

# Genetic Causes of Dementia

Dementia is a syndrome encompassing many intellectual domains that can be broadly defined as an overall decline in intellectual function, including difficulties with language, simple calculations, planning and judgment, motor skills as well as loss of memory. A genetic cause is identified in only a minority of patients, but patients and their family members are frequently concerned about the possible genetic basis of dementia and potential risk to relatives. This article reviews the main genetic causes of dementia. These are summarised in Table 1.

Genetic testing for dementia is a relatively young field and the consensus of expert guidance is that genetic testing should not be used routinely in diagnosis but that, where appropriate, patients should be referred to specialist centres for genetic counselling.<sup>1</sup>

## Alzheimer's disease

Alzheimer's disease (AD) is the commonest cause of dementia, typically causing progressive impairment of episodic memory with more general intellectual decline such as impaired judgment, decision-making, and orientation. Pathologically, AD is characterised by beta-amyloid neuritic plaques, intraneuronal neurofibrillary tangles and amyloid angiopathy. About 25% of patients with AD have one or more first-degree relatives with the disease. Early-onset AD (EOAD), arising before the age of 60, accounts for about 3% of cases.<sup>2</sup> In contrast to AD as a whole, about 60% of EOAD is familial, with 13% of

EOAD cases showing autosomal dominant inheritance.<sup>2</sup> The clinical characteristics of familial and non-familial AD appear to be identical.<sup>3</sup>

## Familial early-onset AD

Three single genes, PSEN1, PSEN2 and APP, are responsible for the majority of cases of early-onset autosomal dominant AD (Table 2). PSEN1 and PSEN2 encode the proteins presenilin-1 and presenilin-2 respectively, while APP encodes the amyloid beta precursor protein. The three proteins are closely involved in AD pathogenesis: presenilins form the catalytic core of the gamma-secretase enzyme complex that produces amyloid beta from amyloid precursor protein. Mutations in PSEN1, PSEN2 and APP increase the relative quantity of the most pathogenic form of amyloid beta, A $\beta$ -42.<sup>4</sup>

Mutations in PSEN1 account for about 65% of familial EOAD cases. Causative mutations are essentially fully penetrant by age 70; 90% of individuals undergo disease onset before the age of 60 and the mean age of onset is 35 with relatively rapid progression.<sup>2</sup> While the identification of a causative mutation in an affected patient is sufficient to make the diagnosis, counselling of unaffected individuals is more difficult. Ideally, an affected family member should be tested first to confirm the mutation in the family. Testing of presymptomatic individuals only predicts an individual's lifetime risk of developing AD but cannot predict age of onset, severity, type of symptoms or rate of progression.<sup>5</sup>



**Edward J Wild, MRCP**, is a Clinical Research Fellow at UCL Institute of Neurology, London and an Honorary Clinical Assistant at the National Hospital for Neurology and Neurosurgery, Queen Square, London. He trained in Cambridge and has worked in clinical neurology in New Zealand and London. His research interest is in identifying imaging and laboratory biomarkers of onset and progression for Huntington's disease and he is webmaster of the UCL HD research website at [www.hdresearch.ucl.ac.uk](http://www.hdresearch.ucl.ac.uk)



**Sarah J Tabrizi, MRCP PhD\***, studied biochemistry and medicine at Edinburgh University, then trained in neurology at the National Hospital for Neurology and Neurosurgery and the Royal Free Hospital. She did her PhD, as an MRC Clinical Training Fellow at UCL studying mitochondrial dysfunction, excitotoxicity and oxidative stress in neurodegeneration. She then undertook further research as a DH National Clinician Scientist, and she is now a tenured Clinical Senior Lecturer in the Department of Neurodegenerative Disease at UCL Institute of Neurology. Her clinical and research interests are in neurogenetics, particularly Huntington's disease, and basic cellular mechanisms of neurodegeneration focusing on protein misfolding disorders.

