

## Review

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# Genetic Heterogeneity of Alzheimer's Disease: Embracing Research Partnerships

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**Abstract.** Studies on the genetics of Alzheimer's disease (AD) have revealed the complexity and heterogeneity of the disease. All our studies have supported this evidence and contribute to the current understanding of the genetic architecture of AD. This report reviews the success of our investigations, focusing on the implications and importance of the genetics of AD, and demonstrates the relevance of research strategies embracing partnerships.

**Keywords:** Alzheimer's disease, autosomal dominant, genetic mutation, genetic risk factor

## FAMILIAL ALZHEIMER'S DISEASE: THE BEGINNING

The qualitative and quantitative aspects of the genetic population of Italy have provided evidence that the country is a genetically heterogeneous nation. According to recent studies [1, 2], there are several genetic groups in different areas of Italy, thus allowing us to study large families, affected by AD, living in the north, central, and south of Italy with different genetic traits. Our group started collaborating with other centers in Italy in 1980 in order to create a DNA bio-bank collecting samples, not only of patients belonging to familial forms of Alzheimer's disease (FAD), but also from non-affected members of the same families. Genetic studies on FAD have provided evidence that AD is a genetically heterogeneous disorder and, over the last 30 years, several families have

been described in which AD is caused by an autosomal dominant gene defect. The genetic history of AD started in 1987 when, in collaboration with Peter St. George-Hyslop, a linkage analyses discovered the first chromosomal location of a defective gene on chromosome 21, thus providing new insights into the nature of FAD [3–7]. In the early 1990s, we studied Italian FAD families through extensive clinical investigations of patients, interviews with relatives, studies of medical records, pedigree analysis, and molecular genetic studies of family members, thereby contributing to the discovery of the pathogenic variations in all three AD candidate genes: *Presenilin 1 (PSEN1)*, *Presenilin 2 (PSEN2)*, and *Amyloid precursor protein (APP)* [5–7].

In 1993, we found the APPVal717Ile mutation segregating with the disease in the first Italian families (FLO12 and FLO13) from central Italy [5]. The mutation was found in all those affected as well as in members below the age of onset of the disease, thus allowing a preclinical diagnosis. Since 1991 [4], 51 different pathogenetic mutations have been described in this gene in 121 families worldwide [8]; to date,

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38/51 families have been described as carrying the APPVal717Ile mutation.

Thanks to collaboration with Amalia Bruni in Lamezia Terme, in southern Italy, we have collected samples from the large Calabrian family, FAD4, which has been described in numerous generations since the 1700s and led to the discovery in 1995 [6] of *PSEN1*, the most important gene responsible for FAD. To date, 215 pathogenic mutations have been described in *PSEN1* [8].

A collaborative effort in 2000 led to the identification of Nicastrin protein [9] as modulator of the presenilin-mediated notch/glp-1 signal transduction and A $\beta$ PP processing.

Moreover, thanks to collaboration with Gabriella Marcon in Udine, in northern Italy, we started collecting samples from several members of a large Italian AD family living in Udine (FLO10) described over several generations, associated with methionine to valine substitution at residue 239 of *PSEN2* [7]. The FLO10 family is characterized by some peculiarities regarding clinical and neuropathologic phenotype compared to sporadic AD [10].

*PSEN2* mutations are rare and mutated patients showed a remarkable variability in age of onset of symptoms, disease duration, and clinical presentation. Today the diagnostic and predictive genetic screening for causal mutations in *APP*, *PSEN1*, and *PSEN2* is already available for patients and their relatives. In any case, causative mutations are only responsible for a small portion of autosomal dominant FAD patients. There are still other genetic factors to discover as most of the families are negative, thus an important proportion of genetic variants in AD pathology are yet to be identified. However, it should be considered that penetrance and gene expression can influence the effect of a mutation.

In our neurogenetics laboratory, we have identified pathogenetic mutations in 5% (5/98), 13% (13/98), and 3% (3/98) of the collected families referred for diagnostic screening for *APP*, *PSEN1*, and *PSEN2*, respectively. Only after 25 years of the description of the first pathogenetic mutation in the *APP* gene [4] has an Italian consensus protocol for Genetic Counseling and Testing for Alzheimer's disease and Frontotemporal Lobar Degeneration been reached [11]. The protocol has been developed in the context of the Italian Dominantly Inherited Alzheimer's and Frontotemporal Network (IT-DIAfN) project, a national network of centers of excellence with expertise in managing patients with familial AD

and frontotemporal dementia (FTD) [12] facilitating research and clinical trials.

