Genetics of dementia

Factsheet 405LP
June 2021

Alzheimer's Society
United Against Dementia

Around 1 in 4 people aged 55 years and over has a close birth relative with dementia. When a person is diagnosed with dementia, they may worry about the risk of developing dementia for other family members, such as their brothers and sisters or their children. Family members related to the person with dementia also often have questions about whether they are likely to develop dementia themselves.

There are many reasons why people get dementia. The most important risk factor is ageing. Dementia can also develop as a result of other health conditions and lifestyle factors. For some people, genetics can also be a factor. This factsheet explains the ways that dementia is inherited and describes when you should seek further advice. It is for anyone who is concerned about dementia running in their family.

Contents

Genetics of dementia

Genes and inheritance

It is well known that children can take after their parents – for example, in the way they look. This is partly because many of the key characteristics of a person are passed down from parents to children in their genes.

What are genes?

Genes are made from a chemical called DNA. They contain information that is needed to make proteins, which the body is built from. Humans have over 20,000 different genes. Most often, a person has two copies of each gene – one inherited from each parent.

The same gene can differ between individuals – these are known as 'gene variants'. These can help to explain why people are different to each other – for instance, why one person has blue eyes and another person has brown eyes.

How can genes cause disease?

Genes often play a role in the development of diseases. This can happen in the two main ways described in this section.

Single-gene diseases

Sometimes, a gene changes and this causes a disease. This is known as a single-gene disease because it is caused by a change in just one gene. Single-gene diseases are often serious, but they are rare.

It is possible to directly inherit a single-gene disease. This means that if a child inherits the same changed gene that a parent has, they are very likely – in some cases almost certain – to develop the same disease.

Dementia can be caused by a single-gene disease, but this is very rare. For more information see 'Dementia caused by a single-gene change' on page 5.

Complex or multiple-gene diseases

Complex diseases are less straightforward. They develop through the interaction between several different factors. These are known as 'risk factors' for that disease. They include:

- the person's environment or lifestyle – for example, their diet and whether they smoke or not
- multiple gene variants – known as 'risk variants' because they increase the person's risk of developing the disease.

It isn't possible to inherit a complex disease in the same way as a single-gene disease. This is because complex diseases are caused by multiple factors acting together.

However, a person with a family history of a complex disease will often have an increased chance of developing it. This is because they are likely to share risk factors with other birth relatives. Despite this increased chance, the person still might never develop the disease.

Nearly all cases of dementia are the result of a complex disease. In these cases, genes may increase the risk of developing dementia, but they don't cause it directly. For more information see 'Dementia caused by a complex disease' on page 6.

Genes and dementia

Dementia caused by a single-gene change

Dementia can be caused by a single-gene change, but it is rare. Of the four most common types of dementia, frontotemporal dementia (FTD) is most likely to be caused by a single-gene change. For more information on types of single-gene dementia see 'Rare types of inherited dementia' on page 8.

When dementia is caused by a single-gene change, it often develops earlier in life. For example, an affected person might get dementia in their 40s or 50s rather than in their 70s or above. This is known as 'young-onset' dementia. For more information see factsheet 440, **What is young-onset dementia?**

When dementia is caused by a single-gene disease, it tends to run strongly in families. A person with a single-gene dementia is likely to have several close relatives who develop the same type of dementia. For example, they may have a grandparent, a parent and a brother who all had frontotemporal dementia (FTD). This is why dementia caused by a single-gene disease is sometimes known as 'familial dementia'.

Can it be inherited?

If a single-gene dementia is present in a family, it is quite likely that a person from that family will develop dementia:

- If one of the parents carries the changed gene, each child has a 1 in 2 chance of inheriting it.
- If one of the children carries the changed gene, any brothers or sisters they have has a 1 in 2 chance of carrying it as well.

For these families, counselling and genetic testing may be helpful – see 'Genetic testing for dementia' on page 10 for more information.

Dementia caused by a complex disease

Many people have some family history of dementia – for example, they may have a parent who developed dementia in their 90s and a brother who developed dementia in his 70s. This is not the same as 'familial dementia' and most often it is not caused by a single-gene change.

