

Genetics and Molecular Biology of Alzheimer's Disease and Frontotemporal Lobar Degeneration

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Abstract

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, whereas frontotemporal lobar degeneration (FTLD) is the most frequent neurodegenerative disorder with a pre-senile onset. The two major neuropathological hallmarks of AD are extracellular amyloid beta plaques and intracellular neurofibrillary tangles. In FTLD the deposition of tau has been observed in a number of cases, but in several brains there is no deposition of tau but instead a positivity for ubiquitin. In some families these diseases are inherited in an autosomal dominant fashion. Genes responsible for familial AD include the amyloid precursor protein (*APP*), presenilin 1 (*PS1*) and presenilin 2 (*PS2*), whereas the main genes responsible for familial FTLD are microtubule-associated protein tau gene (*MAPT*) and progranulin (*GRN*). Concerning sporadic AD, it is known that the presence of the $\epsilon 4$ allele of the apolipoprotein E gene is a susceptibility factor. A number of additional genetic factors contribute to susceptibility for AD and FTLD.

Keywords

Alzheimer's disease, frontotemporal lobar degeneration, mutation, genetics, amyloid, tau, TDP-43, inflammation, oxidative damage

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Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with a prevalence of 5% after 65 years of age. The disease was originally described by Alois Alzheimer and Gaetano Perusini in 1906, and it is clinically characterised by progressive cognitive impairment including impaired judgement, decision-making and orientation, often accompanied, in later stages, by psychobehavioural disturbances as well as language impairment. The two major neuropathological hallmarks of AD are extracellular beta-amyloid (A β) plaques and intracellular neurofibrillary tangles (NFTs). The production of A β , which represents a crucial step in AD pathogenesis, is the result of the cleavage of a bigger precursor, named amyloid precursor protein (APP), which is overexpressed in AD.¹ A β forms highly insoluble and proteolysis-resistant fibrils known as 'senile plaques'.

NFTs are composed of the tau protein. In healthy controls, tau is a component of microtubules, which are the internal support structures for the transport of nutrients, vesicles, mitochondria and chromosomes within the cell. Microtubules also stabilise the growing axons, which are necessary for the development and growth of neurites.¹ In AD, tau protein is abnormally hyperphosphorylated and forms insoluble fibrils, which originate deposits within the cell.

Frontotemporal lobar degeneration (FTLD) occurs most often in the pre-senile period, and age at onset is typically 45–65 years, with a mean in the 50s. Distinctive features in FTLD concern behaviour, including disinhibition, loss of social awareness, overeating and impulsiveness. Despite profound behavioural changes, memory is relatively spared.² In contrast to AD, which is more frequent in women,

FTLD has an equal distribution among men and women. The current consensus criteria³ identify three clinical syndromes: frontotemporal dementia (FTD), progressive non-fluent aphasia (PA) and semantic dementia (SD), which reflect the clinical heterogeneity of FTLD. FTD is characterised by behavioural abnormalities, whereas PA is associated with progressive loss of speech, with hesitant, non-fluent speech output,⁴ and SD is associated with loss of knowledge about words and objects. This variability is determined by the relative involvement of the frontal and temporal lobes, as well as by the involvement of right and left hemispheres.⁵

Despite the majority of AD and FTLD cases being sporadic and likely caused by the interaction between genetic and environmental factors, so far it has been observed that clinically typical AD and FTLD can cluster in families and be inherited in an autosomal dominant fashion, suggesting a genetic cause.

Familial Alzheimer's Disease

In 1987, a region of linkage with AD was reported on the long arm of chromosome 21, which encompassed a region harboring the β -APP gene, a compelling candidate for AD.⁶ The gene is located at chromosome 21q21.22 and encodes for a transmembrane protein that is normally processed into amyloid fragments. In 1991, the first missense mutation in APP was reported.⁷ Since then, 32 different mutations have been described in the β -APP (www.molgen.ua.ac.be/). All of these mutations cause amino acid changes in putative sites for the cleavage of the protein, thus altering the APP processing, such that more pathological A β_{42} is produced.⁸ Interestingly, chromosome

21, in which β -APP resides, is triplicated in Down's syndrome and most cases also manifest AD by 50 years of age. *Post mortem* analyses of Down's patients who die young show diffuse intraneuronal deposits of A β , suggesting that its deposition is an early event in cognitive decline. The discovery of an extra copy of the β -APP gene in familial AD⁹ provides further support that increased A β production can cause the disease.