It is widely held that genetic counseling should be provided by a multidisciplinary team including a geneticist, a neurologist/geriatrician, and a psychologist/psychiatrist according to the following schedule: 1) initial consultation with tailored information on the genetics of the dementias; 2) clinical, psychological, and cognitive assessment; if deemed appropriate, 3) genetic testing following a structured decision tree for gene mutation search; 4) genetic testing result disclosure; 5) psychological support follow-up. This genetic counseling protocol provides Italian centers with a line of shared practice for dealing with the requests for genetic testing for familial AD and FTD from patients and at-risk relatives, who may also be eligible participants for novel prevention clinical trials [11].

In recent years, new biomarkers, such as amyloid- $\beta$  (A $\beta$ ) accumulation in cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging, have been included in AD diagnostic criteria [13] in addition to genetic mutations. Their use in clinical practice allows discrimination between healthy control subjects and AD but also could help to detect preclinical and prodromal AD [14–16]. The combination of neuroimaging, biomarkers, and genetic tests helps, in most cases, to clinically diagnose accurately.

However, we have recently described a case of dementia clinically compatible with the FTD spectrum in an APP Ala713Thr-mutation carrier in which both [ $^{18}$ F] Florbetapir PET uptake and A $\beta$ <sub>1-42</sub> CSF levels were normal [17]; thus the genetic diagnosis was in contrast with the lack of evidence of A $\beta$  pathology assessed by both CSF analysis and amyloid imaging. Even genetic analysis can sometimes help or complicate the diagnosis. Moreover, mutations in genes related to other types of dementia, such as FTD, can be detected in patients with AD phenotype [18–23].

For example, the mutation p.R406W in Microtubule associated protein Tau (*MAPT*), a known causal gene for FTD, has been repeatedly reported in pedigrees with a clinical presentation of AD [21]. Mutations in two other FTD genes, Progranulin (*GRN*) and Chromosome 9 open reading frame 72 (*C9orf72*), have also been described in clinical AD cohorts [22, 23]. It may be important to include screening of these genes in the genetic diagnostic work-up, because *APP*, *PSEN1*, and *PSEN2* account only for a small proportion of autosomal dominant AD.

## GENETIC RISK FACTORS: A CONTINUOUS DISCOVERY

Linkage studies on familial cases have revealed the genetic bases associated with the disease; however, they were not sufficient to explain late onset-sporadic forms (LOAD). LOAD is complex and genetically heterogeneous; genes and environmental risk factors contribute together to the onset and progression of the disease.

Technological advances in high-throughput genotyping and sequencing allow testing of several thousands of samples (and patients and controls) that can be used for genome-wide association studies (GWAS). GWAS in fact report genetic variants and loci that are enriched in populations with a disease trait compared with unaffected individuals.

The most important results have been possible thanks to collaborative strategies which have created genetic consortia such as Alzheimer's Disease Genetics Consortium (ADGC), Genetic and Environmental Risk in Alzheimer's disease (GERAD), European Alzheimer's Disease Initiative (EADI), Cohorts for Heart and Aging in Genomic Epidemiology (CHARGE), Genetic and Environmental Risk for Alzheimer's Disease (GERAD)/ Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease (PERADES) Consortium, the Alzheimer's Disease Genetic Consortium (ADGC), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), and the European Alzheimer's disease Initiative (EADI). In 2013, the International Genomics of Alzheimer's Project (IGAP) was launched with all the consortia joined together.

GWAS and IGAP have significantly advanced knowledge regarding the genetic heterogeneity of AD by identifying 30 additional genetic risk loci [24]. Several GWAS were performed [25–29] and later combined in a meta-analysis [30, 31] to report new AD susceptibility loci in European populations. A GWAS in African Americans identified variants in Apolipoprotein E (*APOE*) and ATP-binding cassette transporter (*ABCA7*) as genome-wide significant [32]. A GWAS in Asian populations identified AD-associated genome-wide significant variants in or near *APOE* and *SORL1* [33].

