried that they are more likely to develop dementia themselves.

Genes are the means by which characteristics are passed down through families. They can play a role in the development of dementia, but their effects are complicated and how and whether dementia is passed down – the ‘patterns of inheritance’ – vary considerably. This factsheet outlines what we currently know about the genetics of dementia and what it may mean for you.

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Genetics of dementia

Genes and inheritance

We all know how children often take after their parents or grandparents. This is in part because some things – physical characteristics, for example – are passed down to us from our parents in the form of about 20,000 different genes.

Genes are the basic units of inheritance. They are made from DNA and are found within almost all the cells of our bodies, packaged in paired structures called chromosomes. In general, everyone has two copies of each gene, one inherited from each parent.

Genes provide the instructions needed to build and maintain our bodies. While much of our DNA is the same for all of us, many genes will differ slightly from person to person. These differences partly account for the physical differences that make each of us unique. They also affect our chances of developing many common diseases.

There are two types of differences that can occur in genes. The first are common genetic ‘variants’. A variant is not a faulty or abnormal gene. Rather, some genes have multiple different forms (the variants), and people can have different forms. Some are more or less common, but for any of these genes there will be a spread of variants throughout a population.

It is important to understand that genes are only part of the picture. Whatever genes you may have inherited, most people can significantly reduce their chances of getting dementia through simple lifestyle choices. These include not smoking, taking regular physical exercise, eating a healthy diet and drinking alcohol only in moderation (if at all). For more information on this see factsheet 450, Risk factors for dementia.
The role that each gene variant plays in determining any of our characteristics is generally quite small. Most of our individual qualities (e.g., height, risk of diabetes) reflect the combined effects of many of these variants acting together, as well other factors like our lifestyle or environment. Inheritance of a characteristic that is influenced by a genetic variant is not simple – the inheritance follows a complex pattern.

In contrast, the second type of differences that can occur in genes are rare and are called ‘mutations’. The effect of a mutation tends to be greater and can be harmful – a gene with a mutation is a faulty gene. Sometimes a particular characteristic can be traced back to a mutation in a single gene. One example is the gene for Huntington’s disease – if an individual inherits a faulty copy of the Huntington’s disease gene, they will go on to develop the disease. In these cases, the gene and characteristic are generally inherited in a relatively simple way.

The inheritance of dementia can follow either of these patterns. A few families have a simple inheritance pattern due to single-gene mutations. Many more families have a complex inheritance pattern due to multi-gene variants.

While inheriting dementia directly (through a single-gene mutation) is rare, genes are thought to play some role in almost all cases of dementia. This is because the different genetic variants we all have affect our chance of developing the condition to some degree. Our genetic variants also play a role in determining how healthy we are in other ways, such as our cardiovascular health. This means that they indirectly raise or lower our chances of developing dementia.

Genes are very important in building and maintaining our bodies, but most of a person’s physical characteristics and their chances of developing particular diseases also depend a lot on their environment and lifestyle. Whether or not we develop a disease can depend on whether we smoke, exercise, have a healthy diet and so on, as well as the genes we were born with and how old we are. This matters because people tend to think of the effects of genes as inevitable or completely fixed, but in most cases this is not true.
Genes and dementia

There are four common types of dementia: Alzheimer’s disease, vascular dementia, dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD). How important genes are in these different dementias varies considerably. For example, the role of genes in FTD seems to be much greater than in vascular dementia.

This section gives an overview of the role of genetics in these different dementias.

Alzheimer’s disease

Alzheimer’s disease is the most common form of dementia and the genetics of Alzheimer’s is the best understood of all the common dementias. Studies of how Alzheimer’s disease appears in families show that there can be both simple (single-gene mutation) and complex (multi-gene variant) inheritance patterns. The genes involved in each kind of inheritance are different.