The other two genes causing familial AD are presenilin 1 (*PSEN1*) (14q24.3) and *PSEN2* (1q31-q42).^{10,11} Presenilins represent a central component of γ -secretase, the enzyme responsible for originating A β from the C-terminal fragment of the APP protein. Mutations in presenilins also alter APP cleavage, leading to an increased production of A β_{42} . So far, 178 mutations in *PSEN1* have been identified and 14 additional mutations have been found in the homologous gene *PSEN2* (www.molgen.ua.ac.be/).

Most variants in *PSEN1* are missense mutations resulting in single-amino-acid substitutions. Some are more complex, for example small deletions or splice mutations. The most severe mutation in *PSEN1* is a donor-acceptor splice mutation that causes a two-amino-acid substitution and an in-frame deletion of exon 9. However, the biochemical consequences of these mutations for γ -secretase assembly seem to be limited.^{12,13} All of these clinical mutations are likely to cause a specific gain of toxic function for *PSEN1*, determined by an increase of the ratio between A β_{42} and A β_{40} amyloid peptides, thus indicating that presenilins might modify the way in which γ -secretase cuts APP.

Mutations in presenilins occur in the catalytic subunit of the protease responsible for determining the length of A β peptides, thereby generating toxic A β fragments. However, presenilins also have non-proteolytic functions,^{14,15} the disruption of which might also contribute to familial AD pathogenesis.

Despite several carriers developing the disease early (at 40–50 years of age) with a typical AD phenotype, in some cases patients carrying the same mutation develop signs and symptoms resembling FTD instead of AD.¹⁶ In addition, other mutations are associated with myoclonus, seizures, bilateral spasticity, parkinsonian features or ataxia.¹⁷

Sporadic Alzheimer's Disease

Risk genes are likely to be numerous, displaying intricate patterns of interaction with each other as well as with non-genetic variables, and – unlike classical Mendelian ('simplex') disorders – exhibit no simple mode of inheritance. Mainly due to this reason, the genetics of sporadic AD has been labelled 'complex'.¹⁸ The gene mainly related to the sporadic forms of AD is apolipoprotein E (*APOE*),¹⁹ which is located at chromosome 19q13.32 and was initially identified by linkage analysis.²⁰ The relationship between *APOE* and AD has been confirmed in more than 100 studies conducted in different populations. The gene has three different alleles, *APOE*2*, *APOE*3* and *APOE*4*. The *APOE*4* allele is the variant associated with AD. Longitudinal studies in Caucasian populations have shown that carriers for one *APOE*4* allele have a two-fold increase in the risk of AD.²¹ The risk increases in those homozygous for the *APOE*4* allele, and this allelic variant is also associated with an earlier onset of the disease.

Several linkage studies have been performed, giving rise to additional candidate susceptibility loci at chromosomes 1, 4, 6, 9, 10, 12 and 19.

In particular, promising loci have been found at chromosomes 9 and 10.^{22,23} Recently, a wide genome analysis identified variants at *CLU* (which encodes clusterin or ApoJ) on chromosome 8 and phosphatidylinositol binding clathrin assembly protein (*PICALM*) on chromosome 11 associated with AD.²⁴ Data on *CLU* were contemporarily replicated in an independent study that, in addition, demonstrated that *CR1*, encoding the complement component (3b/4b) receptor 1 and located on chromosome 1, is associated with AD.²⁵

Also, a large number of candidate gene studies have been performed in order to search for a robust risk factor for the sporadic form of the disease. Several studies mainly focused on genes clearly involved in the pathogenesis of AD, such as genes encoding for inflammatory molecules or involved in the oxidative stress cascade.

