This fact sheet describes a condition known as Alzheimer disease and includes the symptoms, causes, and any treatment or testing that is available.

In summary

- There are a number of different conditions that cause dementia. The most common is Alzheimer disease
- In Alzheimer disease, specific changes called plaques and neurofibrillary tangles build up in the brain causing a range of symptoms including the well-recognised sign of memory loss
- Symptoms usually start after the age of 60 years and become more common in older age groups
- Some families have a very rare form of Alzheimer disease that is hereditary and is due to inheriting a faulty copy of three known genes. Symptoms usually start well before 65 years of age. This is called early onset familial Alzheimer disease
- Inheritance of early-onset Alzheimer disease is autosomal dominant and genetic testing is available.

WHAT IS ALZHEIMER DISEASE?

Alzheimer disease is the most common form of dementia, a group of conditions characterised by a gradual build-up of changes in the brain leading to progressive difficulties with memory, language, learning, thinking, reasoning, and undertaking everyday tasks. Changes in personality may also occur. Dementia occurs more frequently with increasing age and is extremely rare under the age of 60 years. Less than 1% of people aged between 60 and 65 have dementia, increasing to at least 25% of people aged over 85 having some evidence of the condition.

AD is defined by 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.

Approximately 25% of all AD is familial, defined by have more than two affected family members.

Of the familial cases of AD approximately 95% is late onset with symptom onset from 60-65 years, and 5% is the rare early onset form with symptoms beginning from the mid-30s onwards (Figure 50.1).

WHAT CAUSES ALZHEIMER DISEASE?

Late-Onset Alzheimer Disease

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. 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, similar to the process of cancer and other age-related illnesses.

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.

Common variations in several genes have been identified which are associated with an increased risk for developing AD in later life, the most well-known being common variants in the ***ApoE* gene**, which contains information for the cells to produce a protein called **apolipoprotein E**.

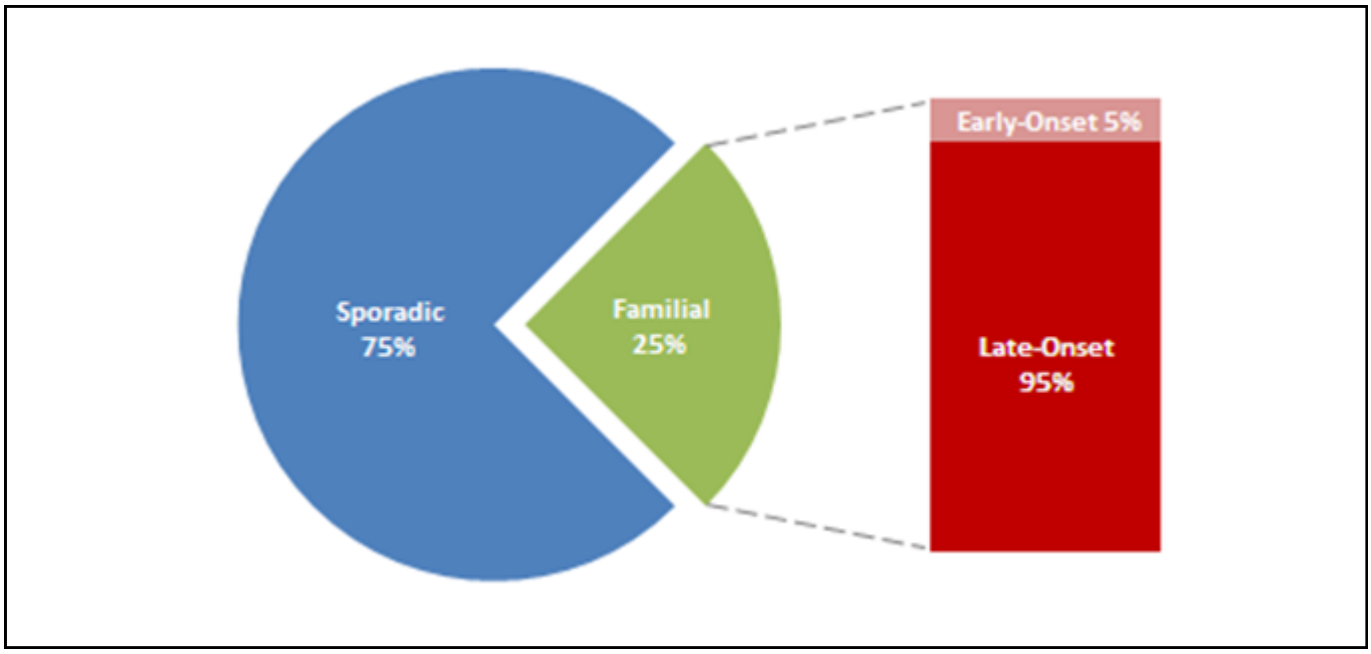

Figure 50.1: *Proportion of cases of AD that are familial, with most of these being late-onset (95%) and few cases of the rare early onset familial form.*

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.*

People with AD are more likely to have either one or two copies of the *ApoE4* form of *the ApoE* gene than people without AD. 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.

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 AD.

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.

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.

