

WHAT IS ALZHEIMER DISEASE?

Dementia is characterised by progressive difficulties with memory, language, learning, thinking and reasoning, as well as problems with everyday tasks and sometimes changes in personality. Dementia occurs with increasing frequency with increasing age. It is extremely rare under the age of 60 and then becomes progressively more common, so that about 25% of individuals aged over 85 will have evidence of it.

Individuals with dementia have a gradual build up of changes in the brain. The most common condition causing dementia is Alzheimer disease, first described by a German physician Alois Alzheimer in 1907. The defining features of Alzheimer disease 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 appear to be most prominent in the parts of the brain relating to language and memory, called the temporal lobes.

Alzheimer can be differentiated from other conditions causing dementia as they generally have different features. For example, Pick's disease preferentially affects the frontal lobes of the brain, which are involved in planning, insight and judgement. Individuals with frontal lobe dementia 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.

ARE GENES INVOLVED IN CAUSING ALZHEIMER DISEASE?

The cells of the body contain information, in the form of genes, for the body to make all the necessary structural components and chemicals to ensure normal function (see Genetics Fact Sheet 1). The information contains instructions that tell the cell the correct amount and type of proteins that need to be produced. Changes to the genetic information can mean that the proteins are not produced in the right amount or with the correct structure and function. A change that impairs the gene product is called a mutation. A mutation makes a gene faulty (see Genetics Fact Sheet 2).

Genes have been implicated in Alzheimer disease in two ways.

- Some families have a form of Alzheimer disease that is hereditary and is associated with one of several genes that are faulty. This is commonly referred to as *familial Alzheimer disease*. Individuals in such families who have inherited the

faulty gene usually are affected with the condition well before 65 years of age. This form of Alzheimer disease is very rare.

- Individuals with Alzheimer disease of 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 Alzheimer disease. About 30% of individuals with Alzheimer disease have such a family history, whereas only about 10% of elderly people generally have a history of dementia in a close relative. At least part of this increased frequency of having close relatives affected with the condition is related to the person's genetic make-up.

FAMILIAL ALZHEIMER DISEASE (YOUNG ONSET)

Everyone usually has the same number and types of genes. In some individuals the information in the genes contains changes (mutations) that make the gene faulty. In the rare families where familial Alzheimer disease or dementia occurs, the condition typically comes on in middle age (usually between 35 and 55). In these families, several different genes have been identified in which mutations cause Alzheimer disease 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 about 20 families in the world

In addition to these, familial dementia can be caused by mutations in a gene called the *TAU* gene, located on chromosome 17, and the prion protein gene on chromosome 20, resulting in familial Creutzfeldt-Kakob disease, Gerstmann-Straüssler-Scheinker disease and fatal familial insomnia. These conditions are different from Alzheimer disease, though they occur at a similar age and may sometimes appear similar during life.

Genetics Fact Sheets 1, 2 & 3 provide more information about genes, chromosomes and mutations.

In each family with familial Alzheimer disease or familial dementia, a mutation in only one of these three genes is causing the Alzheimer disease. The pattern of inheritance of these faulty genes is described as autosomal dominant (see Genetics Fact Sheet 7). Each child of an affected parent has a 50% chance (or 1 chance in 2) of having inherited the particular faulty gene from the affected parent; of course they also have a 50% chance of not having inherited it.

Children who have not inherited the faulty gene are not at risk of developing the disease in middle age (although if they live to be 90

they are presumed to have the same chance as anyone else in the community of developing dementia in later life). Importantly, children who have not inherited the faulty gene cannot pass it on to their own children.

Identifying a mutation as causative of the dementia is complex and depends on

- Determining if all affected members of the family have the same faulty gene
- Checking that it is only found in individuals who have dementia and not in older unaffected family members or in the general population
- Checking in the laboratory that the gene with this mutation causes the biochemical change that leads to the brain cells characteristic of the condition.

Where there is a strong family history of early onset Alzheimer disease or other rare forms of dementia, and a mutation has been identified in one of these genes as causing the dementia in a family, genetic testing may be available. The testing to determine if a person has inherited one of these faulty genes, and will develop the disorder in later life, is available for unaffected at-risk members of these families in conjunction with genetic counselling. This testing is called "presymptomatic testing" (see Genetics Fact Sheet 19) since the test is usually done prior to the onset of any symptoms of the condition.

Genetic counselling that provides an opportunity to discuss all the implications of the testing is essential (see Genetics Fact Sheet 5).

YOUNG-ONSET ALZHEIMER DISEASE WITHOUT APPARENT FAMILY HISTORY

The majority of individuals affected with the condition have no relatives affected. Such individuals are sometimes referred to as "sporadic" cases, some of whom developed the condition because of a new, or *spontaneous* mutation that occurred for unknown reasons in one of the genes in the egg or sperm from which the person developed or at their conception (see Genetics Fact Sheet 2).