Polymorphisms in the interleukin-1 (IL-1) complex, which includes *IL-1 α* , *IL-1 β* , and IL-1 receptor antagonist protein (*IL-1Ra*), are associated with AD in different populations.^{26–28} Several polymorphisms in *IL-6*, which is a potent inflammatory cytokine but has also regulatory functions, have been investigated as well. The *IL-6* gene is located at chromosome 7p21 and polymorphisms exist in the -174 promoter region and in the region of a variable number of tandem repeats (VNTR), which is located in the 3' untranslated region. Both of them have been found to be associated with AD in case-control studies.^{29,30} Investigation of tumour necrosis factor- α (*TNF- α*) polymorphisms was initiated because genome screening suggested a putative association of AD with a region on chromosome 6p21.3, which lies within 20 centimorgans of the *TNF- α* gene. Furthermore, other polymorphisms located in the promoter region of *TNF- α* have been associated with autoimmune and inflammatory diseases.³¹

Polymorphisms in chemokines have been investigated with regard to susceptibility to AD. In particular, monocyte chemoattractant protein-1 (*MCP-1*) and regulated on activation, normal T-cell expressed and secreted (*RANTES*) genes have been widely screened in different neurodegenerative diseases.³² The distribution of the A-2518G variant was determined in different AD populations with concordant results showing no evidence for association of this variant in AD compared with controls.^{33,34}

RANTES promoter polymorphism -403 A/G, found to be associated with several autoimmune diseases, was examined in an AD population, failing to exhibit significant differences between patients and controls.³²

The chemokine receptor 2 (*CCR2*) and *CCR5* genes, encoding for the receptors of MCP-1 and RANTES, respectively, have also been screened for association with AD. The most promising variants involve a conservative change of a valine with an isoleucine at codon 64 of *CCR2* (*CCR2-64I*) and a 32bp deletion in the coding region of *CCR5* (*CCR5 Δ 32*) that leads to the expression of a non-functional receptor. A decreased frequency and an absence of homozygotes for the polymorphism *CCR2-64I* were found in AD, suggesting a protective effect of the polymorphic allele on the occurrence of the disease;³⁵ conversely, no different distribution of the *CCR5 Δ 32* deletion in patients compared with controls was shown.^{35,36}

Another chemokine recently tested for susceptibility with AD is IP-10. A mutation scanning of the gene coding region has been performed in AD patients searching for new variants. The analysis demonstrated the

presence of two previously reported polymorphisms in exon 4 (G/C and T/C), which are in complete linkage disequilibrium, as well as a novel rare polymorphism in exon 2 (C/T). Subsequently, these single nucleotide polymorphisms (SNPs) have been tested in a wide case-control study, but no differences in haplotype frequencies were found.³⁷

Other genes under investigation are related to oxidative stress, a process closely involved in AD pathogenesis. In this regard, genes coding for the nitric oxide synthase (NOS) complex have been screened. The common polymorphism consisting of a T/C transition (T-786C) in *NOS3*, previously reported to be associated with vascular pathologies, has been tested in AD, but no significant differences with controls were found. Nevertheless, expression of *NOS3* in peripheral blood mononuclear cells (PBMCs), from either patients or controls, seems to be influenced by the presence of the C polymorphic allele, and is likely to be dose-dependent, being mostly evident in individuals homozygous for the polymorphic variant. The influence of the polymorphism on *NOS3* expression rate supports the hypothesis of a beneficial effect exerted in AD by contributing to lower oxidative damage.³⁸

An additional variant in the *NOS3* gene has been extensively investigated in AD patients, although the results are still controversial. It is a common polymorphism consisting of a single base change (G894T), which results in an amino acidic substitution at position 298 of *NOS3* (Glu298Asp). Dahiyat et al.³⁹ determined the frequency of the *Glu298Asp* variant in a two-stage case-control study, showing that individuals homozygous for the wild-type allele were more frequent in late-onset AD. However, studies in other populations failed to replicate these results.⁴⁰⁻⁴³

Guidi et al. correlated this variant with total plasma homocysteine (tHcy) levels in patients with AD and controls, demonstrating that the Glu/Glu genotype is correlated with higher levels of tHcy, which represents a known risk factor for AD, and its frequency was increased in AD patients.⁴⁴ Thus, the mechanism by which this genotype contributes to increase the risk of developing AD could be mediated by an increase of tHcy.

