### Important points

- There are a number of different conditions that cause dementia. The most common is Alzheimer disease (AD).
- In AD, specific changes called plaques and neurofibrillary tangles build up in the brain.
- Symptoms usually start after the age of 60 years and become more common in older age groups. About 25% of people over 85 are affected by AD to some extent.
- Some families have a very rare form of AD that is hereditary and is due to inheriting a faulty copy of one of several genes. Symptoms usually start well before 65 years of age. This is called young onset familial AD (also referred to as early-onset familial AD).
- Young-onset familial AD follows a pattern of autosomal dominant inheritance in families. Children and siblings have a 50% chance of carrying the faulty gene involved when a family member has the condition.
- Other forms of dementia that are young-onset and familial have been identified as involving faulty genes, for example, familial Creutzfeldt-Jakob disease (familial CJD).
- Genetic testing for these conditions and young-onset familial AD is available. It is strongly recommended that genetic testing be undertaken in the context of genetic counselling where the implication of having testing, its advantages and disadvantages and limitations can be explored.
- AD occurring in later life (after the age of 65) appears to be due to a combination of genetic and environmental factors.
- The strongest risk factor for developing AD remains increasing age. As people get older, changes in the genes build up in the cells. Some of these changes will make genes important for brain function, faulty.
- Some genes involved in the predisposition to develop AD in later life have been identified, however genetic testing for these predisposing genes is not indicated or recommended.

### Dementia in general

Individuals with dementia have a gradual build up of changes in the brain. The condition is characterised by progressive difficulties with memory, language, learning, thinking and reasoning and undertaking everyday tasks. Changes in personality may also occur.

Dementia occurs more frequently with increasing age. It is extremely rare under the age of 60 (young-onset).

There are a number of different conditions that cause dementia. The most common is AD.

#### What is Alzheimer disease (AD)?

First described by the German physician Alois Alzheimer in 1907, the defining features of AD are characteristic changes in the brain tissue when it is examined under the microscope.

These include plaques, which are deposits of a protein called beta-amyloid, and tangled filaments of proteins (neurofibrillary tangles) that clog up the nerve cells in the ‘thinking’ parts of the brain (the cortex) and cause these cells to deteriorate.

The condition begins gradually, usually with forgetfulness and word-finding difficulty as early signs. The development of plaques and tangles appears to be most prominent in the parts of the brain relating to memory, called the temporal lobes.

Less than 1% of people aged between 60 and 65 have dementia. At least 25% of people aged over 85 will have evidence of the condition.

#### Are genes involved in causing Alzheimer disease?

The cells of the body contain the genes or set of instructions for the cell to make all the necessary proteins (chemicals) for our bodies to grow and work normally (see Genetics Fact Sheet 1).

A gene that contains a variation in the information that stops it working properly is described as faulty. The variation that makes the gene faulty is called a mutation. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

Genes have been implicated in contributing to AD:

- Individuals affected with AD at any age are more likely than others in the community to have a close relative (a parent, brother or sister) who has, or has had, dementia or AD.
- About 25-30% of individuals with AD have such a family history (familial AD). At least part of this increased frequency of having close relatives affected with the condition is related to an individual’s genetic make-up.
- Only a very small proportion of these families, however, have a form of AD that is hereditary and is associated with one of several genes that are faulty. Individuals in such families who have inherited the faulty gene copy are usually affected with the condition well before 65 years of age.
- This may be referred to as young-onset familial AD (also referred to as early-onset familial AD).
- This form of AD is very rare.

### Young-onset (early-onset) familial Alzheimer disease

In about 1 in 100 cases (1%) of AD, the symptoms of the condition usually appear before the age of 65 and generally in middle age (between 35 and 55).

In these families, several different genes have been identified in which mutations cause AD to occur at this young age. The genes are called:

- Presenilin-1, located on chromosome 14 and implicated in over 50% of these rare families.
- Presenilin-2, located on chromosome 1 and implicated in a group of families from an ethnic group known as the Volga Germans, who mostly now live in the USA and Canada.
- Amyloid precursor protein (APP), located on chromosome 21 and implicated in at least 20 families in the world.

#### What is the pattern of inheritance of young-onset (early-onset) familial Alzheimer disease?

Two factors influence the pattern of inheritance of the faulty gene copy causing AD in these families.

1. The AD genes are located on chromosomes 1, 14 and 21, which are all autosomes (one of the numbered chromosomes).
2. The effect of the variation in the particular AD gene copy is ‘dominant’ over the information in the working copy of the gene on the partner chromosome (see Genetics Fact Sheets 1, 4 & 5).

