

Genetics of familial and sporadic Alzheimer's disease

Irene Piaceri¹, Benedetta Nacmias¹, Sandro Sorbi¹

¹Department of Neurological and Psychiatric Sciences, University of Florence and Centro di Ricerca, Trasferimento e Alta Formazione DENOTHE, University of Florence, Largo Brambilla 3, 50134 Firenze

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Familial Alzheimer's disease
 - 3.1. Amyloid precursor protein
 - 3.2. Presenilin genes
 - 3.2.1. Presenilin 1 gene
 - 3.2.2. Presenilin 2 gene
4. Sporadic Alzheimer's disease
 - 4.1. Apolipoprotein E
 - 4.2. Susceptibility genes and Genome wide association studies
 - 4.3. Alzheimer's disease and the genes involved in neurofibrillary tangles
5. Perspective
6. Acknowledgments
7. References

1. ABSTRACT

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder. A majority of cases manifest as a late onset sporadic form but genetically the disease is divided into familial cases and sporadic cases. The familial form is due to mutations in three major genes [amyloid precursor protein (APP) gene, presenilin1 (PSEN1) gene and presenilin 2 (PSEN2) gene]. In contrast, many genetic and environmental factors may contribute to determining the sporadic AD form. Despite many years of research and great progress in the knowledge of the molecular pathogenesis of AD, a full understanding of the etiology of the sporadic form is still not yet in reach. Genome-wide association studies (GWASs) revealed the genetic complexity of the disease and recent studies suggested that epigenetic mechanisms may play an essential role in disease development. This review provides an overview of all the milestones in AD genetic research, as well as the new and promising approach, in order to better understand the genetic profile for predicting the risk of AD.

2. INTRODUCTION

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder characterized by cognitive impairment, a variety of neuropsychiatric symptoms and restriction in the activities of daily living. An expert panel estimated that 24 million people worldwide are affected by dementia, most suffering from AD, and predicted that this would increase by about 81 million by 2040 (1). The most common form of AD is late onset AD (LOAD) that is defined as AD with an age at onset later than 65 years, while early-onset AD (EOAD) accounts for approximately 1% to 6% of all cases and age at onset ranges roughly from 30 years to 65 years. Genetically, AD is usually divided into familial cases with Mendelian inheritance (Familial AD, FAD) and sporadic cases with no familial aggregation. Familial cases are predominantly early-onset (younger than 65 years, early-onset familial AD; EOFAD), but also late onset cases (LOFAD) has been described (2). More than 90% of AD patients appear to be sporadic and usually with a late onset age (older than 65 years, LOAD). FAD is usually due to

Table 1. Mutations in candidate genes linked to Familial Alzheimer's disease

Gene	Locus	Mutations N (%)	Families N (%)	Age at onset range years
APP	21q21.3	32 (7.66)	89 (8.63)	39-67
PSEN 1	14q24.3	185 (43.94)	405 (37.92)	28-79
PSEN 2	1q31-q42	13 (3.11)	22 (2.13)	39-85

rare and highly penetrant mutations in one of three principal genes [amyloid precursor protein (APP), presenilin 1 (PSEN1), presenilin 2 (PSEN2)] (3), although FAD cases due to PSEN1 and PSEN2 mutations with incomplete penetrance have been described (4). The sporadic form is more complex and most likely results from a combination of genetic and environmental influences. The only confirmed genetic risk factor is the presence of the epsilon4 allele in Apolipoprotein E (APOE), although several independent AD genome-wide association studies (GWASs) have provided evidence for novel AD risk factors (3).

3. FAMILIAL ALZHEIMER'S DISEASE

FAD is diagnosed in families that have more than one member with AD (usually multiple affected persons in more than one generation), but it is clinically indistinguishable from the sporadic form. Only 5% of all AD cases can be considered familial with an autosomal dominant inheritance due to mutations in the APP, PSEN1 and PSEN2 genes, and although several hundred families carry one of the mutations in these genes, they account for less than 1% of all cases (2). The determination of the mutations responsible for the disease in these families is an important step to better understand the molecular pathogenesis of AD, along with the clinical implication.

The majority of presenilin mutations cause the increased production of amyloid beta protein (A-beta) 1-42, that is the main component of amyloid plaques deposited in brain tissue. Moreover, it has been demonstrated that the toxicity of beta-amyloid is expressed before the formation of fibrils (5).

3.1. Amyloid precursor protein

The prediction of an AD gene on chromosome 21 was put forward in 1984 when Glenner and Wong reported the amino acid sequence of the main component of beta-amyloid, which they termed "amyloid beta protein" (A-beta), based on their analysis of cerebrovascular amyloid derived from patients with Down's syndrome (6). As predicted by Glenner, the peptide derived from a much larger APP encoding by a gene mapped to chromosome 21. The APP gene is composed of 18 exons, and by alternative splicing can give rise to 10 different isoforms consisting of 563 to 770 amino acid residues. APP 695 is the predominant form in the central nervous system; the others are also present in other tissues. This gene encodes a large integral membrane glycoprotein with a large extracellular domain, a short intracytoplasmic carboxyl terminal and a central part of the beta-amyloid. Two predicted cleavages produce the A-beta peptide from APP. One occurs in the extracellular domain by two enzymes: beta-secretase (identified now as BACE1 or beta-site APP cleaving enzyme 1) and gamma-secretase (comprising four proteins,

one of which is PSEN1) (amyloidogenic pathway). Moreover, another enzyme, alpha-secretase, cleaves APP within the A-beta peptide and prevents the formation of A-beta; this is known as the "non-amyloidogenic pathway" (7,8). The processing of APP by alpha-secretase and gamma-secretase produces the formation of a short beta-amyloid (A-beta 1-40) fragment that is not neurotoxic. In contrast, beta-secretase activity followed by gamma-secretase cleavage produces a different A-beta fragment, called A-beta 1-42. This fragment has been shown to be a more neurotoxic form due to its propensity to rapidly aggregate (8). The first mutation, also known as the London mutation, that causes EOFAD was identified in this gene (9) in exon 17, leading to a valine-to-isoleucine change at amino acid 717 (Val717Ile) (9). To date, over 30 different mutations in APP are currently listed in 89 families worldwide, including non-pathogenic ones (AD mutation database; <http://www.molgen.ua.ac.be/ADMutations/>). Interestingly, most of these mutations are located in exons 16 and 17, near the alpha-secretase cleavage site, in the central part of the beta-amyloid peptide or near the gamma-secretase site of attack, giving rise to an increase or alteration in A-beta production (fragment A-beta 1-42) (10). Mutations in the APP gene are responsible for only a small percentage of all familial cases, about 9% (AD mutation database; <http://www.molgen.ua.ac.be/ADMutations/>; Table 1). All APP mutations are autosomal dominant and cause the disease with complete penetrance; however, in 2009, Di Fede and colleagues described a recessive APP mutation (A673V) with a dominant-negative effect on amyloidogenesis (11).

3.2. Presenilin genes

Linkage analysis and positional cloning studies have identified a family of two homologous genes that are known as presenilins (PSEN1 and PSEN2) and are involved in the majority of FAD cases (12,13,14). The structure of the two genes is very similar and they encode for two proteins that have high homology, around 67%. PSEN1 and PSEN2 are important determinants of gamma-secretase activity responsible for proteolytic cleavage of APP and NOTCH receptor proteins (15). Most of presenilin mutations lead to increased production of A-beta 1-42, altering the ratio of A-beta 1-42 to A-beta 1-40. It has been suggested that the toxicity of A-beta is expressed before the formation of fibrils resulting in a possible early preclinical event in presenilin mutation carriers (2). Most of PSEN1 and PSEN2 mutations are missense mutations causing amino acid substitution in proteins and, like APP mutations, are autosomal dominant.