The great majority of people with young-onset Alzheimer disease will have developed the condition because of some other reason, probably a combination of their genetic make-up with as yet unknown environmental influences. It is not known at this stage how many of these individuals in fact have a mutation, or what the non-genetic causes (if any) are. However some studies of individuals with Alzheimer disease but who have no family history of the condition, have found a very low rate of mutations in the genes known to be involved.

ALZHEIMER DISEASE IN LATER LIFE

While Alzheimer disease and other forms of dementia are 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. Looking at it another way, most people with dementia (about 95%) are over 65 years of age. About 30% of these people will have had a parent, brother or sister with dementia, while only about 10% of older people without dementia in the population will have a relative who is affected.

So people with dementia are about three times more likely to have or have had a parent or sibling with dementia. This apparent clustering of people with dementia in some families is known to be 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 earlier-onset familial Alzheimer disease.

The first gene to be identified that is associated with Alzheimer disease in later life is called APOE. It is located on the long arm of chromosome 19 (19q).

The APOE gene occurs in three forms known as E2, E3 and E4. Each contains slightly different information but all issue instructions to the cells for the same task: to produce an essential protein called *apolipoprotein E*. The function of this protein is to guide cholesterol through the bloodstream. Everyone has two copies of the APOE gene, one copy inherited from each parent. The most common form of the gene is E3.

Scientists have found that people with Alzheimer disease are more likely to have either one or two copies of the E4 form of the APOE gene. This is not a faulty gene: it is present in many healthy members of the community, and it is known that it is possible to have this form of the gene and not develop dementia despite living to 90 years of age. Similarly, about half of the people with Alzheimer disease do not have the E4 form of the gene.

Importantly, the E4 form of the APOE gene is neither necessary nor sufficient for the development of Alzheimer disease.

WHAT THEN IS THE CONNECTION BETWEEN THE APOE GENE AND ALZHEIMER DISEASE?

A likely explanation is that people with the E4 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 Alzheimer disease in the majority of people 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 Alzheimer disease in people with the E4 form of the APOE gene, but there must also be other potential causes, since severe head injury is quite rare.

It should be noted however that people who carry one copy of the E2 form of the APOE gene appear to be somewhat protected against developing Alzheimer disease, at least until much later in life.

Nevertheless, until more is known about the role of the APOE gene in Alzheimer disease, having a test to determine the form of the gene that a person has inherited (to "predict" whether a person is at increased risk or predisposed to develop the condition) is neither indicated nor recommended.

THE APOE GENE STORY IS VERY COMPLEX!

Indeed the relationship between a person's APOE genetic make-up and their other genes is likely to have an impact on the development of Alzheimer disease. Several other genes have been examined in relation to Alzheimer disease but changes in their information has not yet been found to have a consistent effect when studied by different research groups. The search for other genes likely to be involved is continuing. So too is the search for factors that may increase a person's risk of developing the condition and factors that may protect a person.

It is important to remember that the strongest risk factor for developing Alzheimer disease remains increasing age. As we get older changes in the genes build up in the cells. Some of these changes will be mutations in genes important for brain function.

WHAT ARE OTHER RISK FACTORS THAT MIGHT LEAD TO ALZHEIMER DISEASE?

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

Age: The risk of developing dementia, and therefore Alzheimer disease, increases exponentially with a person'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 or Trisomy 21 (see Genetics Fact Sheet 27) who live to adulthood will develop Alzheimer disease. This fact led to the association of mutations in the gene located on chromosome 21 with the development of the young-onset form of Alzheimer disease.

Other factors: Many environmental factors have been explored as possible risk factors for Alzheimer disease. None has 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 Alzheimer disease is now widely accepted. As noted previously, head injury is uncommon, and

therefore would not account for more than a small proportion of individuals with Alzheimer disease. 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 Alzheimer disease 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 might protect women against Alzheimer disease, but when this theory was tested in a large, well-conducted trial (the Women's Health Initiative Memory Study), the opposite effect was found. Therefore, hormone replacement therapy to be taken to give protection against Alzheimer disease cannot be recommended.

WHAT CAN BE DONE IF A PERSON THINKS HE OR SHE MAY BE AT RISK FOR DEVELOPING ALZHEIMER DISEASE?

New drugs are being developed for the treatment and prevention of Alzheimer disease.

Genetic counselling (see Genetics Fact Sheet 5) provides an opportunity for family members with a confirmed family history of the condition affecting members over several generations to discuss the risk of having inherited a predisposition to develop Alzheimer disease. In some cases, genetic testing may be possible. Such testing should only be undertaken when all the implications have been considered.

Information in this Fact Sheet is sourced from:

OMIM(TM), Online Mendelian Inheritance in Man. This database is a catalogue of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by [NCBI](http://www.ncbi.nlm.nih.gov/omim/), the National Center for Biotechnology Information: <http://www.ncbi.nlm.nih.gov/omim/>

The Alzheimer research Forum <http://www.alzforum.org>

Alzheimer's Australia <http://www.alzheimers.org.au>

Other Genetic Fact Sheets referred to in this Fact Sheet: 1, 2, 3, 5, 7, 19 and 27.