Familial Alzheimer’s disease

In just over 600 families worldwide, studies reveal many close family members who are affected by Alzheimer’s disease across successive generations. This pattern of ‘familial clustering’ of Alzheimer’s disease suggests there is a mutation within a single gene that causes the disease. In these cases, the mutation is being passed down in the DNA from parent to child, across several generations.

People with one of these extremely rare mutations tend to develop Alzheimer’s disease early, in their 30s, 40s or 50s. This is much younger than in the majority of people who develop the disease. (Dementia that starts before the age of 65 is known as young-onset or early-onset dementia, whereas dementia that starts after 65 is called late-onset.)

Studies of the affected families show that their Alzheimer’s disease is usually caused by a mutation in one of just three genes. (In a few families no mutation is found. They probably have a different but unknown, even rarer, mutation.)
These three genes are the amyloid precursor protein (APP) gene and two presenilin genes (PSEN-1 and PSEN-2):

- More than 450 known families worldwide carry a mutation in the PSEN-1 gene on chromosome 14. This causes up to 80 per cent of all familial Alzheimer’s disease, with symptoms appearing as early as 30 years of age.
- More than 100 known families worldwide have a mutation in the APP gene on chromosome 21, which affects production of the protein beta-amyloid. A build-up of beta-amyloid in the brain is thought to be a major factor in the development of Alzheimer’s disease.
- More than 30 known families have a mutation in the PSEN-2 gene on chromosome 1, causing familial Alzheimer’s disease that can start later than for PSEN-1.

It is important to note that these mutations are extremely rare. Among people with early-onset Alzheimer’s disease – which is itself uncommon – only about 1 in 10 has a very strong family pattern of inheritance. However, when symptoms start very early, for example in a person’s 30s, the chance that the disease has been inherited is higher than 1 in 10. When all Alzheimer’s disease starting at any age is considered, fewer than 1 in 100 cases are thought to be caused by mutations in these three genes.

It is likely that if you inherit a mutation in one of these genes you will develop Alzheimer’s disease at a comparatively early age. Unfortunately, in these cases adopting a healthy lifestyle is not likely to reduce your chances of getting the disease.

A child of someone with one of these mutations has a 50 per cent (or 1 in 2) chance of inheriting the mutation. Just like tossing a coin, each child has an equal chance of inheriting or not inheriting the mutation. If you have a full brother or sister with a mutation, you will also have a 50 per cent chance of having it. People who do not inherit the mutation cannot pass it on to their children.
A family tree showing strong inheritance of a mutation (dark figures) across three generations. The affected grandfather had three children. Two of these three inherited the mutation. Of these two, the daughter has one affected male child and the affected son has no children. The two (and any future) children of the unaffected son are free of the mutation.

Risk genes for Alzheimer’s disease
The vast majority of people with Alzheimer’s disease do not inherit it from a parent as a single-gene mutation with a simple inheritance pattern. Instead, the inheritance follows a more complex pattern. The disease might skip a generation, affect people on both sides of the family, appear seemingly from nowhere or not be passed on at all.

More than 20 gene variants (or regions within the DNA) have now been identified which affect – to different degrees – the chances of a person developing Alzheimer’s disease. The effects of these genes are subtle. Different variants act to slightly increase or decrease the risk of a person developing Alzheimer’s disease, but do not directly cause it. These ‘risk genes’ interact with each other and with other factors, such as age and lifestyle, to influence someone’s overall risk of getting the disease.

Unlike familial Alzheimer’s disease, this multi-gene form generally affects older people, with symptoms starting after the age of 65. The gene with the greatest known effect on the risk of developing late-onset Alzheimer’s disease is called apolipoprotein E (APOE). This gene is found on
chromosome 19 and the APOE protein plays a role in handling fats in the body, including cholesterol. The APOE gene comes in three variants, which are named with the Greek letter epsilon (ε): APOE e2, APOE e3 and APOE e4.