However, *NOS-1* is the isoform most abundantly expressed in the brain. Recent genetic analyses demonstrated that the double mutant genotype of the synonymous C276T polymorphism in exon 29 of the *NOS1* gene represents a risk factor for the development of early-onset AD,⁴⁵ whereas the dinucleotide polymorphism in the 3' untranslated region of *NOS1* is not associated with AD.⁴⁶ The distribution of a functional polymorphism and a variable number of tandem repeats (VNTR) was analysed in a case-control study.⁴⁷ The functional variant considered is located in exon 1c, which is one of the nine alternative first exons (named 1a-1i), resulting in *NOS1* transcripts with different 5' untranslated regions.⁴⁸ Three SNPs have been identified in exon 1c, but only the G-84A variant displays a functional effect, as the A allele decreases the transcription levels by 30% in *in vitro* models.⁴⁹ Regarding exon 1f, a VNTR polymorphism has been recently reported in its putative promoter region, termed *NOS1* Ex1f-VNTR. This VNTR is highly polymorphic and consists of different numbers of dinucleotides (B-Q), which, according to their bimodal distribution, have been dichotomised into short (B-J) and long (K-Q) alleles for association studies. Both Ex1c G-84A and Ex1f-VNTR are associated with psychosis and prefrontal functioning in a population of patients with schizophrenia.⁵⁰ Both Ex1c and Ex1f transcripts are found in the hippocampus and the frontal cerebral cortex, i.e. brain

regions implicated in the pathogenesis of schizophrenia as well as AD. The presence of the short (S) allele of *NOS1* Ex1f-VNTR represents a risk factor for the development of AD. The effect is cumulative, as in S/S carriers the risk is doubled. Most interestingly, the effect of this allele is likely to be gender-specific, as it was found in females only. In addition, the S allele was shown to interact with the *APOE*4* allele in both males and females, increasing the risk of developing AD by more than 10-fold.⁴⁷

Familial Frontotemporal Lobar Degeneration

FTLD is a heterogeneous disease characterised by a strong genetic component in its aetiology, as up to 40% of patients report a family history of the disease in at least one family member.⁵¹ In 1994 an autosomal dominantly inherited form of FTLD with parkinsonism was linked to chromosome 17q21.2.⁵² Subsequently, other familial forms of FTLD were found to be linked to the same region, resulting in the denomination 'frontotemporal dementia and parkinsonism linked to chromosome 17' (FTDP-17) for this class of diseases.

In 1998, the *MAPT* gene on chromosome 17q21, which encodes the microtubule associated protein tau, was described as the cause of the disease in these families.⁵³⁻⁵⁵ Currently, 44 different mutations in the *MAPT* gene have been described in a total of 132 families (www.molgen.ua.ac.be/). *MAPT* mutations are either non-synonymous or deletion, silent mutations in the coding region, or intronic mutations located close to the splice-donor site of the intron after the alternatively spliced exon 10.⁵⁶ Mutations are mainly clustered in exons 9-13, except for two recently identified mutations in exon 1.⁵⁷ As regards possible effects on *MAPT* mutations, different mechanisms are involved, depending on the type and location of the mutation. Many of them disturb the normal splicing balance, producing altered ratios of the different isoforms. A number of mutations promote the aggregation of tau protein, whereas others enhance tau phosphorylation.⁵⁸

However, after the discovery of *MAPT* as a causal gene for FTDP-17, there were still numerous families with autosomal dominant FTLD genetically linked to the same region of chromosome 17q21, which contains *MAPT*, but in whom no pathogenic mutations had been identified despite extensive analysis of this gene.⁵⁹⁻⁶¹ The neuropathological phenotype in these families was similar to the microvacuolar type observed in a large proportion of idiopathic FTD cases with ubiquitin immunoreactive neuronal inclusions. Moreover, clinically, the disease in these families was consistent with diagnostic criteria for FTLD.³ Sequence analysis of the whole *MAPT* region failed to find a mutation and tau protein appeared normal in these families.⁶² Moreover, the minimal region containing the disease gene for this group of families was approximately 6.2Mbp in physical distance. This region, defined by markers D17S1787 and D17S806, is particularly gene-rich, containing around 180 genes. Collectively, these data strongly argued against *MAPT* and pointed to another gene. Systematic candidate gene sequencing of all remaining genes within the minimal candidate region was performed and after sequencing 80 genes, including those prioritised on known function, the first mutation in the progranulin gene (*GRN*) was identified. It consists of a 4bp insertion of CTGC between coding nucleotides 90 and 91, causing a frame shift and premature termination in progranulin (C31LfsX34).⁶³ These results have been contemporarily replicated by Cruts et al., who analysed other families with FTLD with ubiquitin-positive inclusion (FTLD-U) disease without *MAPT* pathology, finding a mutation five base

