



Genetics and dementia

Introduction

Many people with dementia are concerned that their disease may have been inherited and that they may pass it on to their children. Family members of people with dementia are also sometimes concerned that they might be more likely to develop dementia themselves. This information sheet outlines the present state of knowledge about the inherited risk of dementia.

Genes and dementia

Genes are the unique set of instructions inside our bodies which make each of us an individual. There are many thousands of different genes, each carrying a different instruction.

We have two copies of each gene. One copy is inherited from each of our parents. When we have children, we pass on only one copy of each of our genes.

There are millions of combinations of genes that we could inherit, and the effect of each gene is not yet known, although scientists are rapidly expanding our knowledge. There can be different versions of the same gene which may work differently or not as well. This can cause a genetic condition or disease and some gene faults may lead to a person developing dementia.

However, the vast majority of cases of dementia are not caused by an inherited genetic fault. Dementia is so common that having one or two close relatives with dementia in itself is not evidence of a family link.

The genetic factors associated with dementia

The genetic factors associated with Alzheimer's disease and other forms of dementia can be summarised as follows:

- There is no single gene responsible for all cases of dementia
- Genetic factors only directly cause the disease in a very small number of families with dementia
- Among cases without a family link, there is often a genetic component to the disease; however, inherited factors alone do not explain why some people develop it and others do not.

Early onset Alzheimer's disease

We use the term Familial Alzheimer's disease in families where a genetic fault directly causes the disease. Familial Alzheimer's disease usually affects younger people (under the age of 65) rather than older people. Only a very small number of families are affected. These particular genetic faults can result in people developing Alzheimer's disease in their 30s and 40s. However, it is important to remember that most cases of early onset Alzheimer's disease are not inherited.

On average, half of the children of a person with one of these rare familial Alzheimer's disease genetic faults inherit the faulty gene. Almost all those who inherit it develop Alzheimer's disease at a comparatively early age. People who do not inherit the faulty gene cannot pass it on to their children.

The genetic factors for familial early onset Alzheimer's disease

- A small number of families worldwide have a genetic fault in a gene called amyloid precursor protein (APP), which affects production of the protein amyloid. Amyloid build-up in the brain has been linked to Alzheimer's disease.
- A slightly larger number of families carry a fault in a gene called presenilin-1 leading to early onset familial Alzheimer's disease.
- A very small group of families has a fault in a gene called presenilin-2 causing early onset familial Alzheimer's disease.

Late onset Alzheimer's disease

Late onset Alzheimer's disease (over 65) is not inherited in the same way as some cases of early onset Alzheimer's disease. Many factors combine to alter a person's risk of developing late onset Alzheimer's disease so that some develop it in later life and others do not. Genetic and environmental factors are both involved. Most of these factors are not fully understood. We do know that having a close family member with the condition increases risk – but only by a small amount. Other factors such as other illnesses, diet, levels of activity and random chance, are probably more significant in the development of Alzheimer's disease in later life. See Further reading section below for more information about risk factors and dementia.

Genetic factors for late onset Alzheimer's disease

The best known genetic factor for late onset Alzheimer's disease is a gene called apolipoprotein E (ApoE). It comes in three forms ApoE2, ApoE3 and ApoE4. We all have two copies of the gene, which may be the same version as each other or different.

The ApoE risk is different from how familial Alzheimer's disease is inherited. Having one or two copies of ApoE4 increases the chance of developing the disease, but does not make it

certain. One or two copies of ApoE3 are associated with an average risk, and the risk of developing Alzheimer's disease for people with two copies of ApoE2 is reduced. Some other factor, not yet understood, must also contribute.

Some researchers think that ApoE4 does not affect whether a person will get the disease but, rather, *when* they get it, causing people with ApoE4 to develop the disease before people with ApoE2. Because ApoE testing cannot accurately predict who will develop the disease it is generally not available to patients and their families except as part of a research study.

Vascular dementia

There are no established direct genetic causes for vascular dementia but the ApoE gene described above is a risk factor for vascular dementia as well as Alzheimer's disease. There are known genes that contribute to some of the risk factors for vascular dementia, such as high cholesterol levels, high blood pressure and diabetes.

Down's syndrome

People with Down's syndrome are at particular risk of developing Alzheimer's disease

Huntington's disease

Huntington's disease is a progressive hereditary disease caused by a particular gene. The symptoms of Huntington's disease usually develop when people are 30-50 years old, although they can start much earlier or much later and can vary from person to person, even in the same family. The course of the disease also varies for each person and dementia can occur at any stage.

Other dementias

Other forms of dementia can be inherited. Some people with fronto-temporal dementia or Pick's disease have a very strong family history. In some of these cases, a genetic change has been found in the TAU gene. These inherited forms of dementia are rare.

There are other very rare causes of inherited dementia with changes in different genes, such as the PRP gene in inherited CJD and the NOTCH gene in a rare disorder called CADASIL. A few families worldwide have an inherited dementia, the cause of which has yet to be discovered.

Genetic testing and counselling for people at risk of familial dementias

Anyone who is worried about inheriting a form of dementia and who has a relative with the condition should speak first to their GP. Although scientists are discovering more about the genetics of late onset Alzheimer's disease there are no approved tests for this condition. However, if you have more than one close family member affected by early onset dementia, and particularly if your family members first showed signs of the disease between the ages of 30 and 50, you may be referred to a regional clinical genetics department. Here you will be given more information and an opportunity to discuss the risk to yourself and other family members.

For a few families it may be possible to identify a gene change that is responsible for the disease in that family but for most families this will not be the case.

However, if such a change is found in your family this raises the possibility of testing to see if you too have the change. This sort of testing is called predictive testing and is currently available to people with Huntington's disease in the family, for example. Before having a predictive test you will be offered extensive counselling to make sure it is the right decision for you.

The pros and cons of genetic testing

A genetic test might:

- Identify people who might benefit from Alzheimer's drugs
- Help people plan for the future

- Help genetic researchers understand the disease better and so lead to improved treatment
- Lead to problems getting a mortgage or life insurance in the future (although in March 2005 the government announced a continuation of the moratorium on insurance companies using genetic information to November 2011)
- Raise anxiety without offering any useful treatment.

Testing for genes which are risk factors, like ApoE4, but not predictive as in familial Alzheimer's disease, is not done. This sort of test is not helpful because a higher risk does not necessarily mean someone will develop the illness and a lower risk does not mean they won't, and there is no treatment to offer someone at high risk.

Further reading

Alzheimer Scotland (2006). Dementia – how to reduce your risk. Free information leaflet.

Alzheimer Scotland (2006). Good for You Good for Your Brain: the evidence on risk reduction and dementia. £5.00

Available from Alzheimer Scotland, 22 Drumsheugh Gardens, Edinburgh EH3 7RN. Tel: 0131 243 1453 or visit www.goodforyourbrain.org

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Alzheimer Scotland

22 Drumsheugh Gardens, Edinburgh EH3
7RN

Telephone: 0131 243 1453

Fax: 0131 243 1450

Email: alzheimer@alzscot.org

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