We each have two copies of the APOE gene, and these may be the same as each other or different. Therefore everyone is born with one of the six possible combinations: e2/e2, e2/e3, e3/e3, e2/e4, e3/e4 or e4/e4. The combination we have affects our risk of Alzheimer’s disease, as follows:

- APOE e4 is associated with a higher risk of Alzheimer’s disease. About 25 per cent of the general population inherits one copy of APOE e4. This increases their lifetime risk of developing Alzheimer’s disease by a little more than two times, on average. People with APOE e4 also tend to develop Alzheimer’s at a younger age.

- About 2 per cent of the population gets a ‘double dose’ of the APOE e4 gene – one from each parent. This increases their risk of developing Alzheimer’s disease by about three to five times, on average. However, they are still not certain to develop Alzheimer’s disease.

- About 60 per cent of the population has a ‘double dose’ of the APOE e3 gene and is at average risk. Up to a quarter of this group develops Alzheimer’s disease by their late 80s.

- The APOE e2 variant of the gene is associated with a lower risk of Alzheimer’s – people with it are slightly less likely to develop the disease. In the general population, 11 per cent have one copy of APOE e2 and one copy of APOE e3, while 0.5 per cent (1 in 200) have two copies of APOE e2.

For a long time, APOE was the only gene to be consistently linked to the risk of late-onset Alzheimer’s disease. However, recent scientific advances have allowed researchers to test many more genes to see whether there are other gene variants linked to Alzheimer’s disease.

This has revealed several other genes that have variants linked to increased or decreased risk of Alzheimer’s. These include genes known as CLU, CR1, PICALM, BIN1, ABCA7, MS4A, CD33, EPHA1 and CD2AP. These are thought to have roles in inflammation and immunity, fat metabolism or transport within cells. The variants of these genes affect a person’s
If you have a close relative (parent or sibling) who has been diagnosed with late-onset Alzheimer’s disease, your chances of developing the disease rise slightly compared to someone with no family history of the disease. However, it does not mean that dementia is inevitable for you.

risk of developing Alzheimer’s disease much less than APOE. Researchers suspect that there are many more risk genes that have not yet been discovered.

If a birth relative has been diagnosed with Alzheimer’s disease, it is natural for you to wonder whether you are at increased risk. If you have a close relative (parent or sibling) who has been diagnosed with late-onset Alzheimer’s disease, your chances of developing the disease rise slightly compared to someone with no family history of the disease. However, it does not mean that dementia is inevitable for you. Everyone can reduce their overall risk by adopting a healthy lifestyle.

For more information about Alzheimer’s disease see factsheet 401, What is Alzheimer’s disease?.

**Vascular dementia**

Vascular dementia is the second most common type of dementia. There are no known single-gene mutations for the more common forms of vascular dementia but researchers are looking for multi-gene variants or ‘risk genes’ for the condition.

**Familial vascular dementia**

Some very rare forms of vascular dementia are caused by gene mutations. 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 like familial Alzheimer’s disease.

**Risk genes for vascular dementia**

Some studies have reported links between APOE (which plays a role in Alzheimer’s disease – see above) and vascular dementia, but others have
not. It seems that APOE e4 may be a risk factor for vascular dementia, but a weaker one than it is for Alzheimer’s disease. It is not clear whether APOE e2 is associated with lower risk of vascular dementia as it is with Alzheimer’s.

In addition, researchers have found several genes that affect a person’s chances of developing conditions such as high cholesterol, high blood pressure and type 2 diabetes. These conditions matter because they can significantly raise a person’s chances of developing vascular dementia later in life. Similarly, a family history of stroke or heart disease – both closely linked to vascular dementia – can raise a person’s risk of developing it.

Overall, however, genes seem to play a much smaller role in the development of the common forms of vascular dementia than they do in late-onset Alzheimer’s disease. Lifestyle choices (eg diet and exercise) are probably even more important in vascular dementia risk than they are in Alzheimer’s disease.

For information about this type of dementia see factsheet 402, What is vascular dementia?.

**Frontotemporal dementia (FTD)**

Frontotemporal dementia (FTD) quite often runs in families, especially the behavioural form of the condition. Of the four most common dementias, FTD is the one in which genes have the largest impact.