**Table 1: Genetic causes of dementia.**

Disorder	Gene (protein)	Clinical test available
Alzheimer's disease	<i>PSEN1</i> (presenilin-1)	•
	<i>PSEN2</i> (presenilin-2)	•
	<i>APP</i> (amyloid precursor protein)	•
	<i>ApoE</i> (apolipoprotein E)	
Frontotemporal dementia	<i>MAPT</i> (tau)	•
	<i>PGRN</i> (progranulin)	
	<i>VCP</i> (valosin-containing protein)	
	<i>CHMP2B</i> (chromatin-modifying protein 2B)	
Huntington's disease	<i>IT15</i> (huntingtin)	•
Familial prion disease	<i>PRNP</i> (prion protein)	•
CADASIL	<i>Notch3</i> (notch 3)	•
FBD	<i>BRI</i> (integral membrane protein 2B)	

**Table 2: Genetic causes of familial early-onset Alzheimer's disease (EOAD). Familial EOAD accounts for less than 0.5% of all AD.**

Gene	Percentage of familial cases	Mean age at onset	Comments
<i>PSEN1</i>	65%	35	Rapid progression. Fully penetrant by age 70.
<i>PSEN2</i>	<2%	55	Slower progression. 95% penetrance.
<i>APP</i>	Mutation	51	May show vascular pathology.
	Duplication	8%	Strong association with cerebral amyloid angiopathy.

## Abbreviations

AD - Alzheimer's disease • CADASIL - Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy • CJD - Creutzfeldt-Jakob disease • EOAD - Early-onset Alzheimer's disease • FBD - Familial British dementia with angiod angiopathy • FTD - Frontotemporal dementia • fvFTD - frontal-variant frontotemporal dementia • HD - Huntington's disease • LOAD - Late-onset Alzheimer's disease • PrP - Prion protein

## Correspondence to:

Sarah Tabrizi,  
Department of  
Neurodegenerative disease,  
UCL Institute of Neurology,  
National Hospital for Neurology  
and Neurosurgery,  
London, WC1N 3BG, UK.  
Tel. 08451 555 000  
Fax. 0207 676 2180  
Email. [sarah.tabrizi@prion.ucl.ac.uk](mailto:sarah.tabrizi@prion.ucl.ac.uk)

**Table 3: Genetic causes of frontotemporal dementia (FTD). Autosomal dominant cases account for 10-40% of FTD.**

Gene	Percentage of autosomal dominant cases	Comments
<i>MAPT</i>	18%	<i>Tau-positive cases. Associated with frontal variant or Parkinsonism.</i>
<i>PGRN</i>	23%	<i>Tau-negative cases with TDP-43 protein inclusions.</i>
<i>VCP</i>	Rare	<i>Inclusion body myopathy, Paget's disease and FTD</i>
<i>CHMP2B</i>	Rare	<i>Danish pedigree</i>
<i>Chromosome 9 loci</i>	<i>Unknown</i>	<i>FTD with motor neurone disease</i>

Mutations in *PSEN2* are rare, accounting for less than 2% of cases of familial EOAD. Age at onset tends to be later than in *PSEN1*-associated AD, with a mean of 55 years. Disease duration is longer and there is more clinical overlap with the sporadic form of AD. Penetrance is nearly complete (95%) but there have been reports of individuals unaffected over the age of 80.<sup>6</sup> *PSEN2* testing is available clinically, but counselling should warn that the onset is even more variable than for *PSEN1* mutations.

APP mutations account for around 15% of familial EOAD cases. Clinical genetic testing is not available for APP mutations but may be performed on a research basis. The mean age at onset is 51 years.<sup>2</sup> Though most cases of AD associated with APP mutations are typical, there may be amyloid angiopathy causing vascular features such as white matter infarcts.<sup>7</sup> As well as within-gene mutations, APP duplications have recently been found to cause early-onset AD with vascular features. Such duplications, which appear to account for about 8% of autosomal dominant EOAD, are not detected by mutation screening and must be sought specifically.<sup>8</sup>

#### Late-onset AD

Symptoms of AD begin after the age of 60 in about 97% of cases. Late-onset (LOAD) is referred to as AD type 2. Familial clustering is found in about 25% of cases of (LOAD), although only a small fraction are caused by *PSEN1*, *PSEN2* and APP mutations making population genetic testing inadvisable.<sup>1</sup> Only one genetic locus, ApoE- $\epsilon$ 4, has been consistently shown to be associated with age-at-onset in LOAD. Between 34 and 65% of individuals with AD carry at least one copy of the ApoE- $\epsilon$ 4 allele (rather than  $\epsilon$ 2 or  $\epsilon$ 3), which is present in only about 25% of the population. Most subjects homozygous for the ApoE- $\epsilon$ 4 allele will develop AD by the age of 80, while 26-50% of heterozygotes will develop AD. The presence of the ApoE- $\epsilon$ 4 allele is moderately specific for AD and a strong predictor of a diagnosis of AD in a subject with memory impairment. However, the risk of the ApoE- $\epsilon$ 4 allele remains relative and open to distressing

misinterpretation and it is advised that testing, though clinically available, should not be used in asymptomatic individuals.