3.2.1. Presenilin 1 gene

The PSEN1 gene is located on chromosome 14 (locus 14q24.3) and encodes a 467-amino acid

transmembrane protein that forms the catalytic core of the gamma-secretase complex. The first mutation identified in the PSEN1 gene as determinant for autosomal dominant EOFAD was reported in 1995 (13). To date, 185 pathogenic PSEN1 mutations have been identified in 405 AD families, making PSEN1 mutations the most common known genetic cause of EOFAD, although mutation frequency is highly dependent on the population studied (<http://www.molgen.ua.ac.be/ADMutations>) (Table 1). PSEN1 mutations cause the most severe forms of the disease, with an earlier age of onset and a considerable phenotypic variability (16). They are characterized by relatively rapid progression of the disease that is also often associated with seizures, myoclonus and language deficits. However, some of the clinical phenotypes have been associated with specific mutations, although most of them do not strongly depend on the genetic location of the mutation so other genetic or epigenetic factors may be involved (17). The median age of onset of the disease in families carrying PSEN1 mutations is about 45 years with a range of 28-79 years (18), correlated with the position of the mutation in a particular region of the gene. Several mutations associated with very early onset of cognitive decline are located within transmembrane domains and Miklossy *et al.* hypothesized that these substitutions may drastically alter the protein conformation (19). PSEN1 mutations penetrance is complete, but there are some exceptions that may be due to many factors which contribute to reduced penetrance (16).

3.2.2. Presenilin 2 gene

The PSEN2 gene is located on chromosome 1 (locus 1q31-q42) and encodes a 448-amino acid peptide with tissue-specific alternative splicing. Like PSEN1, PSEN2 is a transmembrane protein that is a part of the gamma-secretase responsible for the cleavage of A-beta. The first PSEN2 mutation was identified in 1995 in a collection of FAD pedigrees having a common ethnic background (Volga German) (12). To date, 20 mutations in PSEN2 have been identified in 22 families (<http://www.molgen.ua.ac.be/ADMutations>), making this gene a rare cause of FAD (Table 1). However, the pathogenicity is well documented in only thirteen identified mutations. For the others, it remains unclear (<http://www.molgen.ua.ac.be/ADMutations>).

The first mutation identified was the missense mutation and it resulted in the substitution of an isoleucine for an asparagine at residues 141 (N141I). The clinical phenotype associated with this mutation is the best characterized to date. The mean age of onset associated with N141I is 53.7 (range 39 to 75 years) with a disease duration of about ten years. The first symptoms were problems with memory, thinking or orientation and the disease was slow and progressive (20). However, the clinical features of PSEN2-affected families appear to differ from the clinical features of PSEN1-affected families. PSEN2 families show a wide range in age of onset (39-85 years) and the age of onset is highly variable among PSEN2-affected members of the same family, which may be due to the influence of other genetic or environmental factors (Table 1) (20).

4. SPORADIC ALZHEIMER'S DISEASE

About 95% of all cases of AD are considered sporadic forms of the disease. Over 60% of all sporadic cases are not associated with APOE, suggesting that other genetic and environmental factors may contribute to determining the disease.

4.1. Apolipoprotein E

The best-documented susceptibility gene for the development of AD is the APOE gene. This gene encodes for a 299-amino acid lipoprotein binding amyloid proteins. Specifically, APOE exists in three common polymorphic forms (epsilon2, epsilon3 and epsilon4; rs429358) and one of them (epsilon4) is strongly associated with an increased risk of AD, not only in a homozygous state, but also in a heterozygous one. In contrast, the epsilon2 allele is associated with decreased risk. APOE is the main apolipoprotein in the brain that plays an important role in cholesterol homeostasis. The role of APOE in the predisposition to AD is well established (one copy of the epsilon 4 allele increases the risk by about 3-fold, two copies by about 12-fold), but the mechanism by which APOE is involved in the pathogenesis of AD is still not clear (21). One of the suggested mechanisms is linked to the ability of APOE to bind beta-amyloid, playing a role in A-beta conversion from monomeric and non-toxic forms to oligomers and fibrils. This is confirmed by the presence of APOE in both senile plaques and intracellular neurofibrillary tangles (NFTs), two important hallmarks of AD (22). Another possible mechanism may be due to the neurotoxic effects of APOE isoforms, independently of the interaction with beta-amyloid. The differences in amino acid in the three common isoforms alter the protein structure and influence the functional properties, including lipid regulation. APOE isoforms could have different effects via lipoprotein receptors leading to alternative neuronal signaling in the nervous system. Abnormal cholesterol metabolism contributes to impaired redistribution of lipids and cholesterol, which may affect neuronal plasticity (23). It is still unclear whether lipid dysregulation contributes to cerebral hypometabolism or whether the hypometabolism is secondary to altered A-beta metabolism or brain injury. Indeed, the regions typically involved in A-beta plaque deposition in AD patients coincide in normal brain with the regions that metabolize glucose by aerobic glycolysis. This is confirmed in subjects carrying the APOE epsilon4 allele who showed, through PET (Positron Emission Tomography) studies, reduced cerebral glucose metabolism (24) 20 years before disease onset. To date, APOE has been considered only an important risk factor for AD, but recently a multicenter study (17,000 subjects) demonstrating that the APOE risk is more similar to those of major genes in Mendelian diseases, urging a reappraisal of the impact of APOE in AD (25).

4.2. Susceptibility genes and Genome-wide association studies

In the past decade, a lot of candidate genes and regions emerging from genetic linkage and smaller scale association studies have been identified, but have often

Table 2. Main genetic variants identified by GWAS

Gene	Locus	Polymorphism	Ethnicity ¹	OR (95% CI) ¹	P-value ¹
APOE	19q13	APOE_e2/3/4	All	3.685 (3.30-4.12)	<1E-50
BIN1	2q14	rs744373	All	1.166 (1.13-1.20)	1.59E-26
CLU	8p21.1	rs11136000	Caucasian	0.879 (0.86-0.90)	3.37E-23
ABCA7	19p13.3	rs3764650	All	1.229 (1.18-1.28)	8.17E-22
CR1	1q32	rs3818361	Caucasian	1.174 (1.14-1.21)	4.72E-21
PICALM	11q14	rs3851179	Caucasian	0.879 (0.86-0.9)	2.85E-20
CD33	19q13.3	rs3865444	All	0.893 (0.86-0.93)	2.04E-10
CD2AP	6p12	rs9349407	All	1.117 (1.08-1.16)	2.75E-09
EPHA1	7q34	rs11767557	All	0.90 (0.86-0.93)	6.0E-10

¹according to the AlzGene database

proven difficult to replicate consistently. The emergence of robust genome-wide association methodologies promises to explain the genetic etiology of the common sporadic forms of complex diseases such as AD (26). Despite numerous years of research, only one common genetic variant (the epsilon4 allele) of APOE has been considered a risk factor for LOAD. It has become clear that the majority of common genetic variants contribute only slightly to an increased risk for the disease, but in combination they have an important impact on disease predisposition. In the last four years, 22 published GWASs in AD have discovered additional candidate genes (<http://www.alzgene.org>) (27-48). Despite this exciting potential, GWAS results are not homogeneous and need further confirmation, and it is unclear whether GWASs can help explain most of the underlying genetic risk for AD. In 2007, the first published LOAD GWAS identified 16 different genetic loci associated with AD, using a selected set of 17,343 single nucleotide polymorphisms (SNPs) from 11,211 genes (33). To date, more than 50 SNPs have been identified. None of the identified loci showed the same consistent effect or the same level of statistical significance as the APOE epsilon4 allele. The polymorphisms consistently associated with AD risk across the different samples were located in close proximity to APOE, and most likely reflect linkage disequilibrium (LD) with the epsilon 4 allele. This is the case of a set of polymorphisms in Translocase of the Outer Mitochondrial Membrane 40 (TOMM40) gene recently identified in association with LOAD in independent genome-wide studies (27,34). The TOMM40 gene encoding an essential mitochondrial protein is located on chromosome 19, near the APOE locus, and it shows an intriguing LD with the epsilon4 allele. Furthermore, when all the SNPs were entered into a logit model, only the effect of APOE epsilon4 remained significant. These observations jeopardize the possibility that the loci in the TOMM40 gene may contribute to the risk for developing AD independently of APOE status (49).