The pattern of inheritance in families of the faulty gene copy causing AD is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

As shown in **Figure 45.1**, where one of the parents has AD or will develop AD due to having the faulty AD gene copy, **in every pregnancy**, each child has:

- A 1 chance in 2 (50% chance) of having inherited the particular faulty gene copy from that parent.
- An equal chance (50% chance) of not having inherited it.

Children who have not inherited the faulty gene copy are not at risk of developing AD. Importantly, these children cannot pass the faulty gene copy on to their own children.

In **Figure 45.1** the autosomal dominant faulty young-onset (early-onset) EoFAD gene copy causing AD is represented by ‘D’; the working copy by ‘d’. While the father is shown as the parent carrying the faulty EoFAD gene copy, the same situation would arise if it was the mother. AD usually affects men and women equally.

**Young-onset (early-onset) Alzheimer disease without apparent family history**

Many individuals affected with young-onset dementia have no relatives with AD.

Such individuals are sometimes referred to as ‘sporadic’ cases. A small proportion of these individuals developed the condition because of a new (spontaneous) mutation that occurred for unknown reasons in one of the genes involved in the egg or sperm from which the individual developed either during or shortly after their conception (see Genetics Fact Sheet 4).

The cause of the disease for the rest of these individuals is currently unknown.

**Alzheimer disease occurring in later life**

While AD is quite rare in people aged less than 65, it becomes more common in older age groups so that about 25% of people over 85 are affected to some extent.

People with dementia occurring in later life, of which AD is the most common, are about three times more likely to have or have had a parent or sibling with dementia. This implies that the development of AD is related (at least to some extent) to the influence of their genetic make-up, but the genetic basis and inheritance pattern is different to that described for the young onset familial AD.

Common variations in several genes have been identified which are associated with an increased risk for developing AD in later life.

Common variation in the ApoE gene has for some time been linked to the development of AD in later life. The ApoE gene is located on the long (‘q’) arm of chromosome 19 (19q) and contains information for the cells to produce the protein called apolipoprotein E. Despite confirmation that certain forms of the ApoE gene contributes to risk for AD, in many studies, the ApoE gene lacks the necessary characteristics required for clinical diagnostic testing, or predictive genetic testing in individuals who do not have symptoms (see Genetics Fact Sheet 21).

Common variation in a number of other genes has also been found to be risk factors for AD. The role of these genes in AD is less certain than it is for ApoE, and a recent example is the SORL1 gene. Genetic testing for these genes is also unlikely to be helpful.

**What is the connection between the ApoE gene and Alzheimer disease?**

Everyone has two copies of the ApoE gene, one copy inherited from each parent. The ApoE gene occurs in three forms known as ApoE2, ApoE3 and ApoE4 and each contains slightly different information but all issue instructions to the cells for the production of apolipoprotein E. The most common form of the gene is ApoE3.

Individuals with AD are more likely to have either one or two copies of the ApoE4 form of the ApoE gene. Importantly, the ApoE4 form of the ApoE gene is not a faulty gene and it is neither necessary nor sufficient for the development of AD.

- Many healthy members of the community have one or both copies of the gene in the ApoE4 form.
- It is possible to have a copy of the ApoE4 form of the gene and not develop dementia despite living to say 90 years of age.
- About half of those affected with AD do not have a copy of the ApoE4 form of the gene.
- It appears that ApoE4 is involved in transporting the amyloid precursor protein (APP) into the brain cells.

The ApoE gene story is therefore a very complex one.

A likely explanation is that people who have the ApoE4 form of the gene are somehow more susceptible (or predisposed) to some other influence which causes the disease.

This is rather like saying that people with red hair and freckles are more susceptible to sunburn than people with dark skin. The problem is that while we know that lying in the sun causes sunburn, we do not yet know what causes AD in the majority of individuals, although there are some clues.

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**Figure 45.1:** Autosomal dominant inheritance when one parent either has a young-onset (early-onset) familial AD (EoFAD) or has the faulty EoFAD gene copy. The autosomal dominant faulty EoFAD gene copy is represented by ‘D’, the working copy by ‘d’.
For example, there is evidence to suggest that a severe head injury leading to loss of consciousness may bring on AD in people who have the ApoE4 form of the ApoE gene, but there must also be other potential causes, since severe head injury is quite rare.

It should be noted that people who have one copy of the ApoE2 form of the ApoE gene appear to be somewhat protected against developing AD, at least until much later in life. Therefore, until more is known about the role of the ApoE gene in AD, having a test to determine the form of the gene that an individual has inherited (to ‘predict’ whether a person is at increased risk or predisposed to develop the condition) is neither indicated nor recommended.