Instead, this pattern is likely to be caused by a combination of factors that are shared by members of the family. This includes non-genetic risk factors – for example, members of the same family may all smoke or have an unhealthy diet, which are both risk factors for dementia. For more information on risk factors see factsheet 450, **Risk factors for dementia**.

It is also likely to be partly genetic – a person may inherit the same dementia risk variants as other members of their family. This could include variants in genes such as APOE (see 'Which gene variants increase the risk of dementia?' on page 7).

Can it be inherited?

People who are related to each other by birth are more likely to have the same risk variants as each other. However, risk variants for dementia do not directly cause dementia (like a single-gene change does). This means that it's not possible to directly inherit dementia through risk variants.

However, a person who has dementia risk variants is at higher risk of developing dementia than someone who does not have risk variants. Despite this higher risk, they still might not develop dementia.

Which gene variants increase the risk of dementia?

The most well-known risk variants for dementia are for Alzheimer's disease. These are in the apolipoprotein E gene – more commonly known as the 'APOE' gene. This gene has three common variants: APOE2, APOE3 and APOE4. Of these three, APOE4 is the one that most increases a person's risk of developing dementia.

A person can have no copies, one copy or two copies of APOE4 – depending on what they inherited from their parents. The more copies of APOE4 that a person has (none, one or two), the higher the risk is of them developing Alzheimer's disease. APOE variants are also risk factors for dementia with Lewy bodies (DLB) and vascular dementia.

However, APOE variants do not directly cause dementia. Some people have two copies of APOE4 but never develop dementia. Many people do develop dementia even though they have no copies of APOE4. This is why testing for APOE is not helpful in telling whether or not someone will develop dementia – see 'Genetic testing for dementia' on page 10 for more information on this.

Over 20 other genetic variants have also been identified as risk variants for Alzheimer's disease. However, most of these variants only increase a person's risk of developing Alzheimer's very slightly.

People with risk variants for dementia can still reduce their chances of developing the condition by leading a healthy lifestyle. For example, if the person eats a well-balanced diet, is physically active, doesn't smoke and doesn't drink too much alcohol, they will reduce their overall risk of developing dementia. For more information see booklet 35, Dementia: Reducing your risk.

Rare types of inherited dementia

All four of the most common types of dementia have familial forms that are caused by single-gene changes.

Familial Alzheimer's disease

Familial Alzheimer's disease is a type of Alzheimer's that is caused by a single-gene change. It is very rare.

Familial Alzheimer's disease is usually caused by a change in one of three genes. These are the PSEN-1 gene, the APP gene and the PSEN-2 gene. Most cases of familial Alzheimer's (4 out of 5) are caused by a change in the PSEN-1 gene. In these cases, dementia symptoms can begin as early as 30 years of age.

In some families no change is found in any of these three genes. These families probably have a different gene change that is even rarer and is not yet known about.

The genetic changes that cause familial Alzheimer's disease are very rare. Out of 100 people who have Alzheimer's, less than 1 of those people will have it because of a single-gene change. 99 out of 100 people who have Alzheimer's disease will have it because of genetic risk variants and non-genetic factors such as their lifestyle.

Familial frontotemporal dementia (FTD)

In most types of dementia, the cause is very rarely a single-gene change. However, in frontotemporal dementia (FTD), single-gene changes are much more common. About 3 or 4 in every 10 people who develop FTD have it because of a single-gene change. This means that FTD often runs strongly in families, especially the behavioural form of the dementia.

Familial FTD has been linked to changes in at least nine genes. The most commonly affected genes are progranulin (GRN), tau (MAPT) and C9orf72.

Nearly everyone who inherits one of these changes will develop familial FTD. However, this is not always the case. Some people may carry the changed gene but not develop FTD during their lifetime.

Familial vascular dementia

Some very rare forms of vascular dementia are caused by single-gene changes. For example, a change in a gene called NOTCH3 causes a rare type of vascular dementia called cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy – more commonly known as 'CADASIL'.

A person with CADASIL has a 1 in 2 chance of passing on the changed gene to each child they have. Like other types of familial dementia, CADASIL tends to develop at an earlier age than the more common vascular dementia – the average age at diagnosis is about 50 years. For more information on CADASIL see factsheet 442, **Rarer causes of dementia**.

Familial dementia with Lewy bodies (DLB)

Dementia with Lewy bodies (DLB) can be caused by a single-gene change, but this is extremely rare.