pairs into the intron following the first non-coding exon of the *GRN* gene (IVS0+5G-C). This is predicted to prevent splicing out of intron 0, leading the messenger RNA (mRNA) to be retained within the nucleus and subjected to nuclear degradation.⁶⁴ At present there is no obvious mechanistic link between the mutations in *MAPT* and *GRN*, currently assuming that their proximity on chromosome 17 is simply a coincidence. Progranulin is known by several different names, including granulin, acrogranin, epithelin precursor, proepithelin, and prostate cancer (PC)-cell-derived growth factor.⁶⁵ The protein is encoded by a single gene on chromosome 17q21 that produces a 593-amino-acid, cysteine-rich protein with a predicted molecular weight of 68.5kDa. The full-length protein is subjected to proteolysis by elastase, and this process is regulated by a secretory leukocyte protease inhibitor (SLPI).⁶⁶ Progranulin and the various granulin peptides are implicated in a range of biological functions including development, wound repair and inflammation by activating signalling cascades that control cell-cycle progression and cell motility.⁶⁵ Excess progranulin appears to promote tumour formation and hence can act as a cell survival signal. Despite the increasing literature on the function of progranulin, its role in neuronal function and survival remains unclear. In the human brain, *GRN* is expressed in neurons but significantly is also highly expressed in activated microglia,⁶³ with the result that *GRN* expression is increased in many neurodegenerative diseases.

Since the original identification of null mutations in FTLD in 2006, numerous novel mutations have been reported, spanning most exons, and to date 68 *GRN* mutations have been described (www.molgen.ua.ac.be/).

The majority of mutations identified create functional null alleles, causing premature termination of the *GRN* coding sequence. This leads to the degradation of the mutant RNA by non-sense-mediated decay, creating a null allele.^{63,64} The presence of a null mutation causes a partial loss of functional progranulin protein, which in turn leads eventually to neurodegeneration (haploinsufficiency mechanism), although how loss of *GRN* causes neuronal cell death remains unclear. Estimates of the frequency of *GRN* mutations in typical FTD patient populations suggests that they account for about 5–10% of all FTD cases, although numbers vary markedly depending on the nature of the populations considered.^{64,67,68}

Neuropathology analysis has revealed that ubiquitin immunoreactive neuronal cytoplasmic and intranuclear inclusions were present in all cases with FTDP-17 where pathological findings were available.⁶⁹ Furthermore, soon after the identification of mutations in *GRN*, biochemical analyses demonstrated that truncated and hyper-phosphorylated isoforms of the TAR-DNA binding protein (TDP-43) are major components of the ubiquitin-positive inclusions in families with *GRN* mutations as well as in idiopathic FTD and a proportion of amyotrophic lateral sclerosis (ALS) cases.⁷⁰ TDP-43 is a ubiquitously expressed and highly conserved nuclear protein that can act as a transcription repressor, an activator of exon skipping or a scaffold for nuclear bodies through interactions with survival motor neuron protein. Under pathological conditions, TDP-43 has been shown to relocate from the neuronal nucleus to the cytoplasm, a consequence of which may be the loss of TDP-43 nuclear functions.⁷⁰ The mechanism by which loss of progranulin leads to TDP-43 accumulation and whether this is necessary for neurodegeneration in this group of diseases remain to be clarified.