The most important loci associated with LOAD identified by different GWA studies are located in 8 genes involved in new pathways (with considerable overlap shown by some genes) of the disease process which do not directly link to amyloid (50): *CLU* (clusterin, chr 8), *PICALM* (phosphatidylinositol binding clathrin assembly protein, chr 11), *CR1* (complement component [3b/4b] receptor 1, chr 1) (34,38), *BIN1* (bridging integrator 1, chr 2), *ABCA7* (ATP-binding cassette transporter member 7, chr 19), *CD33* (sialic acid binding Ig-like lectin 3, chr 19), *EPHA1* (ephrin type-A receptor 1 chr 7) and *CD2AP* (CD2-associated protein chr 6) (36,40) (Table 2; Figure 1.). The

clusterin protein encoding by the *CLU* gene, also known as apolipoprotein J (APOJ), has been observed in amyloid deposits (A-beta is one of its ligands) (51), and its levels seem to be increased in AD patients' cerebrospinal fluid (52), supporting the observed genetic association. The clearance of A-beta can be mediated by *CLU* enhancing endocytosis (53) and/or through transport across the blood-brain barrier (54). The *PICALM* gene encodes the ubiquitous protein involved in clathrin-mediated endocytosis (CME) (55) which is an essential step in intracellular trafficking of proteins, lipids, growth factors and neurotransmitters. Moreover, it is indispensable for neurotransmitter release at the presynaptic membrane, which is important for memory formation and neuronal function, and it may play a role in A-beta clearance from the brain (56). The significant association reported for the 5' end in *PICALM* rs3851179 is a reduced risk for LOAD (34). In addition to *PICALM*, it has been suggested that *CR1* also provides a protective role in AD, through the binding of C3b and subsequent A-beta clearance (38). *CR1* encodes a complement receptor type 1 that plays an important role in the regulation of the complement cascade and the clearance of immune complexes (57). Although the functional relevance of the polymorphism in *CR1* for LOAD is still unclear, it is conceivable that the genetic variation affects AD through neuroinflammation independently of its function in A-beta clearance. *BIN1*, as *PICALM*, is implicated in CME, which allows the internalization and transport of lipids, and is a critical component of synaptic vesicle recycling (58). *BIN1* may influence the formation of the other main pathological features of AD brains, the NFTs, linking the microtubule cytoskeleton with the cellular membrane (59). *ABCA7* encodes an ATP-binding cassette (ABC) transporter, which plays a role in transporting a wide range of substrates across cell membranes (60). It is highly expressed in brain, particularly in the hippocampal CA1 neurons and microglia (61,62). *ABCA7* is involved in many pathways linked directly and indirectly with APP processing: efflux of lipids from cells to lipoprotein particles, regulation of APP processing and inhibition of beta-amyloid secretion (63). *CD33* is a member of the sialic-acid-binding immunoglobulin-like lectins (Siglec) family and mediates endocytosis through a mechanism independent of clathrin (64). Moreover, it promotes cell-cell interactions and regulates the functions of cells in innate and adaptive immune systems (65). *EPHA1* is a member of the ephrin receptor subfamily, which plays roles in cell and axon guidance and in synaptic development and plasticity (66,67). *CD2AP* is a scaffold adaptor protein that is associated with cortactin, a protein also involved in the

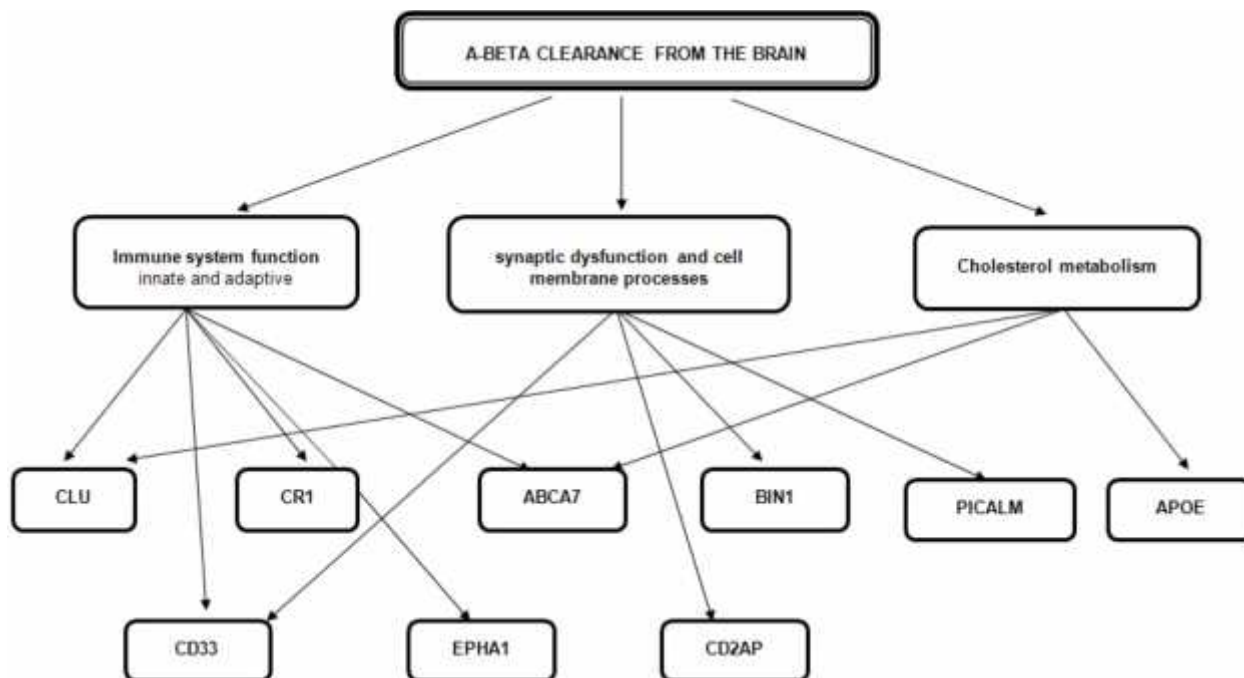


Figure 1. Simplified summary showing the possible involvement of the novel susceptibility genes identified by GWA studies in the pathophysiology of AD.

regulation of receptor-mediated endocytosis (68), such as the previously described genes, PICALM, BIN1 and CD33. The described genes are involved in different pathways that highlight additional mechanisms associated with the disease process, and the result of these finding may make it possible to consider that A-beta may have a minor role in the LOAD pathogenesis.

4.3. Alzheimer's disease and the genes involved in neurofibrillary tangles

In addition to extracellular beta-amyloid plaque, NFTs are another important hallmark of AD and the genes involved in their production may have a key role in the development of AD. The major component of NFTs is Tau, a microtubule-associated protein that is abnormally hyperphosphorylated and forms insoluble fibrils. Tau protein is encoded by the *MAPT* (Microtubule Association Protein Tau) gene, located on chromosome 17, and it is expressed predominantly in the neurons of the peripheral and central nervous system. Physiologically, the protein is a component of microtubules and it has a role in stabilizing the growing axons, neuronal polarity and signal transduction (1,69). The pathways linking Tau and A-beta are not clear, but Tau expression appears to be necessary for A-beta toxicity in *ex vivo* experiments (70). The toxic gain of function combined with the loss of function of normal Tau could compromise axonal transport and contribute to synaptic degeneration (71). The genetic link between *MAPT* and AD started with the identification of a strong association between AD and a Tau haplotype (H1c) (72). Since 2007, several studies have analyzed the *MAPT* gene in EOFAD patients as well, identifying two mutations (in particular, c.1920+16 C>T NM_001123066.3 and R406W) associated with an AD-like phenotype (73,74).

Moreover, a study in 2009 identified the *MAPT* deltaK280 mutation in a LOAD patient with no documentation of a family history (75). The pathological role of this mutation is not yet clear, but in light of these studies, screening of the *MAPT* gene should be considered in families with AD-like phenotype not carrying mutations in known AD genes. In AD brain, the distribution of Tau hyperphosphorylated within neurons with NFTs overlaps with the distribution of another protein, TDP-43 (Transactive response DNA-binding protein 43), encoded by the *TARDBP* gene on chromosome 1. This is a nuclear protein involved in several neurodegenerative diseases (76). TDP-43 inclusion is detected in approximately 25-30% of sporadic AD, raising the hypothesis that *TARDBP* mutations or SNPs may be involved in AD pathogenesis. To date, screening of this gene in AD patients showed conflicting results (76,77,78). Only a rare mutation in exon 3 (p.Ala90Val) of an unclear pathogenic nature was identified in three different patients sharing a common founder (77). These results suggest that *TARDBP* mutations or SNPs are not a significant cause of AD; however, other studies will be necessary to better understand the genetic role of *TARDBP* in AD pathogenesis. After many years of research studying the involvement of genetics in AD, one of the most controversial research fields is still the identification of AD genes possibly implicated in NFTs. Indeed, the presence of NFTs is just the final pathway of a slow neuronal degeneration, thus it is important to study not only the genes involved in fibril formation or structure, but also the genes involved in all the molecular and cellular mechanisms resulting in NFTs. In fact, it was hypothesized that the imbalance between phosphorylation (by kinases) and de-phosphorylation (by phosphatases) may play a major role in the development of the tau pathology. Thus,

Genetics of Alzheimer's disease

the identification of the kinases or phosphatases responsible in tau phosphorylation is a crucial issue; still very important is the identification of all genetic or epigenetic mechanisms possibly influencing their function.