Down's syndrome and dementia

People who have Down's syndrome are at higher risk of developing dementia, though not everyone with Down's syndrome will develop it. 1 in 3 will develop dementia in their 50s. This increases to almost 2 in 3 people with Down's syndrome who are over the age of 60. When dementia does develop, it is often Alzheimer's disease.

This higher risk of dementia is linked to the extra copy of chromosome 21 that most people with Down's syndrome have. Chromosomes are made of DNA and chromosome 21 carries the amyloid (APP) gene. The extra chromosome means that people with Down's syndrome have an extra copy of the APP gene. This is thought to cause a build-up of amyloid plaques in the brain which may cause Alzheimer's disease.

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

Genetic testing for dementia

It is possible to be tested for single-gene changes and some of the risk variants linked to dementia. However, genetic testing for dementia is not always appropriate.

In some cases, it may seem likely that a person's dementia is caused by a single-gene change – for example, if the person has a very strong family history of dementia. In these cases, it may be appropriate to offer genetic testing to the person and to their family.

However in most families dementia will not be caused by a single-gene change. In these cases, genetic testing will not be appropriate.
This is because testing for risk variants (like APOE4) does not provide any certainty about the person's chances of developing dementia.

Testing for single-gene changes

Genetic testing for single-gene causes of dementia is available through the NHS.

There are two different types of genetic testing – diagnostic testing and predictive testing. These are used for different purposes.

Diagnostic testing

A diagnostic genetic test is for a person whose dementia is thought to be caused by a single-gene change. It can be helpful in several ways:

- It can provide certainty about the person's diagnosis. This may then help the person and their family to come to terms with the diagnosis and allow them to plan for the future.
- It can help them decide if they want to have children and, if so, how they might avoid passing the disease on (see 'Testing for family planning' on page 13).
- It makes it possible for members of the person's family to have predictive testing if they want to (see 'Predictive testing' on page 11).

Diagnostic testing is usually carried out as part of an assessment in a clinic – for example, a memory clinic. The test usually involves taking a blood sample.

To see whether genetic testing might be useful, the doctor will collect information on the person's medical history and that of their close family. If possible, the doctor will collect information on at least three generations of the family. The medical history will include details of:

- any family members diagnosed with dementia
- any family history of mental illness (such as schizophrenia or bipolar disorder)
- any family history of strokes or neurological conditions (such as Parkinson's disease or motor neurone disease).

Diagnostic testing for familial dementia is only normally recommended if the person has developed symptoms very early on (for example in their 30s or 40s) or if there is a particular familial pattern.

If the doctor does not find a strong family history of dementia, they will not recommend that the person take a diagnostic genetic test.

Predictive testing

Predictive genetic testing can be helpful for relatives of a person who has a single-gene change that causes dementia. A genetic test allows those relatives to know if they have the same gene change that will cause dementia in the future.

To be assessed for a predictive test, a person or family will need to be referred to a clinical genetics service. This is a centre where specialist doctors and genetic counsellors work.

Having the test can be helpful for the following reasons:

- It can remove the anxiety of not knowing – especially as the person approaches the age at which any symptoms of dementia are likely to start.
- It can give the person the option of entering into a clinical trial.
- It can help with family planning (see 'Testing for family planning' on page 13).

However, predictive testing can be stressful. If a person receives a positive test result, they will know for certain that they will develop dementia. This can be very difficult information to take in.

For this reason, predictive genetic testing will only be done with genetic counselling both before and after the test. This is to make sure that the person is aware of what it means to have the result of a genetic test, both for them and for their family. Many people have counselling but don't then go on to take a test.

It's important to note that a person with a negative test result may still develop dementia. The predictive test only shows whether a person will develop the type of dementia that is related to that specific single-gene change. It does not rule out the possibility of that person developing dementia because of other factors.

Predictive testing and getting insurance

Insurers are not allowed to ask anyone to take a predictive genetic test for dementia, or to declare the results of a test. A positive result (where the person has the changed gene) cannot be used to refuse someone life insurance or charge them a higher premium.

Testing for family planning

If someone is known to carry a single-gene change that causes dementia, this may affect their plans to start a family. This is because there is a 1 in 2 chance of inheriting the same changed gene for any children they have.