#### Frontotemporal dementia

Frontotemporal dementia (FTD) is the second commonest cause of early-onset dementia after AD. It is a neurodegenerative illness encompassing three clinical syndromes characterised by behavioural and language disturbance: frontal-variant FTD (fvFTD), progressive non-fluent aphasia and semantic dementia. There is also clinical overlap between FTD and corticobasal degeneration, progressive supranuclear palsy and motor neurone disease. Pathologically, FTD usually causes intracellular inclusions that either are composed of tau protein or are tau-negative, ubiquitin-positive.

Thirty to fifty percent of FTD patients have a positive family history, with autosomal dominant inheritance in 10-40%. About 18% of those with autosomal dominant inheritance are found to have mutations in the *MAPT* gene encoding tau protein.<sup>9</sup> Clinical testing for *MAPT* mutations is available. Most cases of FTD due to mutations affecting tau result in either fvFTD or FTD with parkinsonism; primary language impairment is unusual in such cases.<sup>10</sup> Genetic causes of FTD are summarised in Table 3.

Mutations in the *PGRN* gene, encoding progranulin, were recently described as a cause of ubiquitin-positive FTD.<sup>11</sup> Interestingly, the intracellular inclusions in progranulin-mutation cases of FTD contain not progranulin, but TDP-43, a protein involved in transcriptional regulation. The link between progranulin and TDP-43 is not yet known.<sup>12</sup> Genetic testing for progranulin mutations is not available clinically, but early analyses suggest that progranulin mutations are common in FTD, accounting for about 10% of cases overall, and 23% of those with a positive family history.<sup>13</sup>

Several other genetic loci have been implicated in rare subtypes of FTD but cannot yet be tested for clinically. Inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia is caused

by mutations in *VCP*; mutations in *CHMP2B* have been found in a large Danish FTD pedigree; and FTD with motor neurone disease has been linked to two separate loci on chromosome 9.<sup>14</sup>

#### Huntington's disease

Huntington's disease (HD) is a fully penetrant autosomal dominant disorder caused by CAG triplet repeat expansions in the gene encoding the huntingtin protein. It classically produces a triad of chorea, dementia and behavioural disturbance, but the phenotype is highly variable and cognitive changes can precede the movement disorder by several years. The dementia of HD is usually of the subcortical-frontal type, with impulsivity, irritability and poor planning but normal memory. The behavioural phenotype encompasses depression, anxiety, irritability and psychosis.<sup>15</sup> HD genetic testing is widely available and should be accompanied by detailed genetic counselling.

#### Familial prion disease

Familial prion diseases are caused by mutations in the *PRNP* gene encoding the prion protein (PrP). Abnormal PrP promotes the conversion of normal PrP to the pathological form, resulting in aggregation and spongiform neurodegeneration. The vast majority of prion disease (about 80%) is sporadic, namely sporadic Creutzfeldt-Jakob disease (CJD). Acquired forms (variant CJD) are rarer. About 10-15% of prion disease is familial.

Familial prion diseases were traditionally classified into three forms: Gerstmann–Straussler–Scheinker syndrome is characterised by slowly progressive ataxia followed by dementia; fatal familial insomnia causes insomnia, hallucinations, autonomic dysfunction and motor impairment; and familial CJD causes rapidly progressive dementia, myoclonus and electroencephalographic abnormalities. These clinical categories are increasingly replaced by the general term 'familial prion disease', with specific mutations identified by genetic testing. Over 30 different *PRNP* mutations have been described: some cause specific phenotypes,

Patients with genetic dementia represent a small fraction of the total dementia caseload, but possible genetic risk causes great concern among patients and relatives

others a broad range of abnormalities.<sup>16</sup> PRNP gene sequencing is available clinically.

### Inherited vascular dementias

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by mutations in Notch3. It is the most common genetic cause of stroke and produces progressive dementia with stepwise deteriorations, particularly in executive function, with onset in the 30s-60s. Dementia often precedes other symptoms of stroke and 30-40% of subjects also have migraine headaches. Magnetic resonance imaging invariably reveals white matter T2 hyperintensities and lacunar infarcts.