5. PERSPECTIVES

To date, all of the described genetic factors do not completely explain the pathophysiology of AD; indeed, studies on the possible risk factors for the sporadic forms often appear to be conflicting, not replicable or inconclusive. The gene-environment interaction plays an important role in the majority of sporadic AD cases. Epigenetic studies provide the tools for understanding the interaction between genes and environmental factors and thus represent the new frontier for gaining insight into the genetics of AD (79). Recent studies have suggested that epigenetic mechanisms may play an essential role in the disease development. It is clear that epigenetic dysregulation at various levels is associated with the disease and it mediates the AD risk. Nonetheless, it is not yet fully understood whether epigenetic changes are a cause or a consequence of the disease. In fact, to date, only a few studies have been carried out and have primarily analyzed samples of patients already in the advanced stage of the disease. In order to clarify the importance of the epigenetic mechanism and the dynamics of DNA methylation, further prospective investigations will be necessary (80) on both the early-stages and the advanced phases of AD. In conclusion, the genetic component of some cases of dementia has long been recognized (81), with the identification of the first locus on chromosome 21. At the beginning, the low incidence of these cases in the overall demented population has lead clinicians working on dementia to consider the genetic component to be of little practical relevance. Despite many years of research and great progress in the knowledge of the molecular pathogenesis of AD, a full understanding of the etiology of the sporadic form is still out of reach. However, new discoveries found by GWASs could characterize an important proportion of the genetic architecture contributing to the development of the disease. After almost 25 years (81), important results have been obtained with genetic studies. Indeed, since the first pathogenetic mutation was identified in 1991 (9), the description of over 220 different mutations and the identification of new susceptibility genes has kindled new interest. To date, although its utility in clinical practice is still often unclear, the genetic approach deserves critical discussion and provides ample stimulus for further research.

6. ACKNOWLEDGMENTS

This study was supported by Grants from the Cassa di Risparmio di Firenze 2010 and the Ministry of Health 2010 convenzione 39 sottoprogetto 2.

7. REFERENCES

1.C. Ballard, S. Gauthier, A. Corbett, C. Brayne, D. Aarsland and E. Jones: Alzheimer's disease. *Lancet* 377, 1019-1031 (2011)

2. L.M. Bekris, C.E. Yu, T.D. Bird and D.W. Tsuang: Genetics of Alzheimer Disease. *J Geriatr Psychiatry Neurol* 23, 213–227 (2010)

3. L. Bertram, C.M. Lill and R.E. Tanzi: The genetics of Alzheimer disease: back to the future. *Neuron* 68, 270-281 (2010)

4. M.N. Rossor, N.C. Fox, J. Beck, T.C. Campbell and J.Collinge: Incomplete penetrance of familial Alzheimer's disease in a pedigree with a novel presenilin-1 gene mutation. *Lancet* 347, 1560 (1996)

5. N.H. Varvel, K. Bhaskar, A.R. Patil, S.W. Pimplikar, K. Herrup and B.T. Lamb: Abeta oligomers induce neuronal cell cycle events in Alzheimer's disease. *J Neurosci* 28,10786-10793 (2008)

6. G.G. Glenner and C.W. Wong: Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. *Biochem Biophys Res Commun* 122, 1131-1135 (1984)

7. R.E. Tanzi and L. Bertram: Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. *Cell* 120, 545-555. (2005)

8. M. Tabaton and E. Tamagno: The molecular link between beta- and gamma-secretase activity on the amyloid beta precursor protein. *Cell Mol Life Sci* 64, 2211-2218 (2007)

9. A. Goate, M.C. Chartier-Harlin, M. Mullan, J. Brown, F. Crawford, L. Fidani, L. Giuffra, A. Haynes, N. Irving, L. James, R. Mant, P.Newton, K. Rooke, P. Roques, C.Talbot, M. Pericak-Vance, A. Roses, R. Williamson, M. Rossor, M. Owen and J.Hardy: Segregation of a missense mutation in the Amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 349, 704-706 (1991)

10. J. Theuns, E. Marjaux, M. Vandenbulcke, K. Van Laere, S. Kumar-Singh, G. Bormans, N. Brouwers, M. Van den Broeck, K. Vennekens, E. Corsmit, M. Cruts, B. De Strooper, C. Van Broeckhoven and R.Vandenberghe: Alzheimer dementia caused by a novel mutation located in the APP C-terminal intracytosolic fragment. *Hum Mutat* 27, 888–896 (2006)

11. G. Di Fede, M. Catania, M. Morbin, G. Rossi, S. Suardi, G. Mazzoleni, M. Merlin, A.R. Giovagnoli, S. Prioni, A. Erbetta, C. Falcone, M. Gobbi, L. Colombo, A. Bastone, M. Beeg, C. Manzoni, B. Francescucci, A. Spagnoli, L. Cantù, E. Del Favero, E. Levy, M. Salmona and F. Tagliavini: A recessive mutation in the APP gene with dominant-negative effect on amyloidogenesis. *Science* 323, 1473-1477 (2009)

12. E.I. Rogaev, R. Sherrington, E.A. Rogaeva, G. Levesque, M. Ikeda, Y. Liang, H. Chi, C. Lin, K. Holman, T. Tsuda, L. Mar, S. Sorbi, B. Nacmias, S. Piacentini, L. Amaducci, I. Chumakov, D. Cohen, L. Lannfelt, P.E. Fraser, J.M. Rommens and P. St George-Hyslop: Familial

Genetics of Alzheimer's disease

Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 376, 775-778 (1995)

13. R. Sherrington, E.I. Rogaev, Y. Liang, E.A. Rogaeva, G. Levesque, M. Ikeda, H. Chi, C. Lin, K. Holman, T. Tsuda, L. Mar, J.F. Foncin, A.C. Bruni, M.P. Montesi, S. Sorbi, I. Rainero, L. Pinessi, L. Nee, I. Chumakov, D. Pollen, A. Brookes, P. Sanseau, R.J. Polinsky, W. Wasco, H.A. Da Silva, J.L. Haines, M.A. Pericak-Vance, R.E. Tanzi, A.D. Roses, P.E. Fraser, J.M. Rommens and P. St George-Hyslop: Cloning of a novel gene bearing missense mutations in early familial Alzheimer's disease. *Nature* 375, 754-760 (1995)

14. S. Sorbi, B. Nacmias, P. Forleo, S. Piacentini, R. Sherrington, E. Rogaev, P. St George Hyslop and L. Amaducci: Missense mutation of S182 gene in Italian families with early-onset Alzheimer's disease. *The Lancet* 346, 439-440 (1995)

15. Y.M. Li, M. Xu, M.T. Lai, Q. Huang, J. L. Castro, J. DiMuzio-Mower, T. Harrison, C. Lellis, A. Nadin, J. G. Neduvellil, R. B. Register, M. K. Sardana, M. S. Shearman, A. L. Smith, X.P. Shi, K.C. Yin, J. A. Shafer and S. J. Gardell: Photoactivated gamma-secretase inhibitors directed to the active site covalently label presenilin 1. *Nature* 405, 689-694 (2000)

16. A.J. Larner and M. Doran: Clinical phenotypic heterogeneity of Alzheimer's disease associated with mutations of the presenilin-1 gene. *J Neurol* 253,139-158 (2006)

17. M. Menéndez: Pathological and clinical heterogeneity of presenilin 1 gene mutations. *J Alzheimers Dis.* 6, 475-482 (2004)

18. D.M. Kovacs and R.E. Tanzi: Monogenic determinants of familial Alzheimer's disease: presenilin1 mutations. *Cell Mol Life Sci* 54, 902-909 (1998)

19. J. Miklossy, K. Taddei, D. Suva, G. Verdile, J. Fonte, C. Fisher, A. Gnjec, J. Ghika, F. Suard, P.D. Mehta, C.A. McLean, C.L. Masters, W.S. Brooks and R.N. Martins: Two novel presenilin-1 mutations (Y256S and Q222H) are associated with early-onset Alzheimer's disease. *Neurobiol Aging* 24, 655-662 (2003)