The search for other genes likely to be involved is ongoing, as is the search for factors that might increase a person's risk of developing AD.

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

HOW IS ALZHEIMER DISEASE INHERITED?

Our body is made up of millions of cells, and in each cell there are recipes, called genes, for structural components and chemicals necessary for the body to function. These genes are packaged onto strands called chromosomes.

Each body cell has 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product for which the gene is a recipe, (usually a protein), is altered or absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

Early-Onset Alzheimer Disease

In about 1 in 100 cases (1%) of AD, the symptoms of the condition appear before the age of 65 and generally in middle age (between 35 and 55). Early -onset familial AD is diagnosed in families with more than one person affected, each with symptoms beginning before the age of 60-65 years, and often with multiple members of the same generation affected before 55 years of age.

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 involved in less than 5% of families worldwide
- *Amyloid precursor protein* (APP), located on chromosome 21 and implicated in at least 20 families in the world.

Mutations in these genes result in production of an abnormal protein product which is prone to aggregate, forming the plaques and tangles in the brain that are characteristic of AD.

The common late-onset form of AD is inherited in **multifactorial** manner, this means that an individual may inherit some genetic predisposition but also has environmental and lifestyle factors that contribute to the development of AD as they get older.

This type of inheritance is not clear cut and with our current knowledge we cannot give an accurate prediction of the risk for relatives of an individual with this late-onset AD.

The rare, early-onset familial form of AD on the other hand, has a pattern of inheritance referred to as **autosomal dominant inheritance**, meaning that a mutation in only one copy of a gene is sufficient to cause AD despite the other copy working properly (Figure 50.2). For every pregnancy in this situation there is:

- 50% chance that a child, either male or female, will inherit only working copies of a gene from their parents and be healthy
- 50% chance that they will inherit one copy of the faulty gene, and one working copy and be predisposed to developing AD
- A mother or a father can pass on an autosomal dominant condition and both male and female children may be affected.

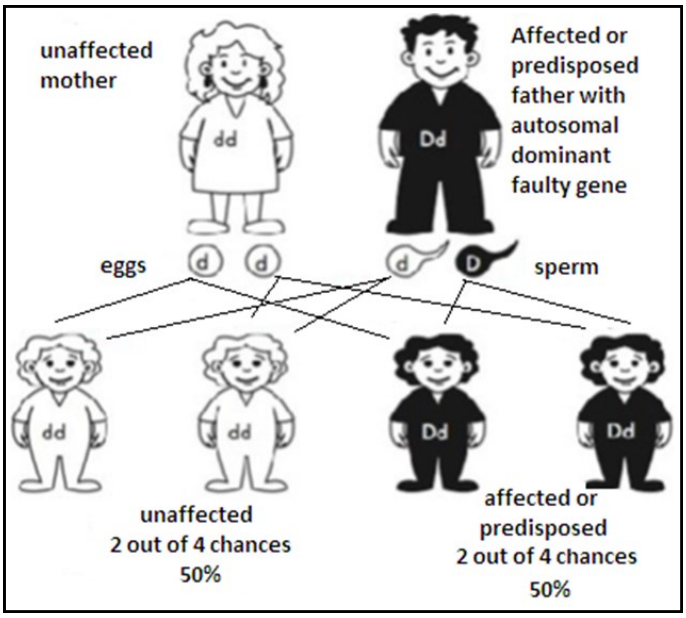

Figure 50.2: *Autosomal dominant inheritance when one parent carries the autosomal dominant faulty gene copy. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.*

IS THERE ANY TESTING AVAILABLE FOR ALZHEIMER DISEASE?

Clinical Testing for Diagnosis of Alzheimer Disease

Testing for AD is available for individuals who demonstrate symptoms of dementia. This may include a neurological assessment to determine what symptoms the individual has, imaging to look closely at the brain for changes suggestive of AD, and ruling out other forms of dementia. Sometimes AD can only be conclusively diagnosed after death, with post-mortem examination to look for characteristic plaques and tangles in the brain.

Genetic Testing

Genetic testing to identify the causative mutation in families with early-onset AD is available, however it can be complex. The first step is a **mutation search** in an affected family member to try and identify the mutation. If this is identified genetic testing can be offered to other family members who are at-risk which is called **predictive testing**. If a mutation cannot be found though, no further genetic testing can be offered in the family.

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 due to limitations in our understanding.

Prenatal testing and PGD

For couples where the familial early onset disease mutation is identified testing may be available during a pregnancy to determine whether or not the baby has inherited the mutation. It may also be possible to undergo pre-implantation genetic diagnosis (PGD) on an embryo created using in vitro fertilisation (IVF). These options are best discussed and considered before pregnancy, when possible, in order to ensure all possible risks, benefits and outcomes are explored.

Treatment Options

Alzheimer disease is incurable, however treatments are available to attempt to slow progression and manage symptoms. Some medications known as **cholinesterase inhibitors** and **NMDA receptor agonists** are approved for use in Alzheimer disease and should be discussed with your treating doctor. Most treatment is determined on an individual basis and in general individuals will eventually require assisted living arrangements of nursing home care.