Indeed the relationship between an individual’s ApoE genetic make-up and the information in other genes is likely to have an impact on the development of AD.

- The search for other genes likely to be involved is ongoing
- The search for factors that may increase an individual’s risk of developing the condition (risk factors) and factors that may protect an individual (protective factors) are also ongoing

It is important to remember that the strongest risk factor for developing AD remains increasing age.

What are other risk factors that might lead to Alzheimer disease?

Studies of identical twins who have inherited the same copies of genes have found that often when one twin develops AD, the other twin remains unaffected. This finding implies that non-genetic causes for AD must exist.

Age: As noted above, the risk of developing AD increases exponentially with an individual’s age. Less than 1% of people aged between 60 and 65 have dementia. The number of people affected with the condition however approximately doubles with every five years increase in age after 65, so that about 25% of people aged over 85 will have it.

Down syndrome: Most individuals with the chromosomal condition called Down syndrome (see Genetics Fact Sheet 28) who live to adulthood will develop AD. An extra copy of chromosome 21 causes Down syndrome, also known as trisomy 21 (there are three copies instead of the usual pair). This association of Down syndrome with AD led to the discovery of gene changes on chromosome 21 causing the development of the young-onset (early-onset) form of AD.

Other factors: Many environmental factors have been explored as possible risk factors for AD. None have yet been found to have a strong influence, although the evidence that a severe head injury leading to loss of consciousness may predispose to the later development of AD is now widely accepted. As noted above, head injury is uncommon, and therefore would not account for more than a small proportion of individuals with AD.

There is some evidence that more years of education early in life may protect against, or delay, the development of dementia in old age.

Several studies have suggested that the use of anti-inflammatory drugs may be protective against AD but the evidence for this is not yet conclusive and is the subject of on-going research.

Similar studies also suggested that hormone replacement therapy (HRT) might protect women against AD, but when this theory was tested in a large, well-conducted trial (the Women’s Health Initiative Memory Study), the opposite effect was found.

HRT taken as a protective measure against AD is therefore neither indicated nor recommended.

Other conditions causing dementia

AD can be differentiated from other conditions causing dementia as they generally have different features.

For example, Pick’s disease or Frontotemporal dementia (FTD) preferentially affects the frontal and temporal lobes of the brain, which are involved in planning, insight and judgement. Individuals with dementia affecting the frontal lobe typically have prominent personality or behavioural changes initially, either instead of or together with memory problems. In these conditions, the brain tissue has a different appearance under the microscope.

Just as with AD, there are other forms of dementia that are young-onset and familial, in which faulty genes are known to be causative. These conditions are different from AD, though they occur at a similar age and may sometimes appear similar during life. For example:

- Familial FTD can be caused by changes in a number of genes, most commonly the TAU and PROGRANULIN genes, both located on chromosome 17
- Variations in the prion protein gene on chromosome 20 results in familial Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease and fatal familial insomnia

What can be done if an individual thinks he or she may be at risk for developing Alzheimer disease or other forms of dementia?

Understanding the genetic basis of AD and other forms of dementia can assist in the development of new drugs for the treatment and prevention of AD.

Where there is young-onset familial AD or another rare form of dementia running in a family, identifying the faulty gene involved is complex. It depends on determining if all affected members of the family have the same faulty copy of the gene; whether it is only found in individuals who have dementia and not in older unaffected family members or in the general population; and whether the copy of the gene with this change causes the biochemical change that leads to the brain features characteristic of the condition.

Where there is a strong family history of young-onset AD or other rare forms of dementia, and a change has been identified in one of these genes as causing the dementia in a family, genetic testing may be available.

The testing to determine whether an individual has inherited one of these faulty genes, and may develop the condition in later life, is available for unaffected at-risk members of these families in conjunction with genetic counselling. This testing is called ‘predictive testing’ (see Genetics Fact Sheet 21) since the test is usually done prior to the onset of any symptoms of the condition. Genetic counselling provides an opportunity to discuss all the implications of the testing and is highly recommended (see Genetics Fact Sheet 3).

As noted above, genetic testing for common variations in risk factor genes such as ApoE and SORL1, to see whether an individual is at increased risk of, or predisposed to developing AD, is neither indicated nor recommended.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 9, 21, 28
Information in this Fact Sheet is sourced from:

Edit history
November 2012
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Acknowledgements previous editions: Dr Henry Brodaty; Prof William Brooks; Bronwyn Butler; Dr Clement Loy; Gayathri Parasivam; Mona Saleh; Prof Ron Trent