20. S. Jayadev, J.B. Leverenz, E. Steinbart, J. Stahl, W. Klunk, C.E. Yu and T.D. Bird: Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2. *Brain* 133, 1143-1154 (2010)

21. P.B. Verghese, J.M. Castellano and D.M. Holtzman: Apolipoprotein E in Alzheimer's disease and other neurological disorders. *Lancet Neurol* 10, 241-252 (2011)

22. E.M. Castano, F. Prelli, T. Wisniewski, A. Golabek, R.A. Kumar, C. Soto and B Frangine: Fibrillogenesis in Alzheimer's disease of amyloid beta peptides and apolipoprotein E. *Biochem J* 306, 599-604. (1995)

23. I.J. Martins, E. Hone, J.K. Foster, S.I. Sünram-Lea, A. Gnjec, S.J. Fuller, D. Nolan, S.E. Gandy and R.N. Martins: Apolipoprotein E, cholesterol metabolism, diabetes, and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. *Mol Psychiatry* 11, 721-736 (2006)

24. A. Drzezga, M. Riemenschneider, B. Strassner, T. Grimmer, M. Peller, A. Knoll, S. Wagenpfeil, S. Minoshima, M. Schwaiger and A. Kurz: Cerebral glucose metabolism in patients with AD and different APOE genotypes. *Neurology* 64, 102-107 (2005)

25. E. Genin, D. Hannequin, D. Wallon, K. Sleegers, M. Hiltunen, O. Combarros, M.J. Bullido, S. Engelborghs, P. De Deyn, C. Berr, F. Pasquier, B. Dubois, G. Tognoni, N. Fiévet, N. Brouwers, K. Bettens, B. Arosio, E. Coto, M. Del Zompo, I. Mateo, J. Epelbaum, A. Frank-Garcia, S. Helisalmi, E. Porcellini, A. Pilotto, P. Forti, R. Ferri, E. Scarpini, G. Siciliano, V. Solfrizzi, S. Sorbi, G. Spalletta, F. Valdivieso, S. Vepsäläinen, V. Alvarez, P. Bosco, M. Mancuso, F. Panza, B. Nacmias, P. Bossù, O. Hanon, P. Piccardi, G. Annoni, D. Seripa, D. Galimberti, F. Licastro, H. Soininen, J.F. Dartigues, M.I. Kambouh, C. Van Broeckhoven, J.C. Lambert, P. Amouyel and D. Campion: APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry* 16(9), 903-907 (2011)

26. N. Ertekin-Taner: Genetics of Alzheimer disease in the pre- and post-GWAS era. *Alzheimers Res Ther* 2, 3 (2010)

27. R. Abraham, V. Moskvina, R. Sims, P. Hollingworth, A. Morgan, L. Georgieva, K. Dowzell, S. Cichon, A.M. Hillmer, M.C. O'Donovan, J. Williams, M.J. Owen and G. Kirov: A genome-wide association study for late-onset Alzheimer's disease using DNA pooling. *BMC Med Genomics* 1, 44 (2008)

28. G.W. Beecham, E.R. Martin, Y.J. Li, M.A. Slifer, J.R. Gilbert, J.L. Haines and M.A. Pericak-Vance: Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. *Am J Hum Genet* 84, 35-43 (2009)

29. L. Bertram, C. Lange, K. Mullin, M. Parkinson, M. Hsiao, M.F. Hogan, B.M. Schjeide, B. Hooli, J. Divito, I. Ionita, H. Jiang, N. Laird, T. Moscarillo, K.L. Ohlsen, K. Elliott, X. Wang, D. Hu-Lince, M. Ryder, A. Murphy, S.L. Wagner, D. Blacker, K.D. Becker and R.E. Tanzi: Genome-wide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to APOE. *Am J Hum Genet* 83, 623-632 (2008)

30. M.M. Carrasquillo, F. Zou, V.S. Pankratz, S.L. Wilcox, L. Ma, L.P. Walker, S.G. Younkin, C.S. Younkin, L.H. Younkin, G.D. Bisceglia, N. Ertekin-Taner, J.E. Crook, D.W. Dickson, R.C. Petersen, N.R. Graff-Radford and S.G. Younkin: Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. *Nat Genet* 41, 192-198 (2009)