In conclusion, the function of progranulin in the brain is currently unclear; why loss of this protein leads to neurodegenerative diseases in mid-life remains to be established, and its possible role as a regulator of repair activity in the central nervous system, as is well known to occur in periphery, remains a challenge for science. The gene encoding for TDP-43, named *TARDBP*, has been extensively studied and a number of mutations found in its C-terminal glycine-rich region. Unexpectedly, the clinical phenotype of carriers was ALS, and aggregates made of TDP-43 have been described in the brain and spinal cord of such patients.⁷¹

A recently published collaborative study⁷² analysed *GRN* in a population of 434 patients with FTLD, including FTD, PA, SD, FTD/ALS, FTD/motor neurone disease (MND), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). Fifty-eight variants were identified, including 24 pathogenic variants. The frequency of *GRN* mutations was 6.9% of all FTLD-spectrum cases, 21.4% of cases with a pathological diagnosis of FTLD-U, 16% of FILD-spectrum cases with a family history of a similar neurodegenerative disease and 56.2% of cases of FTLD-U with a family history. Clinical information was available for 31 *GRN* mutation-positive patients from 28 different families. The most common clinical diagnosis was FTD (n=24); three patients were diagnosed with PA, three with AD and one with CBD. The majority of *GRN* mutations introduced a premature termination codon, suggesting that their corresponding mRNA will be degraded through non-sense-mediated decay, supporting the hypothesis that most *GRN* mutations create a functional null allele.⁷²

Two additional genes have been shown to cause FTLD. In 1995 Brown et al.⁷³ reported linkage to the pericentromeric region of chromosome 3 in a large multigenerational family with FTLD from Denmark. Nevertheless, the aberrant gene in this family has only recently been identified.⁷⁴ It consists of a mutation in the splice acceptor site of exon 6 of charged multivesicular body protein 2B (*CHMP2B*), which is part of the endosomal ESCRTIII complex. The change from G to C results in an alteration of the splice acceptor site of exon 6, causing aberrant mRNA splicing of this transcript, which leads to the insertion of 201 base pairs of the intron between exons 5 and 6. In addition, a further transcript was identified, resulting from the use of a cryptic splice site consisting of 10 base pairs from the 5' end of exon 6. In any case, mutations in *CHMP2B* appear as a rare genetic cause of FTLD mainly due to their rare frequency of occurrence, showing moreover that the *CHMP2B* locus does not increase the risk of FTLD.⁷⁵

Lastly, the first evidence of linkage with chromosome 9q21-22 comes from a study carried out in families with MND and FTD.⁷⁶ Despite the evidence of linkage to chromosome 9q21-22 in several additional FTD-MND families, the gene responsible for the disease in this locus has yet to be identified.⁷⁷⁻⁷⁹

Sporadic Frontotemporal Lobar Degeneration

The most well-known risk factor for late-onset AD, Apo E4, has also been considered as a risk factor for sporadic FTLD. A number of studies have suggested an association between FTLD and the *APOE*4* allele.⁸⁰⁻⁸⁵ However, other authors did not replicate these data.⁸⁶⁻⁸⁸ Recent findings demonstrated an association between the *APOE*4* allele and FTLD in males but not females,⁸⁹ possibly explaining the discrepancies previously reported. An increased frequency of the *APOE*4* allele was described in patients with SD compared with those with FTD and PA.⁸⁷

Concerning the *APOE*2* allele in the development of FTLD, heterogeneous data have been obtained in different populations. Bernardi et al.⁸⁵ showed a protective effect of this allele towards FTLD, but the data were not replicated. A recent meta-analysis comprising a total of 364 FTD patients and 2,671 controls demonstrated an increased susceptibility to FTD in *APOE*2* carriers.⁹⁰

Besides pathogenic mutations, several polymorphisms have been reported to date, both in *MAPT* and *GRN*. An association between PSP and a dinucleotide repeat polymorphism in the intron between *MAPT* exons 9 and 10 was described in 1997.⁹¹ The alleles at this locus carry 11–15 repeats. Subsequently, two common *MAPT* haplotypes, named H1 and H2, were identified.⁹² Homozygosity of the more common allele H1 predisposes to PSP and CBD, but not to AD or Pick disease.^{92,93}

Regarding *GRN*, an association of an SNP located in the promoter with an increased risk of developing FTLD in patients who did not carry causal mutations has recently been demonstrated.⁹⁴

Lastly, a known polymorphism in *MCP-1* (A-2518G) has been shown to exert a protective effect towards the development of FTLD,⁹⁵ whereas *NOS3* G894T (Glu298Asp) and *NOS1* C276T SNPs likely increase the risk of developing FTLD.^{96,97} ■