Thanks to collaboration strategies, we have contributed to identifying new genetic variants [25, 29, 31] implicated in AD. To date, there are 30 genes

associated with AD (27 loci associated with AD, mostly through GWAS) distributed on 14 chromosomes [24] confirming the genetic heterogeneity of the disease. Moreover, the GWA approach to the genetics of AD has made it possible to discover the implication of four biological pathways (immune response, endocytosis, cholesterol transport, and proteasome-ubiquitin activity) in the pathogenesis of the disease and as prime targets for AD therapeutic interventions.

The first and most important genetic risk factor was identified in the 1990s when a particular *APOE* genotype was associated to LOAD as it is involved in the A $\beta$  pathway [34]. In 1994, we analyzed the *APOE* gene polymorphism in a sample of Italian AD patients, confirming a significant association between epsilon 4 allele and AD [35, 36]. Since then, the role of *APOE* has been confirmed by hundreds of papers, thus for 17 years the *APOE* gene on chromosome 19q13.2 was the only genetic risk factor for AD. Moreover in 2011 a shift of category of the *APOE* gene from 'risk factor' to 'major gene' was proposed, with semi-dominant inheritance [37] increasing the risk according to age in a collaborative study on 7,351 cases and 10,132 controls with Caucasian ancestry. Since the beginning of this century, several genetic variants in different genes have been analyzed. Following the increasing evidence that suggests a role for nerve growth factor (*NGFB*), brain-derived neurotrophic factor (*BDNF*), nerve growth factor receptor (*NGFR*), and neurotrophic tyrosine kinase receptors 1 and 2 (*NTRK1* and *NTRK2*) in the GRB-associated binding protein 2 (*GAB2*) genes in AD, we analyzed single nucleotide polymorphisms (SNPs) within these genes in a population of Italian AD patients and healthy controls. Our results suggested that genetic variants of the neurotrophic system and *GAB2* genes might confer susceptibility to AD [38, 39].

Neurotrophins are a family of proteins that are essential for the development, differentiation, and survival of neurons [40]. Polymorphisms in genes of the neurotrophin system may determine an increased risk for developing AD.

GRB-associated binding protein 2 (*GAB2*, 11q14.1) has been proposed as a candidate gene, but with contrasting results. *GAB2* is a scaffolding protein [41], possibly affecting tau, amyloid, and other AD-related pathological mechanisms.

Moreover, we also analyzed the genotype and allele distributions of the Pro86Leu polymorphism of the Calcium homeostasis modulator 1

(*CALHMI*) gene, rs5984894, in the protocadherin 11 X-linked (*PCDH11X*) gene and *PICALM* (phosphatidylinositol-binding clathrin assembly protein) in Italian AD patients [42–44]. Our results did not confirm an association between the *CALHMI* variation, the *PCDH11X* or *PICALM* and AD, thus suggesting a genetic heterogeneity among the various populations. Furthermore, we have provided evidence of the importance of epistatic effect and epigenetics [45, 46] in the expression of genes involved in the disease.

In 1995, we studied the relationship between ApoE genotype and the clinical expression of the disease in *APP* mutated families and found that ApoE genotype influences the age at onset of the disease, providing evidence of epistatic effect [45]. In 2015, for the first time, we studied, how epigenetic changes (DNA methylation) in peripheral blood of AD patients can influence disease expression [46]. In fact, the several genetic factors (mutations and risk factors) already described cannot fully explain the onset and progression of AD, especially for the sporadic form of the disease [24]. The scientific community considers the complex combination of genetic and environmental factors the major modifier for risk of the disease [47]. Epigenetic modifications of the DNA may occur during development or later during adult life and it is one of the ways through which environmental factors interact with genetic ones [48]. Up to now, DNA methylation changes have been investigated in brain tissues in all genes associated with familial AD cases (*APP*, *PSEN1*, *PSEN2*, and *MAPT*), but the results are contradictory. In 1990, the first studies dealing with DNA methylation levels in the brain of patients with AD reported no significant difference between brain DNA of AD patients compared with healthy subjects [49, 50]. It is essential to take into account that the results are conflicting due to the different brain regions and the multiple cell types analyzed, indeed DNA methylation is a dynamic process that can produce tissue-specific changes [51] and differences are observed across different regions within the brain [52]. Our study on lymphocytes found a strong hypomethylation status (<20% methylation) in the three gene promoters (*APP*, *PSEN1*, *PSEN2*) in Italian AD patients with respect to healthy control subjects, with statistically significant differences. Although our study analyzed lymphocytes, which are not representative of the methylation levels in the brain, this can complete the picture of the role of epigenetic mechanisms and their relation to the disease.