**Familial frontotemporal dementia**

About 10–15 per cent of people with FTD have a very strong family history of the condition. This means having three or more relatives with FTD across at least two generations.

A similar number of people with FTD have a weaker family history of dementia, but not necessarily of frontotemporal dementia.

In up to 30 per cent of all people with FTD, the condition is known to be caused by a mutation in a single gene. At least eight genes – including some with very rare mutations – are so far known to cause FTD, and more
are likely to be discovered. Of the different types of FTD, the behavioural form – the most common form of FTD – is the one that is inherited most often. Semantic dementia, in contrast, is only rarely inherited.

Most familial frontotemporal dementia is caused by mutations in three genes. These are a recently discovered gene called C9ORF72, and genes for the proteins tau (MAPT) and progranulin (GRN). The particular mutation that a person has tends to influence their symptoms. For example, C9ORF72 is linked to both FTD and motor neurone disease and some affected families have a history of both conditions.

If someone has one of these faulty genes, then each of their children has a 50 per cent chance of inheriting the mutation. Each sibling of someone with the mutation also has a 50 per cent chance of having inherited the mutation. As with familial Alzheimer’s disease, nearly everyone who inherits the mutation will develop FTD, with the exception of C9ORF72. For reasons that are not clear, some people have the C9ORF72 mutation but do not go on to develop FTD.

Risk genes for frontotemporal dementia
In the past few years, researchers have begun to look for ‘risk genes’ (acting like APOE) for FTD. For example, variants in a gene called TMEM106B affect someone's chances of developing FTD.

For more information about this type of dementia see factsheet 404, What is frontotemporal dementia (FTD)?.

Dementia with Lewy bodies (DLB)
The genetics of dementia with Lewy bodies (DLB) are not well understood – there are just not as many research studies as there have been for Alzheimer’s disease and frontotemporal dementia. There are a few studies that suggest birth relatives of an affected family member may be at slightly higher risk, but this is not conclusive.

Familial dementia with Lewy bodies
There are only a few known families in which DLB seems to follow a strong inheritance pattern and no mutations have so far been identified.
Risk genes for dementia with Lewy bodies
Several gene variants have recently been linked to a higher risk of DLB. The APOE e4 variant is thought to be the strongest genetic risk factor for DLB, as it is for Alzheimer’s disease. Variants in two other genes, glucocerebrosidase (GBA) and alpha-synuclein (SNCA), also affect the risk of a person developing DLB. Alpha-synuclein is the main protein within Lewy bodies, which are found in both DLB and Parkinson’s disease. The GBA and SNCA genes are also both important in Parkinson’s disease.

It is not surprising that the gene variants associated with DLB also play a role in Alzheimer’s disease (APOE) and Parkinson’s disease (GBA, SNCA). This is because the symptoms of DLB overlap with those of both Alzheimer’s disease and Parkinson’s, and the diseases share some common underlying features.

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

Other conditions
Some other conditions that are not forms of dementia themselves can raise a person’s risk of developing dementia. This section covers some of these conditions.

Down’s syndrome
People with Down’s syndrome are at particular risk of developing dementia. This is usually 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 because most people with Down’s have an extra copy of chromosome 21. They therefore have an extra copy of the amyloid precursor protein gene (APP) that is found on that chromosome. APP has been linked to the development of 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 the HTT gene on chromosome 4. Symptoms include problems with mental abilities, including sometimes dementia, as well as problems with behaviour and movement. Huntington’s is inherited in a single-gene mutation pattern. Someone with Huntington’s disease therefore has a 50 per cent chance of passing it on to each child.

Huntington’s disease was the first single-gene condition for which genetic testing was widely available, in 1994. Affected families are routinely offered genetic counselling – that is, professional advice and support on the issues surrounding inheritance and genetic testing. Guidelines that were first developed for families with Huntington’s disease have now been adapted to counselling for genetic dementias (see ‘Genetic testing and counselling’ below).