31. K.D. Coon, A.J. Myers, D.W. Craig, J.A. Webster, J.V. Pearson, D.H. Lince, V.L. Zismann, T.G. Beach, D. Leung,

Genetics of Alzheimer's disease

- L. Bryden, R.F. Halperin, L. Marlowe, M. Kaleem, D.G. Walker, R. Ravid, C.B. Heward, J. Rogers, A. Papassotiropoulos, E.M. Reiman, J. Hardy and D.A. Stephan: A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset *alzheimer's* disease. *J Clin Psychiatry* 68, 613-618 (2007)
32. T.M. Feulner, S.M. Laws, P. Friedrich, S. Wagenpfeil, S.H. Wurst, C. Riehle, K.A. Kuhn, M. Krawczak, S. Schreiber, S. Nikolaus, H. Förstl, A. Kurz and M. Riemenschneider: Examination of the current top candidate genes for AD in a genome-wide association study. *Mol Psychiatry* 15, 756-766 (2010)
33. A. Grupe, R. Abraham, Y. Li, C. Rowland, P. Hollingworth, A. Morgan, L. Jehu, R. Segurado, D. Stone, E. Schadt, M. Karnoub, P. Nowotny, K. Tacey, J. Catanese, J. Sninsky, C. Brayne, D. Rubinsztein, M. Gill, B. Lawlor, S. Lovestone, P. Holmans, M. O'Donovan, J.C. Morris, L. Thal, A. Goate, M.J. Owen and J. Williams: Evidence for novel susceptibility genes for late-onset *alzheimer's* disease from a genome-wide association study of putative functional variants. *Hum Mol Genet* 16, 865-873 (2007)
34. D. Harold, R. Abraham, P. Hollingworth, R. Sims, A. Gerrish, M.L. Hamshere, J.S. Pahwa, V. Moskvina, K. Dowzell, A. Williams, N. Jones, C. Thomas, A. Stretton, A.R. Morgan, S. Lovestone, J. Powell, P. Proitsi, M.K. Lupton, C. Brayne, D.C. Rubinsztein, M. Gill, B. Lawlor, A. Lynch, K. Morgan, K.S. Brown, P.A. Passmore, D. Craig, B. McGuinness, S. Todd, C. Holmes, D. Mann, A.D. Smith, S. Love, P.G. Kehoe, J. Hardy, S. Mead, N. Fox, M. Rossor, J. Collinge, W. Maier, F. Jessen, H. van den Bussche, I. Heuser, J. Kornhuber, J. Wiltfang, M. Dichgans, L. Frölich, H. Hampel, M. Hüll, D. Rujescu, A.M. Goate, J.S. Kauwe, C. Cruchaga, P. Nowotny, J.C. Morris, K. Mayo, K. Sleegers, K. Bettens, S. Engelborghs, P.P. De Deyn, C. Van Broeckhoven, G. Livingston, N.J. Bass, H. Gurling, A. McQuillin, R. Gwilliam, P. Deloukas, A. Al-Chalabi, C.E. Shaw, M. Tsolaki, A.B. Singleton, R. Guerreiro, T.W. Mühleisen, M.M. Nöthen, S. Moebus, K.H. Jöckel, N. Klopp, H.E. Wichmann, M.M. Carrasquillo, V.S. Pankratz, S.G. Younkin, P.A. Holmans, M. O'Donovan, M.J. Owen and J. Williams: Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet* 41, 1088-1093 (2009)
35. E.L. Heinzen, A.C. Need, K.M. Hayden, O. Chiba-Falek, A.D. Roses, W.J. Strittmatter, J.R. Burke, C.M. Hulette, K.A. Welsh-Bohmer and D.B. Goldstein: Genome-Wide Scan of Copy Number Variation in Late-Onset *alzheimer's* Disease. *J Alzheimers Dis* 19, 69-77 (2010)
36. P. Hollingworth, D. Harold, R. Sims, A. Gerrish, J.C. Lambert, M.M. Carrasquillo, R. Abraham, M.L. Hamshere, J.S. Pahwa, V. Moskvina, K. Dowzell, N. Jones, A. Stretton, C. Thomas, A. Richards, D. Ivanov, C. Widdowson, J. Chapman, S. Lovestone, J. Powell, P. Proitsi, M.K. Lupton, C. Brayne, D.C. Rubinsztein, M. Gill, B. Lawlor, A. Lynch, K.S. Brown, P.A. Passmore, D. Craig, B. McGuinness, S. Todd, C. Holmes, D. Mann, A.D. Smith, H. Beaumont, D. Warden, G. Wilcock, S. Love, P.G. Kehoe, N.M. Hooper, E.R. Vardy, J. Hardy, S. Mead, N.C. Fox, M. Rossor, J. Collinge, W. Maier, F. Jessen, E. Rüther, B. Schürmann, R. Heun, H. Kölsch, H. van den Bussche, I. Heuser, J. Kornhuber, J. Wiltfang, M. Dichgans, L. Frölich, H. Hampel, J. Gallacher, M. Hüll, D. Rujescu, I. Giegling, A.M. Goate, J.S. Kauwe, C. Cruchaga, P. Nowotny, J.C. Morris, K. Mayo, K. Sleegers, K. Bettens, S. Engelborghs, P.P. De Deyn, C. Van Broeckhoven, G. Livingston, N.J. Bass, H. Gurling, A. McQuillin, R. Gwilliam, P. Deloukas, A. Al-Chalabi, C.E. Shaw, M. Tsolaki, A.B. Singleton, R. Guerreiro, T.W. Mühleisen, M.M. Nöthen, S. Moebus, K.H. Jöckel, N. Klopp, H.E. Wichmann, V.S. Pankratz, S.B. Sando, J.O. Aasly, M. Barcikowska, Z.K. Wszolek, D.W. Dickson, N.R. Graff-Radford, R.C. Petersen, Alzheimer's Disease Neuroimaging Initiative, C.M. van Duijn, M.M. Breteler, M.A. Ikram, A.L. DeStefano, A.L. Fitzpatrick, O. Lopez, L.J. Launer, S. Seshadri, CHARGE Consortium, C. Berr, D. Champion, J. Epelbaum, J.F. Dartigues, C. Tzourio, A. Alperovitch, M. Lathrop, EADI Consortium, T.M. Feulner, P. Friedrich, C. Riehle, M. Krawczak, S. Schreiber, M. Mayhaus, S. Nicolhaus, S. Wagenpfeil, S. Steinberg, H. Stefansson, K. Stefansson, J. Snaedal, S. Björnsson, P.V. Jonsson, V. Chouraki, B. Genier-Boley, M. Hiltunen, H. Soininen, O. Combarros, D. Zelenika, M. Delepine, M.J. Bullido, F. Pasquier, I. Mateo, A. Frank-Garcia, E. Porcellini, O. Hanon, E. Coto, V. Alvarez, P. Bosco, G. Siciliano, M. Mancuso, F. Panza, V. Solfrizzi, B. Nacmias, S. Sorbi, P. Bossù, P. Piccardi, B. Arosio, G. Annoni, D. Seripa, A. Pilotto, E. Scarpini, D. Galimberti, A. Brice, D. Hannequin, F. Licastro, L. Jones, P.A. Holmans, T. Jonsson, M. Riemenschneider, K. Morgan, S.G. Younkin, M.J. Owen, M. O'Donovan, P. Amouyel and J. Williams: Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat Genet* 43, 429-435 (2011)
37. X. Hu, E. Pickering, Y.C. Liu, S. Hall, H. Fournier, E. Katz, B. Dechairo, S. John, P. Van Eerdewegh, H. Soares and Alzheimer's Disease Neuroimaging Initiative: Meta-analysis for genome-wide association study identifies multiple variants at the BIN1 locus associated with late-onset *alzheimer's* disease. *PLoS One* 6, e16616 (2011)
38. J.C. Lambert, S. Heath, G. Even, D. Champion, K. Sleegers, M. Hiltunen, O. Combarros, D. Zelenika, M.J. Bullido, B. Tavernier, L. Letenneur, K. Bettens, C. Berr, F. Pasquier, N. Fiévet, P. Barberger-Gateau, S. Engelborghs, P. De Deyn, I. Mateo, A. Franck, S. Helisalmi, E. Porcellini, O. Hanon, European Alzheimer's Disease Initiative Investigators, M.M. de Pancorbo, C. Lendon, C. Dufouil, C. Jaillard, T. Leveillard, V. Alvarez, P. Bosco, M. Mancuso, F. Panza, B. Nacmias, P. Bossù, P. Piccardi, G. Annoni, D. Seripa, D. Galimberti, D. Hannequin, F. Licastro, H. Soininen, K. Ritchie, H. Blanché, J.F. Dartigues, C. Tzourio, I. Gut, C. Van Broeckhoven, A. Alperovitch, M. Lathrop and P. Amouyel: Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* 41, 1094-1099 (2009)

