



# Alzheimer's disease and genetics

*Alzheimer's disease as a genetic disorder*

**A**lzheimer's disease (AD) with early onset (before age 60 years) rarely runs in families. These inherited forms of AD are passed on in a very similar way to disorders like Huntington's disease and are exceedingly rare – only a few hundred families are affected with the inherited form of AD throughout the world. In these families a change, or mutation, in a gene causes AD and these changes are passed from one generation to another. As there is a 50% chance of inheriting any particular gene from either parent, a characteristic pattern of inheritance is seen whereby half of any generation is affected. The mutated gene does not skip generations and can affect males and females equally.

The genetics of late onset (after 60 years) AD is very different. It is known that a family history of AD increases the risk of developing this disorder but exactly by how much is not certain. It is likely that many genes result in an increased risk for late onset AD but it is certain that no single gene will be enough to cause the disorder.

## Genes associated with early onset Alzheimer's disease

Three genes are known to cause the rare early onset familial AD. The amyloid precursor protein (APP) gene on chromosome 21, the presenilin-1 (PS-1) gene on chromosome 14, and the presenilin-2 (PS-2) gene on chromosome 1. Of these the PS-1 gene is probably the most common but all are still very rare causes of a particular type of AD. Patients with Down's syndrome (3 copies of chromosome 21) almost always develop AD in middle age, probably because they have 3 copies of the APP gene. It is probable that other genes causing early familial AD remain to be discovered.

## Genes associated with late onset Alzheimer's disease

Only one gene has been definitely associated with late onset AD. The apolipoprotein E gene (APOE) on chromosome 19, which has three common variants, E2, E3 and E4. The E4 type increases the risk of developing AD and the E2 type probably decreases the risk or is protective. However, many people with AD do not have the E4 type gene and many people with the E4 type gene do not have AD. As one copy of each gene is inherited from each parent, everyone has two copies of the APOE gene. Those carrying two APOE4s have the most risk of developing AD but not all people with two APOE4s will develop the disease.

Many other genes are likely to be found that increase the risk of developing AD but the amount of risk associated with each of these genes is likely, if anything, to be even lower than that associated with APOE. Other genes found by some researchers to be associated with AD include a minor change in PS-1, the -1 antichymotrypsin gene, the serotonin transporter gene, the butyrylcholinesterase E gene, various APOE receptor genes and a region on chromosome 12. None of these genes has yet been unequivocally linked with AD.

## Clinical uses of genetic testing

Genes associated with AD might be used for:

- prediction
- diagnosis
- susceptibility testing
- helping with patient management

## Early onset Alzheimer's disease

Early onset AD is quite a different case to late onset AD. For early onset AD predictive testing and diagnostic testing is possible with all three genes (APP, PS-1 and PS-2). Predictive testing indicates which individuals will eventually develop an inherited condition whereas diagnostic testing confirms a diagnosis which has already been made. In these cases, detecting mutation will help with diagnosis and enable relatives to receive genetic counselling and testing. Individuals with a family member affected by early onset familial AD should contact a genetics centre for more advice.

## Late onset Alzheimer's disease

Testing for the APOE gene is unlikely to aid diagnosis because many patients have AD without the APOE4 type. Indeed, the APOE4 type may be a risk factor for other dementias, as it has been shown that some individuals with vascular and other forms of dementia also have the APOE4 type. Although diagnostic testing of the APOE gene has been suggested by some, this is not recommended by most experts at present. Use of APOE tests to predict which unaffected individuals will develop AD is NOT recommended.

Genetic testing may in the future help to decide who will get the most benefit from drugs designed to treat AD, or to identify types of AD needing particular treatment. It is of research interest only and not (yet) clinically useful.

## Genetic testing and genetic counselling

Genetic testing is a simple blood test, whereas genetic counselling is the

clinical process that precedes and follows this testing. Counselling is designed to ensure patients receive accurate information, only proceed to testing if appropriate and are helped to adjust to any information they receive as a result of the testing. Huntington's disease counselling is given using an internationally agreed protocol. Some individuals decide against testing after receiving counselling. Early research showed that many at risk of Huntington's disease, on being asked, indicated that they would want to be tested – but, in fact, relatively few decided to proceed with the test.

For early onset AD, genetic counselling to accompany testing should follow the guidelines accepted for Huntington's disease. For late onset Alzheimer's disease, although genetic testing is not recommended at present, relatives should have access to good information eg that there is a chance that they may be at risk of developing the disease and understand that genetic testing is a possibility but does have serious implications. If genetic testing for late onset AD is ever recommended, a procedure for counselling will need to be considered.

### Information on Alzheimer's disease genetics

General information on the genetics of AD can be obtained from national Alzheimer associations. Individuals wanting more information regarding their own family and are concerned they may inherit AD should approach a genetics centre. Sometimes it is necessary to do this through a general practitioner. Consensus guidelines have been developed by some organisations eg ADI (consensus statement on predictive testing for Alzheimer's disease, available from ADI secretariat), NIA (National Institute of Ageing, USA). Some information is available on the internet although, as with any information on the internet, caution needs to be exercised in ensuring that the information comes from a reliable source.

Some reliable sources of information on the internet about Alzheimer's disease are:

<http://www.alzforum.org/members/research/gene> (molecular genetics of AD)

<http://dsmallpc2.path.unimelb.edu.au/ad.html> (Alzheimer's web)

<http://www.coa.uky.edu/ADReview> (Alzheimer's Disease Review)

<http://www.medinfo.cam.ac.uk/phgu> (Public Health Genetics Unit, Cambridge)

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