Genetic testing and counselling
If you have a relative with a form of dementia and you are worried about inheriting the condition, you should speak to your GP.

Most people with the more common types of dementia will be reassured to know that the pattern of dementia in their family is down to chance, risk genes, medical factors or shared lifestyles.

With dementia becoming more widely diagnosed, 1 in 4 people aged over 55 now has a close birth relative with the condition. However, when all dementia is looked at, the fraction that is inherited as a simple single-gene mutation is very small.

Routine testing (that is, not just for research purposes) is currently available on the NHS for mutations in several genes that cause dementia. They are the Huntington’s disease gene (HTT), the three familial Alzheimer’s disease genes (APP, PSEN-1, PSEN-2), and several frontotemporal dementia genes (including MAPT, GRN and C9ORF72). As explained below, these tests are only offered in very specific circumstances and with proper counselling.

Routine testing for risk genes like APOE is not available on the NHS and is not generally recommended.
Testing for single-gene mutations
There are two different kinds of testing for the single-gene mutations that cause dementia: diagnostic genetic testing and predictive genetic testing. Both require a simple blood sample to be taken for testing.

Diagnostic genetic testing
If you have already been diagnosed with dementia, it may benefit you to know if this has been caused by a mutation. For example, it may confirm a diagnosis which affects your drug treatment, or it might make you eligible for a clinical trial.

Testing someone who already has dementia is called ‘diagnostic’ genetic testing. It is not common and is generally only recommended if the dementia shows a very strong pattern of family inheritance.

Knowing the family inheritance pattern means taking a complete medical history across three generations, if possible. This will look for diagnosed dementia, mental illnesses (eg hallucinations, delusions) and neurological conditions (eg Parkinson’s disease, motor neurone disease) in the family. This should include the age when symptoms started, the age at death, medical records and any post-mortem findings. Unless this history suggests a very strong dementia inheritance pattern, it is unlikely that diagnostic genetic testing will find a mutation.

The person being tested will be offered counselling – as far as their dementia allows – before any diagnostic gene test. A supportive family member will also be counselled because a positive test result has implications for them and the person’s relatives. Other family members may or may not wish to know the result.

Note that, even with a very strong dementia inheritance pattern, a negative genetic test is still quite common, particularly in FTD. This doesn’t necessarily rule out the possibility of a genetic explanation for the dementia. It may be that the dementia is caused by a mutation that is not yet known, which can leave families living with uncertainty. Occasionally, a diagnostic genetic test will identify a genetic change which is not a clear mutation. Again, this can leave families living with a degree of uncertainty.
Predictive genetic testing

It is natural for healthy relatives of someone with dementia to be concerned that they are at risk. This is especially likely if a close relative is known to be carrying a mutation, or if there is a very strong pattern of dementia running in the family.

Genetic testing of people who are not affected by dementia to see if they carry a mutation is called ‘predictive’ genetic testing. This is because finding a mutation usually predicts with near-certainty that an individual will go on to develop that type of dementia, if they live long enough. Predictive testing will only be done when a mutation has already been found in the family, for example by diagnostic testing.

There are several reasons why you might choose predictive genetic testing. Firstly, it may remove uncertainty and allow you to plan for the future. Secondly, a positive result may make you eligible for a trial of a new drug. Thirdly, it may open up opportunities if you are planning a family (see ‘Genetic testing in family planning’ below).

However, predictive testing can be a very stressful process. The decision about whether or not to have testing is a difficult and personal one. There are no right or wrong choices, but it is important that you think carefully about being tested and make an informed choice.

If you do decide to be tested, you may have to live with the anxiety of wondering what the result might be, or deal with an inconclusive result. If you are found to have the mutation, this knowledge cannot then be unlearned. There are currently no treatments available that can prevent or slow the progression of the disease for those with a genetic form of dementia. A positive result also won’t tell you when symptoms might start. This is why predictive testing is only done with expert genetic counselling – both before and after testing – over several months.