## CELLULAR AND ANIMAL MODELS TO STUDY AD: NEW STRATEGIES

The study of large AD-affected families carrying genetic mutations in the three major causative genes allowed discovery of the main biochemical pathways involved in the disease. In fact, fibroblasts that express a genetic defect can be obtained with a simple skin biopsy from a mutated subject in order to study the primary pathophysiological mechanisms by which the disease develops.

Today, it is well known that oxidative stress and reduced antioxidant defenses are early events in the pathogenesis of AD. By analyzing peripheral cells carrying *APP* and *PSEN1* gene mutations, it has been possible to show altered levels of oxidative markers supporting the hypothesis that oxidative damage to lipid, protein, and DNA is an important early event in AD pathogenesis [53].

In one collaborative study, we demonstrated that in *APP*-mutated fibroblasts oligomeric structures of  $A\beta_{1-40}$  and  $A\beta_{1-42}$  accumulate quicker near the plasma membrane, and are internalized faster and mostly in *APPV717I* fibroblasts than in age-matched healthy fibroblasts. This mechanism leads to an increase in the production of reactive oxygen species and subsequently to membrane-oxidative injury with a significant impairment of cellular antioxidant capacity [54].

The role of the cellular membrane in destabilization and permeabilization is one of the crucial steps to understanding amyloid cytotoxicity, which leads to early alterations in intracellular redox status and ion homeostasis that potentially culminate in cell death. Recent data on primary fibroblasts from familial AD patients bearing *APPVal717Ile*, *PS-1Leu392Val*, or *PS-1Met146Leu* gene mutations suggest a protective role for raft cholesterol against amyloid toxicity in AD [55].

Moreover, induced pluripotent stem cells derived from skin fibroblasts from subjects carrying pathogenic mutations may be a useful resource for *in vitro* modeling of familial AD [56], allowing the study of new therapeutic strategies against the disease [57].

The triple transgenic mice model (3xTg), known to develop three key characteristics of AD dysfunction (memory impairment, amyloid plaques, and neurofibrillary tangles), has recently provided new insight. In this model, the power of dietary polyphenols against neurodegeneration has been studied by investigating the effects of oleuropein aglycone (OLE), the main phenol in extra virgin olive oil

(EVOO). OLE administration ameliorates memory dysfunction and promotes the proliferation of newborn cells in the subgranular zone of the dentate gyrus of the hippocampus [58]. Recent findings support a beneficial effect of EVOO consumption on all major features of the AD phenotype (behavioral deficits, synaptic pathology, A $\beta$ , and tau neuropathology) and demonstrate that autophagy activation is the mechanism underlying these biological actions. Thus, consumption of EVOO, a major component of the Mediterranean diet, has been associated with reduced incidence of AD [59].

In 2016, the AIRAlzh (*Associazione Italiana Ricerca Alzheimer*) Network was launched in Italy to create an Italian network of young researchers studying AD and other dementias [60]. The main goal of the network is to encourage collaboration between national dementia research centers of excellence to realize projects, proposed by young researchers, focused on the identification of potentially modifiable risk factors and mechanisms of AD and other dementias. Scientific projects are based on these specific fields: Biology (*in vitro* studies including genetics, biomarkers, and pathological mechanisms); Clinical studies (involving human subjects such as pilot studies of pharmacological treatments, neuropsychology, imaging, and epidemiology); and Biotechnology (application of advanced and emerging technologies for the diagnosis and monitoring of dementias). The network encourages synergies and cooperation between young researchers with different research profiles to stimulate a concrete impact on the diagnosis and prevention of AD and other dementias.

In conclusion, network strategies in the field of AD research have provided evidence of the complexity and heterogeneity of the disease and contributed to the understanding of the current genetic architecture of AD. Moreover, genetic studies have allowed the application of new methodologies based on the use of cell and animal models of AD in order to study new therapeutic approaches against the disease.

## DISCLOSURE STATEMENT

Authors' disclosures available online (<http://j-alz.com/manuscript-disclosures/17-0570r1>).

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