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1. Griffin WS, *Am J Clin Nutr*, 2006;83(Suppl.):470S–4.
2. Hou CE, et al., *Can J Psychiatry*, 2004;49(3):164–174.
3. Neary D, et al., *Neurology*, 1998;51:1546–54.
4. Scarpini E, et al., *J Neurol Sci*, 2006;240(1–2):45–51.
5. Rosen HJ, et al., *Neurology*, 2002;58:1608–15.
6. Tanzi RE, et al., *Science*, 1987;235(4791):880–84.
7. Goate A, et al., *Nature*, 1991;349(6311):704–6.
8. Hardy J, et al., *Science*, 2002;297(5580):353–6.
9. Rovelet-Lecrux A, et al., *Nat Genet*, 2006;38:24–6.
10. Sherrington R, et al., *Nature*, 1995;375(6534):754–60.
11. Levy-Lahad E, et al., *Science*, 1995;269(5226):973–7.
12. Steiner H, et al., *J Biol Chem*, 1999;274:7615–18.
13. Bentahir M, et al., *J Neurochem*, 2006;96:732–42.
14. Baki L, et al., *EMBO J*, 2004;23:2586–96.
15. Huppert SS, et al., *Dev Cell*, 2005;8:677–88.
16. Brunì AC, et al., *Neurology*, 2010;74:798–806.
17. Larner AJ, et al., *J Alzheimers Dis*, 2009;17(2):259–65.
18. Bertram L, et al., *J Clin Invest*, 2005;115(6):1449–57.
19. Corder EH, et al., *Science*, 1993;261(5123):921–3.
20. Pericak-Vance MA, et al., *Am J Hum Genet*, 1991;48(6):1034–50.
21. Raber J, et al., *Neurobiol Aging*, 2004;25(5):641–50.
22. Grupe A, et al., *Am J Hum Genet*, 2006;78(1):78–88.
23. Li Y, et al., *Hum Mol Genet*, 2006;15(17):2560–68.
24. Harold D, et al., *Nat Genet*, 2009;41(10):1088–93.
25. Lambert JC, et al., *Nat Genet*, 2009;41(10):1094–9.
26. Du Y, et al., *Neurology*, 2000;55(4):480–83.
27. Grimaldi LM, et al., *Ann Neurol*, 2000;47(3):361–5.
28. Papassotiropoulos A, et al., *Ann Neurol*, 1999;45(5):666–8.
29. Nicoll JA, et al., *Ann Neurol*, 2000;47(3):365–8.
30. Licastro F, et al., *Mech Ageing Dev*, 2003;124:539–48.
31. Collins JS, et al., *Am J Med Genet*, 2000;96(6):823–30.
32. Huerta C, et al., *Neurosci Lett*, 2004;370(2–3):151–4.
33. Fenoglio C, et al., *Neurobiol Aging*, 2004;25(9):1169–73.
34. Combarros O, et al., *Neurosci Lett*, 2004;360(1–2):25–8.
35. Galimberti D, et al., *J Neurol Sci*, 2004;225(1–2):79–83.
36. Combarros O, et al., *Neurosci Lett*, 2004;366(3):312–14.
37. Venturelli E, et al., *Neurosci Lett*, 2006;404(1–2):217–21.
38. Venturelli E, et al., *Neurosci Lett*, 2005;382(3):300–3.
39. Dahiyat M, et al., *Ann Neurol*, 1999;46(4):664–7.
40. Crawford F, et al., *Ann Neurol*, 2000;47(5):687.
41. Sánchez-Guerra M, et al., *J Neurol Neurosurg Psychiatry*, 2001;70:566–7.
42. Tedde A, et al., *J Neurol*, 2002;249:110–11.
43. Monastero R, et al., *Neurosci Lett*, 2003;341:229–32.
44. Guidi I, et al., *Neurobiol Aging*, 2005;26(6):789–94.
45. Galimberti D, et al., *J Neurol*, 2005;252:985–6.
46. Liou YJ, et al., *Am J Med Gen*, 2002;114:687–8.
47. Galimberti D, et al., *Neurobiol Aging*, 2008;29(9):59–65.
48. Wang Y, et al., *Proc Natl Acad Sci U S A*, 1999;96(21):12150–55.