The result of the test will usually affect other family members too, some of whom might not want to know the outcome.

After counselling, most people who have a 50 per cent chance (such as children of the person with the mutation) actually choose not to go ahead
with predictive testing. This may be because not knowing leaves room for hope, whereas the knowledge of a positive test result cannot be reversed.

It is worth noting that a positive predictive gene test cannot be used to discriminate against someone when it comes to buying property, getting insurance or planning financially for their future. This is because there is a moratorium (delay or suspension) on the use of predictive genetic test results agreed by UK insurance companies until at least 2019. This means that, other than in exceptional cases, the companies cannot use the results of predictive genetic tests or require anyone to take a genetic test before taking out insurance.

You will still need to tell the company if asked, as would anyone, about your family history and any diagnostic test results (testing of people who already have a diagnosis). You can also volunteer a predictive test result which is in your favour, if you choose to.

**Genetic testing in family planning**

Being able to test for the genetic mutations that cause familial dementia has now made genetic testing as part of family planning possible. This is an option when one prospective parent is known to carry a single-gene mutation, or is at risk because their parent had a mutation. In these circumstances, genetic testing of the embryo allows the parents to have a child who does not carry the mutation. The technique used is called ‘pre-implantation genetic diagnosis’ (PGD). It is a modified form of in vitro fertilisation in which DNA from very early embryos is tested for a mutation in the lab. Only embryos which do not have the mutation are put back into the mother’s womb.

If successful, PGD means that the baby is almost certain not to have the mutation or to grow up to develop the particular kind of dementia.

It is possible in some centres to use this technology without the at-risk parent themselves knowing if they have inherited the mutation, if they choose not to.

PGD has been used for several years to help couples with Huntington’s disease who are starting a family. It has also recently become available on
the NHS for families affected by familial Alzheimer’s disease or genetic FTD. As with predictive genetic testing, families considering PGD are offered extensive genetic counselling.

**Testing for risk variants**

No test for risk genes like APOE is offered within the NHS, other than in approved research studies. Predictive testing for variants like this provides none of the near-certainty that a positive test for a single-gene mutation offers. Even if you test positive for one or even two copies of APOE e4, you are still not certain to develop Alzheimer’s disease. Likewise, even if you have no APOE e4 variants, you are not certain to remain free from the disease.

In spite of this, tests for APOE variants are available commercially in the UK by sending off a sample of saliva in the post. This is called ‘direct-to-consumer’ genetic testing because it is arranged over the internet without a doctor or counsellor being involved.

Direct-to-consumer genetic testing is controversial and testing for variants like APOE is not recommended by most specialists. This is partly because – as explained above – the results are not that informative. It is also because the private companies that sell the tests do not do enough to help the person interpret their own test results properly.

**Other useful organisations**

**Genetic Alliance UK**
020 7831 0883
contactus@geneticalliance.org.uk
www.geneticalliance.org.uk

This national charity works to improve the lives of patients and families affected by all types of genetic conditions. It provides information about NHS genetics centres and insurance.
Huntington's Disease Association
0151 331 5444 (advice line, 9am–5pm Monday to Friday)
info@hda.org.uk
hda.org.uk

Huntington’s Disease Association supports people affected by Huntington’s disease and provides information and advice to professionals who are supporting affected families.

Rare Dementia Support
07592 540555
contact@raredementiasupport.org
www.ucl.ac.uk/drc/support-groups

Rare Dementia Support provides information and support to people with rare forms of dementia, their families, friends and healthcare professionals. It has support groups that cover rare dementia diagnoses such as frontotemporal dementia, posterior cortical atrophy, primary progressive aphasia, familial Alzheimer’s disease and familial frontotemporal dementia (fFTD).
Factsheet 405LP

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Our information is based on evidence and need, and is regularly updated using quality-controlled processes. It is reviewed by experts in health and social care and people affected by dementia.

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