39. H. Li, S. Wetten, L. Li, P.L. St Jean, R. Upmanyu, L. Surh, D. Hosford, M.R. Barnes, J.D. Briley, M. Borrie, N. Coletta, R. Delisle, D. Dhalla, M.G. Ehm, H.H. Feldman, L. Fornazzari, S. Gauthier, N. Goodgame, D. Guzman, S. Hammond, P. Hollingworth, G.Y. Hsiung, J. Johnson, D.D. Kelly, R. Keren, A. Kertesz, K.S. King, S. Lovestone, I. Loy-English, P.M. Matthews, M.J. Owen, M. Plumpton, W. Pryse-Phillips, R.K. Prinjha, J.C. Richardson, A. Saunders, A.J. Slater, P. St George-Hyslop, S.W. Stinnett, J.E. Swartz, R.L. Taylor, J. Wherrett, J. Williams, D.P. Yarnall, R.A. Gibson, M.C. Irizarry, L.T. Middleton and A.D. Roses: Candidate single-nucleotide polymorphisms from a genome wide association study of Alzheimer disease. *Arch Neurol* 65, 45-53 (2008)
40. A.C. Naj, G. Jun, G.W. Beecham, L.S. Wang, B.N. Vardarajan, J. Buross, P.J. Gallins, J.D. Buxbaum, G.P. Jarvik, P.K. Crane, E.B. Larson, T.D. Bird, B.F. Boeve, N.R. Graff-Radford, P.L. De Jager, D. Evans, J.A. Schneider, M.M. Carrasquillo, N. Ertekin-Taner, S.G. Younkin, C. Cruchaga, J.S. Kauwe, P. Nowotny, P. Kramer, J. Hardy, M.J. Huentelman, A.J. Myers, M.M. Barmada, F.Y. Demirci, C.T. Baldwin, R.C. Green, E. Rogaeva, P. St George-Hyslop, S.E. Arnold, R. Barber, T. Beach, E.H. Bigio, J.D. Bowen, A. Boxer, J.R. Burke, N.J. Cairns, C.S. Carlson, R.M. Carney, S.L. Carroll, H.C. Chui, D.G. Clark, J. Comeveaux, C.W. Cotman, J.L. Cummings, C. Decarli, S.T. Dekosky, R. Diaz-Arrastia, M. Dick, D.W. Dickson, W.G. Ellis, K.M. Faber, K.B. Fallon, M.R. Farlow, S. Ferris, M.P. Frosch, D.R. Galasko, M. Ganguli, M. Gearing, D.H. Geschwind, B. Ghetti, J.R. Gilbert, S. Gilman, B. Giordani, J.D. Glass, J.H. Growdon, R.L. Hamilton, L.E. Harrell, E. Head, L.S. Honig, C.M. Hulette, B.T. Hyman, G.A. Jicha, L.W. Jin, N. Johnson, J. Karlawish, A. Karydas, J.A. Kaye, R. Kim, E.H. Koo, N.W. Kowall, J.J. Lah, A.I. Levey, A.P. Lieberman, O.L. Lopez, W.J. Mack, D.C. Marson, F. Martiniuk, D.C. Mash, E. Masliah, W.C. McCormick, S.M. McCurry, A.N. McDavid, A.C. McKee, M. Mesulam, B.L. Miller, C.A. Miller, J.W. Miller, J.E. Parisi, D.P. Perl, E. Peskind, R.C. Petersen, W.W. Poon, J.F. Quinn, R.A. Rajbhandary, M. Raskind, B. Reisberg, J.M. Ringman, E.D. Roberson, R.N. Rosenberg, M. Sano, L.S. Schneider, W. Seeley, M.L. Shelanski, M.A. Slifer, C.D. Smith, J.A. Sonnen, S. Spina, R.A. Stern, R.E. Tanzi, J.Q. Trojanowski, J.C. Troncoso, V.M. Van Deerlin, H.V. Vinters, J.P. Vonsattel, S. Weintraub, K.A. Welsh-Bohmer, J. Williamson, R.L. Wolzter, L.B. Cantwell, B.A. Dombroski, D. Beekly, K.L. Lunetta, E.R. Martin, M.I. Kamboh, A.J. Saykin, E.M. Reiman, D.A. Bennett, J.C. Morris, T.J. Montine, A.M. Goate, D. Blacker, D.W. Tsuang, H. Hakonarson, W.A. Kukull, T.M. Foroud, J.L. Haines, R. Mayeux, M.A. Pericak-Vance, L.A. Farrer and G.D. Schellenberg: Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset alzheimer's disease. *Nat Genet* 43, 436-441 (2011)
41. S.E. Poduslo, R. Huang, J. Huang and S. Smith. Genome screen of late-onset alzheimer's extended pedigrees identifies TRPC4AP by haplotype analysis. *Am J Med Genet B Neuropsychiatr Genet* 150B, 50-55 (2009)
42. S.G. Potkin, G. Guffanti, A. Lakatos, J.A. Turner, F. Kruggel, J.H. Fallon, A.J. Saykin, A. Orro, S. Lupoli, E. Salvi, M. Weiner, F. Macchiardi and Alzheimer's Disease Neuroimaging Initiative. Hippocampal atrophy as a quantitative trait in a genome-wide association study identifying novel susceptibility genes for Alzheimer's disease. *PLoS One* 4, e6501 (2009)
43. E.M. Reiman, J.A. Webster, A.J. Myers, J. Hardy, T. Dunckley, V.L. Zismann, K.D. Joshipura, J.V. Pearson, D. Hu-Lince, M.J. Huentelman, D.W. Craig, K.D. Coon, W.S. Liang, R.H. Herbert, T. Beach, K.C. Rohrer, A.S. Zhao, D. Leung, L. Bryden, L. Marlowe, M. Kaleem, D. Mastroeni, A. Grover, C.B. Heward, R. Ravid, J. Rogers, M.L. Hutton, S. Melquist, R.C. Petersen, G.E. Alexander, R.J. Caselli, W. Kukull, A. Papassotiropoulos and D.A. Stephan: GAB2 alleles modify Alzheimer's risk in APOE epsilon4 carriers. *Neuron* 54,713-20 (2007)
44. S. Seshadri, A.L. Fitzpatrick, M.A. Ikram, A.L. Destefano, V. Gudnason, M. Boada, J.C. Bis, A.V. Smith, M.M. Carassquillo, J.C. Lambert, D. Harold, E.M. Schrijvers, R. Ramirez-Lorca, S. Dobbie, W.T. Longstreth, A.C. Janssens, V.S. Pankratz, J.F. Dartigues, P. Hollingworth, T. Aspelund, I. Hernandez, A. Beiser, L.H. Kuller, P.J. Koudstaal, D.W. Dickson, C. Tzourio, R. Abraham, C. Antunez, Y. Du, J.I. Rotter, Y.S. Aulchenko, T.B. Harris, R.C. Petersen, C. Berr, M.J. Owen, J. Lopez-Arrieta, B.N. Vardarajan, J.T. Becker, F. Rivadeneira, M.A. Nalls, N.R. Graff-Radford, D. Campion, S. Auerbach, K. Rice, A. Hofman, P.V. Jonsson, H. Schmidt, M. Lathrop, T.H. Mosley, R. Au, B.M. Psaty, A.G. Uitterlinden, L.A. Farrer, T. Lumley, A. Ruiz, J. Williams, P. Amouyel, S.G. Younkin, P.A. Wolf, L.J. Launer, O.L. Lopez, C.M. van Duijn, M.M. Breteler, CHARGE Consortium, GERAD1 Consortium and EADI1 Consortium: Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA* 303, 1832-1840 (2010)
45. R. Sherva, C.T. Baldwin, R. Inzelberg, B. Vardarajan, L.A. Cupples, K. Lunetta, A. Bowirrat, A. Naj, M. Pericak-Vance, R.P. Friedland and L.A. Farrer: Identification of novel candidate genes for Alzheimer's disease by autozygosity mapping using genome wide SNP data. *J Alzheimers Dis* 23, 349-359 (2011)
46. E.M. Wijsman, N.D. Pankratz, Y. Choi, J.H. Rothstein, K.M. Faber, R. Cheng, J.H. Lee, T.D. Bird, D.A. Bennett, R. Diaz-Arrastia, A.M. Goate, M. Farlow, B. Ghetti, R.A. Sweet, T.M. Foroud, R. Mayeux and NIA-LOAD/NCRAD Family Study Group: Genome-wide association of familial late-onset alzheimer's disease replicates BIN1 and CLU and nominates CUGBP2 in interaction with APOE. *PLoS Genet* 7, e1001308 (2011)
47. J.H. Lee, R. Cheng, S. Barral, C. Reitz, M. Medrano, R. Lantigua, I.Z. Jiménez-Velazquez, E. Rogaeva, P. St George-Hyslop and R. Mayeux: Identification of Novel Loci for Alzheimer Disease and Replication of CLU, PICALM, and BIN1 in Caribbean Hispanic Individuals. *Arch Neurol* 68, 320-328 (2011)
48. A.C. Naj, G.W. Beecham, E.R. Martin, P.J. Gallins, E.H. Powell, I. Konidari, P.L. Whitehead, G. Cai, V.