49. Saur D, et al., *Proc Natl Acad Sci*, 2004;101(6):1662–7.
50. Reif A, et al., *Mol Psychiatry*, 2006;11(3):286–300.
51. Snowden JS, et al., *Br J Psychiatry*, 2002;180:140–43.
52. Wilhelmsen KC, et al., *Am J Hum Genet*, 1994;55:1159–65.
53. Hutton M, et al., *Nature*, 1998;393:702–5.
54. Poorkaj P, et al., *Ann Neurol*, 1998;43:815–25.
55. Spillantini MG, et al., *Proc Natl Acad Sci U S A*, 1998;95:7737–41.
56. Rademakers R, et al., *Hum Mutat*, 2004;24(4):277–95.
57. Rademakers R, et al., *Mol Psychiatry*, 2002;7:1064–74.
58. Goedert M, et al., *Biochim Biophys Acta*, 2005;1739:240–50.
59. Lendon CL, et al., *Neurology*, 1998;50:1546–55.
60. Rosso SM, et al., *Brain*, 2001;124:1948–57.
61. van der Zee J, et al., *Brain*, 2006;129:841–52.
62. Cruts M, et al., *Hum Mol Genet*, 2005;14:1753–62.
63. Baker M, et al., *Nature*, 2006;442:916–19.
64. Cruts M, et al., *Nature*, 2006;442:920–24.
65. He Z, et al., *J Mol Med*, 2003;81:600–12.
66. Zhu J, et al., *Cell*, 2002;111:867–78.
67. Gass J, et al., *Hum Mol Genet*, 2006;15(20):2988–3001.
68. Snowden JS, et al., *Brain*, 2006;129:3091–3102.
69. Mackenzie IR, et al., *Brain*, 2006;129:853–67.
70. Neumann M, et al., *Science*, 2006;314:130–33.
71. Pesiridis G, et al., *Hum Mol Genet*, 2009;18(2):R156–62.
72. Yu CE, et al., *Arch Neurol*, 2010;67(2):161–70.
73. Brown J, et al., *Hum Mol Genet*, 1995;4:1625–8.
74. Skibinski G, et al., *Nat Genet*, 2005;37:806–8.
75. Rizzu P, et al., *Am J Med Genet B Neuropsychiatr Genet*, 2006;141:944–6.
76. Hosler BA, et al., *JAMA*, 2000;284:1664–9.
77. Morita M, et al., *Neurology*, 2006;66(6):839–44.
78. Vance C, et al., *Brain*, 2006;129:868–76.
79. Le Ber I, et al., *Neurology*, 2009;72:1669–76.
80. Farrer LA, et al., *Exp Neurol*, 1995;136:1625–80.
81. Gustafson L, et al., *Dement Geriatr Cogn Disord*, 1997;8:240–43.
82. Helisalmi S, et al., *Neurosci Lett*, 1996;205:61–4.
83. Stevens M, et al., *Neurology*, 1997;48:1526–9.
84. Fabre SF, et al., *Exp Neurol*, 2001;168:413–18.
85. Bernardi L, et al., *Neurobiol Aging*, 2006;27(5):702–9.
86. Geschwind D, et al., *Ann Neurol*, 1998;44:134–8.
87. Short RA, et al., *Arch Neurol*, 2002;59:611–15.
88. Riemenschneider M, et al., *J Neurol Neurosurg Psychiatry*, 2002;72:639–41.
89. Srinivasan R, et al., *J Neurol Neurosurg Psychiatry*, 2006;77:154–8.
90. Verpillat P, et al., *Eur J Hum Genet*, 2002;10:399–405.
91. Conrad C, et al., *Ann Neurol*, 1997;41(2):277–81.
92. Baker M, et al., *Hum Mol Genet*, 1999;8(4):711–15.
93. Di Maria E, et al., *Ann Neurol*, 2000;47(3):374–7.
94. Galimberti D, et al., *J Alzheimers Dis*, 2010;19(1):171–7.
95. Galimberti D, et al., *J Alzheimers Dis*, 2009;17(1):125–33.
96. Venturelli E, et al., *Eur J Neurol*, 2009;16(1):37–42.
97. Venturelli E, et al., *Eur J Neurol*, 2008;15(1):77–81.