In these cases, it is possible to try an approach called 'pre-implantation genetic diagnosis' (PGD). PGD involves the following steps:

1. An egg is fertilised outside of the body – a process known as 'in vitro fertilisation' (IVF).
2. The embryo is left to develop for a few days.
3. Some cells are safely removed from the embryo.
4. The DNA from these cells is tested for the specific gene change.
5. Embryos without the gene change are implanted into the womb, where they should continue to develop.

Not every attempt works. However, when PGD is successful, it allows people affected by a familial dementia to have a child who is almost certain not to have the genetic change that the affected parent has. This means that the child will not develop the type of dementia caused by that gene change.

Some people may think that they have a single-gene change and want to use PGD to make sure that their child does not have it. However, they may want to avoid finding out whether they themselves have the changed gene. It is possible in some centres to use the technology without the parent finding out if they themselves have the change.

The NHS provides PGD services for families affected by familial Alzheimer's disease or familial FTD. These families have to meet certain requirements to qualify for NHS funding and the NHS will only fund a set number of attempts.

As with predictive genetic testing, families considering PGD are offered genetic counselling both before and after they go through the testing process.

Testing for genetic risk variants

It is possible to have a genetic test for dementia risk variants, but this is not recommended outside a research setting. This is because knowing whether someone has genetic risk variants does not mean knowing for certain whether they will develop dementia. A person who has risk variants may have a higher risk of developing dementia, but even someone at a higher risk may never develop the condition.

For this reason, the NHS does not provide testing for dementia risk variants. However, testing kits can still be bought over the internet. These involve sending a sample of saliva to the testing company by post. The company then analyses the saliva sample and sends the person their results. These tests are known as 'direct-to-consumer' (DTC) tests.

DTC tests are not as reliable as testing in an accredited genetics lab and they may not be accurate. DTC testing does not usually involve the input of a doctor, genetic counsellor or other health professional. This means that people may not understand what the test results mean for them and for their family's future risk of dementia.

The Royal College of GPs has advised GPs to ignore the results of DTC tests if people come to them with questions about inheritance. GPs will only refer people to genetics services if they find a strong family history of dementia. They will not consider a DTC test result when making a referral.

For these reasons, DTC genetic tests are not recommended by Alzheimer's Society and most organisations who support people affected by dementia.

Checking for dementia risk variants using a direct-to-consumer genetic test is not recommended. If a person's family history suggests that they may have a single-gene change that causes dementia, they should be able to get a genetic test in a clinical genetics service.

Other useful organisations

Association of British Insurers (ABI)

020 7600 3333
info@abi.org.uk
www.abi.org.uk
https://www.abi.org.uk/data-and-resources/tools-and-resources/genetics/

The Association of British Insurers (ABI) is a trade association made up of UK insurance companies. Members of the ABI have agreed to a ban on the use of predictive genetic test results in insurance cover.

CADASIL Support UK

info@cadasilsupport.co.uk
www.cadasilsupportuk.co.uk

CADASIL Support UK is a patient support group. It allows people affected by this rare condition to help each other and share their experiences, mostly on social media forums.

Genetic Alliance UK

0300 124 0441
contactus@geneticalliance.org.uk
www.geneticalliance.org.uk

Genetic Alliance UK is a national charity that 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.

Rare Dementia Support

020 3325 0828
contact@raredementiasupport.org
www.raredementiasupport.org

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.

Factsheet 405LP

Last reviewed: June 2021

Next review due: June 2024

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.

Reviewed by: Dr Nick Bass, Associate Professor, UCL Division of Psychiatry

This factsheet has also been reviewed by people affected by dementia.

To give feedback on this factsheet, or for a list of sources, please email **publications@alzheimers.org.uk**

People affected by dementia need our support more than ever. With your help we can continue to provide the vital services, information and advice they need.
To make a single or monthly donation, please call us on **0330 333 0804** or go to **alzheimers.org.uk/donate**

Alzheimer's Society is the UK's leading dementia charity. We provide information and support, improve care, fund research, and create lasting change for people affected by dementia.

For support and advice, call us on **0333 150 3456** or visit **alzheimers.org.uk**

Alzheimer's Society operates in England, Wales and Northern Ireland.
Registered charity number 296645.

Alzheimer's Society
United Against Dementia