Genetics of Alzheimer's disease

- Haroutunian, W.K. Scott, J.M. Vance, M.A. Slifer, H.E. Gwirtsman, J.R. Gilbert, J.L. Haines, J.D. Buxbaum and M.A. Pericak-Vance: Dementia revealed: novel chromosome 6 locus for late-onset *alzheimer* disease provides genetic evidence for folate-pathway abnormalities. *PLoS Genet.* 6, e1001130 (2010)
49. C.E. Yu, H. Seltman, E.R. Peskind, N. Galloway, P.X. Zhou, E. Rosenthal, E.M. Wijsman, D.W. Tsuang, B. Devlin and G.D. Schellenberg: Comprehensive analysis of APOE and selected proximate markers for late-onset *alzheimer's* disease: patterns of linkage disequilibrium and disease/marker association. *Genomics* 89, 655-665 (2007)
50. K.Morgan: The three new pathways leading to Alzheimer's disease. *Neuropathol Appl Neurobiol* 37, 353-357 (2011)
51. P.L. McGeer, T. Kawamata and D.G. Walker: Distribution of clusterin in Alzheimer brain tissue. *Brain Res* 579, 337-341 (1992)
52. A.M. Nilsseldid, P. Davidsson, K. Nägga, N. Andreasen, P. Fredman and K. Blennow: Clusterin in cerebrospinal fluid: analysis of carbohydrates and quantification of native and glycosylated forms. *Neurochem Int* 48, 718-728 (2006)
53. M.M. Bartl, T. Luckenbach, O. Bergner, O. Ullrich and C.Koch-Brandt: Multiple receptors mediate apoJ-dependent clearance of cellular debris into nonprofessional phagocytes. *Exp Cell Res* 271, 130-141 (2001)
54. R.D. Bell, A.P. Sagare, A.E. Friedman, G.S. Bedi, D.M. Holtzman, R. Deane and B.V. Zlokovic: Transport pathways for clearance of human Alzheimer's amyloid beta-peptide and apolipoproteins E and J in the mouse central nervous system. *J Cereb Blood Flow Metab* 27, 909-918 (2007)
55. F. Tebar, S.K. Bohlander and A. Sorkin: Clathrin assembly lymphoid myeloid leukemia (CALM) protein: localization in endocytic-coated pits, interactions with clathrin, and the impact of overexpression on clathrin-mediated traffic. *Mol Biol Cell* 10, 2687-2702 (1999)
56. A. Harel, F. Wu, M.P. Mattson, C.M. Morris, P.J. Yao: Evidence for CALM in directing VAMP2 trafficking. *Traffic* 9, 417-429 (2008)
57. R. Khera and N.Das: Complement Receptor 1: disease associations and therapeutic implications. *Mol Immunol* 46, 761-772 (2009)
58. S.M. Smith, R. Renden, H. von Gersdorff: Synaptic vesicle endocytosis: fast and slow modes of membrane retrieval. *Trends Neurosci* 31, 559-68 (2008)
59. B. Meunier, M. Quaranta, L. Daviet, A. Hatzoglou and C. Leprince: The membrane-tubulating potential of amphiphysin 2/BIN1 is dependent on the microtubule-binding cytoplasmic linker protein 170 (CLIP-170). *Eur J Cell Biol* 88, 91-102 (2009)
60. W.S. Kim, C.S. Weickert and B. Garner: Role of ATP-binding cassette transporters in brain lipid transport and neurological disease. *J. Neurochem* 104, 1145-1166 (2008)
61. W.S. Kim, M.L. Fitzgerald, K. Kang, K. Okuhira, S.A. Bell, J.J. Manning, S.L. Koehn, N. Lu, K.J. Moore, M.W. Freeman: Abca7 null mice retain normal macrophage phosphatidylcholine and cholesterol efflux activity despite alterations in adipose mass and serum cholesterol levels. *J Biol Chem* 280, 3989-3995 (2005)
62. W.S. Kim, G.J. Guillemin, E.N. Glaros, C.K. Lim and B. Garner: Quantitation of ATP-binding cassette subfamily-A transporter gene expression in primary human brain cells. *Neuroreport* 17, 891-896 (2006)
63. A.W. Jehle, S.J. Gardai, S. Li, P. Linsel-Nitschke, K. Morimoto, W.J. Janssen, R.W. Vandivier, N. Wang, S. Greenberg, B.M. Dale, C. Qin, P.M. Henson and A.R. Tall: ATP-binding cassette transporter A7 enhances phagocytosis of apoptotic cells and associated ERK signaling in macrophages. *J Cell Biol* 174, 547-556 (2006)
64. H. Tateno, H. Li, M.J. Schur, N. Bovin, P.R. Crocker, W.W. Wakarchuk and J.C. Paulson: Distinct endocytic mechanisms of CD22 (Siglec-2) and Siglec-F reflect roles in cell signaling and innate immunity. *Mol Cell Biol* 27, 5699-5710 (2007)
65. P.R. Crocker, J.C. Paulson and A. Varki: Siglecs and their roles in the immune system. *Nat Rev Immunol.* 7, 255-266 (2007)
66. A. Martinez and E. Soriano: Functions of ephrin/Eph interactions in the development of the nervous system: emphasis on the hippocampal system. *Brain Res Brain Res Rev* 49, 211-226 (2005)
67. K.O. Lai and N.Y. Ip: Synapse development and plasticity: roles of ephrin/Eph receptor signaling. *Curr Opin Neurobiol* 19, 275-283 (2009)
68. D.K. Lynch, S.C. Winata, R.J. Lyons, W.E. Hughes, G.M. Lehrbach, V. Wasinger, G. Corthals, S. Cordwell and R.J. Daly: A Cortactin-CD2-associated protein (CD2AP) complex provides a novel link between epidermal growth factor receptor endocytosis and the actin cytoskeleton. *J Biol Chem* 278, 21805-21813 (2003)
69. N. Shahani and R. Brandt: Functions and malfunctions of the tau proteins. *Cell Mol Life Sci* 59, 1668-1680 (2002)
70. S. Oddo, A. Caccamo, J.D. Shepherd, M.P. Murphy, T.E. Golde, R. Kaye, R. Metherate, M.P. Mattson, Y. Akbari, and F.M. LaFerla: Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron* 39, 409-421 (2003)

Genetics of Alzheimer's disease

71. R.J. Castellani, R.K. Rolston and M.A. Smith: Alzheimer disease. *Dis Mon* 56, 484-546 (2010)
72. T.M. Caffrey and R. Wade-Martins: Functional MAPT haplotypes: bridging the gap between genotype and neuropathology. *Neurobiol Dis* 27, 1-10 (2007)
73. M. Doran, D.G. du Plessis, E.J. Ghadiali, D.M. Mann, S. Pickering-Brown and A.J. Larner: Familial early-onset dementia with tau intron 10 + 16 mutation with clinical features similar to those of Alzheimer disease. *Arch Neurol* 64, 1535-1539 (2007)
74. A.J. Larner: Mutation negative "early-onset familial Alzheimer disease": consider screening for tau gene mutations. *Alzheimer Dis Assoc Disord.* 22, 194-195 (2008)
75. P. Momeni, A. Pittman, T. Lashley, J. Vandrovцова, E. Malzer, C. Luk, C. Hulette, A. Lees, T. Revesz, J. Hardy and R. de Silva: Clinical and pathological features of an Alzheimer's disease patient with the MAPT Delta K280 mutation. *Neurobiol Aging.* 30, 388-393 (2009)
76. A.C. Wilson, B.N. Dugger, D.W. Dickson and D.S. Wang: TDP-43 in aging and Alzheimer's disease - a review. *Int J Clin Exp Pathol* 4, 147-155 (2011)
77. N. Brouwers, K. Bettens, I. Gijssels, S. Engelborghs, B.A. Pickut, H. Van Mieghem, A.G. Montoya, M. Mattheijssens, K. Peeters, P.P. De Deyn, M. Cruts, K. Sleegers and C. Van Broeckhoven: Contribution of TARDBP to Alzheimer's disease genetic etiology. *J Alzheimers Dis* 21, 423-430 (2010)
78. N. Ticozzi, A.L. Leclerc, M. van Blitterswijk, P. Keagle, D.M. McKenna-Yasek, P.C. Sapp, V. Silani, A.M. Wills, R.H. Jr Brown and J.E. Landers: Mutational analysis of TARDBP in neurodegenerative diseases. *Neurobiol Aging.* 32, 2096-2099 (2011)
79. F. Coppedè and L. Migliore: Evidence linking genetics, environment, and epigenetics to impaired DNA repair in Alzheimer's disease. *J Alzheimers Dis* 20, 953-966 (2010)
80. L. Chouliaras, B.P. Rutten, G. Kenis, O. Peerbooms, P.J. Visser, F. Verhey, J. van Os, H.W. Steinbusch and D.L. van den Hove: Epigenetic regulation in the pathophysiology of Alzheimer's disease. *Prog Neurobiol* 90, 498-510 (2010)
81. P.H. St George-Hyslop, R.E. Tanzi, R.J. Polinski, J.L. Haines, L. Nee, P.C. Watkins, R.H. Myers, R.G. Feldman, D. Pollen, D. Drachman: The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science* 235, 885-90 (1987)

Abbreviations: AD: Alzheimer's disease; FAD: Familial Alzheimer's disease; EOFAD: Early-onset familial Alzheimer's disease; LOAD: Late-onset Alzheimer's disease; APP: amyloid precursor protein; PSEN1: presenilin 1; PSEN2: presenilin 2; APOE: Apolipoprotein

E; A-beta: amyloid beta protein; BACE1: beta-site APP cleaving enzyme 1; GWAS: Genome-wide association studies; NFTs: neurofibrillary tangles; PET: Positron Emission Tomography; SNPs: Single Nucleotide polymorphisms; LD: linkage disequilibrium; TOMM40: Translocase of the Outer Mitochondrial Membrane 40; CLU: clusterin; PICALM: phosphatidylinositol binding clathrin assembly protein; CRI: complement component [3b/4b] receptor 1; BIN1: bridging integrator 1; ABCA7: ATP-binding cassette transporter member 7; CD33: sialic acid binding Ig-like lectin 3; EPHA1: ephrin type-A receptor 1; CD2AP: CD2-associated protein; APOJ: apolipoprotein J; CME: clathrin-mediated endocytosis; H1c: tau haplotype; MAPT: Microtubule Association Protein Tau; TDP-43: Transactive response DNA-binding protein 43; SIRT1: sirtuin 1; RARalpha: retinoic acid receptor-alpha

Key Words: Alzheimer's disease, Genes Mutation, Single Nucleotide Polymorphisms, Epigenetics, GWAS, Review

Send correspondence to: Benedetta Nacmias, Department of Neurological and Psychiatric sciences, University of Florence, Largo Brambilla 3, 50134 Florence, Italy, Tel: 390554271379, Fax: 390554271380, E-mail: nacmias@unifi.it