Clinical genetic testing identifies mutations in 90% of affected individuals. Skin biopsy, to look for small vessel abnormalities, is reserved for gene-negative cases.<sup>17</sup>

Familial British dementia with amyloid angiopathy (FBD) also produces vascular dementia but with progressive spastic tetraparesis and cerebellar ataxia. It is caused by mutations in the BRI gene. Clinical genetic testing is not available but it causes abnormal MRI findings typical of vascular dementia.

### Conclusion

Dementia is a significant and increasing problem in neurology. Patients with dementia with a clearly identifiable genetic cause represent a

small fraction of the total dementia caseload, but possible genetic risk causes great concern among patients and relatives. In the coming years, we can expect clinical genetic tests to become available for the genes discussed, as well as the discovery of further causative and modifying genes in dementia.

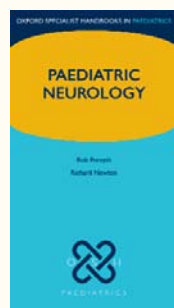
Knowledge of the genes causing the common dementia syndromes, their relative frequencies and the associated clinical pictures is useful in evaluating patients with dementia.

The consensus of expert advice is that genetic testing should be avoided if a given diagnosis is unlikely on clinical grounds and, where performed, should always be preceded by detailed, expert genetic counselling.<sup>1</sup>

### References

- Knopman DS, DeKosky ST, Cummings JL, et al. *Practice parameter: Diagnosis of dementia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology*. Neurology 2001;56:1143-53.
- Campion D, Dumanchin C, Hannequin D, et al. *Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum*. Am J Hum Genet 1999;65:664-70.
- Haupt M, Kurz A, Pollmann S, Romero B. *Alzheimer's disease: identical phenotype of familial and non-familial cases*. J Neurol 1992;239:248-50.
- Brunkan AL, Goate AM. *Presenilin function and gamma-secretase activity*. J Neurochem 2005;93:769-92.
- Bertram L, Tanzi RE. *The current status of Alzheimer's disease genetics: what do we tell the patients?* Pharmacol Res 2004;50:385-96.
- Bird TD, Levy-Lahad E, Poorkaj P, et al. *Wide range in age of onset for chromosome 1-related familial Alzheimer's disease*. Ann Neurol 1996;40:932-6.
- Raux G, Guyant-Marechal L, Martin C, et al. *Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update*. J Med Genet 2005;42:793-5.
- Rovelet-Lecrux A, Hannequin D, Raux G, et al. *APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy*. Nat Genet 2006;38:24-6.
- Goldman JS, Farmer JM, Wood EM, et al. *Comparison of family histories in FTL2 subtypes and related tauopathies*. Neurology 2005;65:1817-9.
- Baba Y, Tsuboi Y, Baker MC, et al. *The effect of tau genotype on clinical features in FTDP-17*. Parkinsonism & Related Disorders 2005;11:205-8.
- Baker M, Mackenzie IR, Pickering-Brown SM, et al. *Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17*. Nature 2006;442:916-19.
- Neumann M, Sampathu DM, Kwong LK, et al. *Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis*. Science 2006;314:130-3.
- Gass J, Cannon A, Mackenzie IR, et al. *Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration*. Hum Mol Genet 2006;15:2988-3001.
- Talbot K, Ansorge O. *Recent advances in the genetics of amyotrophic lateral sclerosis and frontotemporal dementia: common pathways in neurodegenerative disease*. Hum Mol Genet 2006;15 Spec No 2:R182-187.
- Bates G, Harper PS, Jones L, eds. *Huntington's Disease, Third ed*. Oxford: Oxford University Press, 2002.
- Mead S. *Prion disease genetics*. Eur J Hum Genet 2006;14:273-81.
- Amberla K, Waljas M, Tuominen S, et al. *Insidious Cognitive Decline in CADASIL*. Stroke 2004;35:1598-1602.

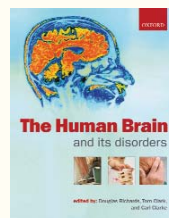
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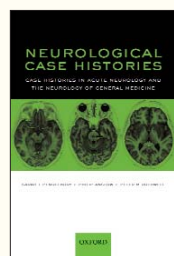


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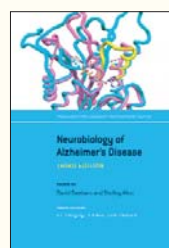
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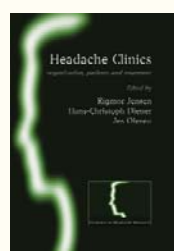
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