Genetics of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia. The genetic approach to the study of Alzheimer's disease undoubtedly continues to provide a significant contribution to understanding the pathogenesis, the diagnosis and the therapeutic perspectives with important ethical implications. The knowledge on the genetics of Alzheimer's disease suggests clinical guidelines for helping families with the disease. Pre-test counseling and the identification of genetic defects are important in both patients and asymptomatic at risk family members. The review highlights the role of genetics in understanding the pathogenesis of Alzheimer's disease.

Keywords: Alzheimer's disease; Genetics; Epigenetics; Genome-wide association study

Abbreviations: PSEN1-Presenilin1; PSEN2-Presenilin 2; APP-Amyloid precursor protein; ApoE-Apolipoprotein E

INTRODUCTION

The incidence of dementia is quickly increasing due to the ageing of the worldwide population. Alzheimer's disease (AD) is the most common type of dementia accounting 50-75% of cases. AD was first identified more than 100 years ago and although research has revealed a great deal about the disease, strong evidences support the genetic etiological hypothesis [1]. Individuals who have a first-degree relative with AD have an increased risk to develop the disease and predominantly show the first clinical symptoms at age earlier than 65 years old (early onset AD, EOAD) [2]. However, the presence of family history, together with age and female sex, is considered the strongest risk factor also for the late-onset AD (age at onset >65 years old, LOAD). The heritability of LOAD forms is estimated of 60-80%, but the genetic predisposition is not attributable to Mendelian pattern [3].

The genetic research of risk factors undoubtedly provided and continues to offer new knowledge about the pathogenesis, the diagnosis and the future therapeutic perspectives with important ethical implications.

Since the discovery of the first pathogenic variation in a family with AD [4]. The scientific community Alzforum (www.alzforum.org) has listed 328 mutations reported in the three principal Alzheimer's disease genes (*Presenilin1*PSEN1,*Presenilin 2 PSEN2* and *Amyloid precursor protein APP* genes). The majority of the mutations (approximately 30%–70%) [5] are located on *PSEN1* gene (almost 278) making the gene the most common known genetic cause of the early familial form of AD (EOFAD).

CAUSATIVE GENES

The APP gene is localized on chromosome 21q21.3; it encodes a transmembrane protein called amyloid precursor protein, whose proteolytic cleavage gives rise small fragments (peptides); two of them are the soluble amyloid precursor protein (sAPP) and amyloid beta (Aβ) peptide [6]. The protein is expressed in many tissues and organs but little is known about its functions, many studies supported its role as a trophic factor for neurons and synapses [7,8].

The discovery of this gene was essential to the study of Alzheimer's disease even if mutations are rarely cause of AD. The majority of the mutations are located in cleavage sites of β- and γ-secretase increasing the total Aβ levels.The sequential proteolytic cleavage of APP by *β*- and *γ*-secretase is called "amyloidogenic pathway" and its alteration leads to the characteristic AD plaques (amyloid deposition) that could be detected several years before onset of the disease [9]. The Aβ deposition can prejudice cognition, neuronal and glial function, neurotransmission and the synaptic physiology [10]. Up to now, a total of 49 mutations in APP in 119 AD families are described (http://www.molgen.ua.ac.be/aDmutations) [11]. Moreover, it has been reported a variant in APP (p.A673T) that makes the protein a less-favorable substrate for β-secretase. It has been shown by *in vitro* and *in vivo* studies that this variant is not associated with an increase of Aβ plaques resulting in a protective effect for cognitive decline [12,13]. Interestingly, another unusual

mutation (p.A673V) that appears to be pathogenic in the homozygous state and protective in the heterozygous state [14] has been described at the same position.

The PSEN1 gene is localized on chromosome 14q24.3, it encoded a protein thatis a subunit of the complex called γ-secretase. Presenilin 1 carries out the major function of the complex and it is described as the proteolytic subunit of γ-secretase.

Mutations in PSEN1 are the major causes of FAD, actually there are known 215 genetic variations in 475 families in the world [11].

The greater part of PSEN1 mutations interfere with the function of the γ-secretase complex altering the processing of APP that leads to the overproduction of the toxic amyloid-β peptide.

PSEN1 mutations are clinically characterized by an earlier age at onset respect to the other genes mutations, the median age of onset is about 45 years, however the range is 28-79 years [15]. Depending on the sites where the mutations occur, the impact on the final protein is different and consequently the variability of the disease onset. In particular, transmembrane domain mutations are associated to a very early onset and a rapid progression of the cognitive decline.

The PSEN2 gene is localized onchromosome1q 42.13 and encodes a trasmembrane protein very similar to Presenilin1 protein and both take part to the processing of amyloid precursor protein.

Up to now, 15 PSEN2 mutations in 31 families have been described (http://www.molgen.ua.ac.be/aDmutations) [11]. Mutations in this gene account for less than 5 percent of all early-onset cases of the disease so they appear to be rare.As for PSEN1, the mechanism by which the mutations cause AD is the disruption of the processing of amyloid precursor protein, leading to the overproduction of amyloid beta peptide [16]. Differently to PSEN1, PSEN2 mutations have an oldest age of symptom onset and a variability of phenotype also among the carriers of the same mutation.

SUSCEPTIBILITY GENES

Genetically, late-onset AD is considered a polygenic and multifactorial disorder [17]. The genetic components interact with the environmental factors and may influence the disease appearance and transmission [Figure 1]. For many years, the only genetic risk factor was the Apolipoprotein E (ApoE) [18]. Although, recent advances in molecular genetics suggest that many genes can work together to impact the predisposition of the disease [19], the APOE remains the major gene known to increase the disease risk [20]. The Apolipoprotein E combines with lipids in the vessels to form lipoproteins that are responsible for packaging cholesterol and other fats and carrying them through the bloodstream. There are at least three different alleles of the APOE gene in humans. The major alleles are called e2, e3, and e4. The most common allele is e3, which is found in more than half of the general population. The APOE e4 allele is associated to the risk to develop Alzheimer disease [21,22].

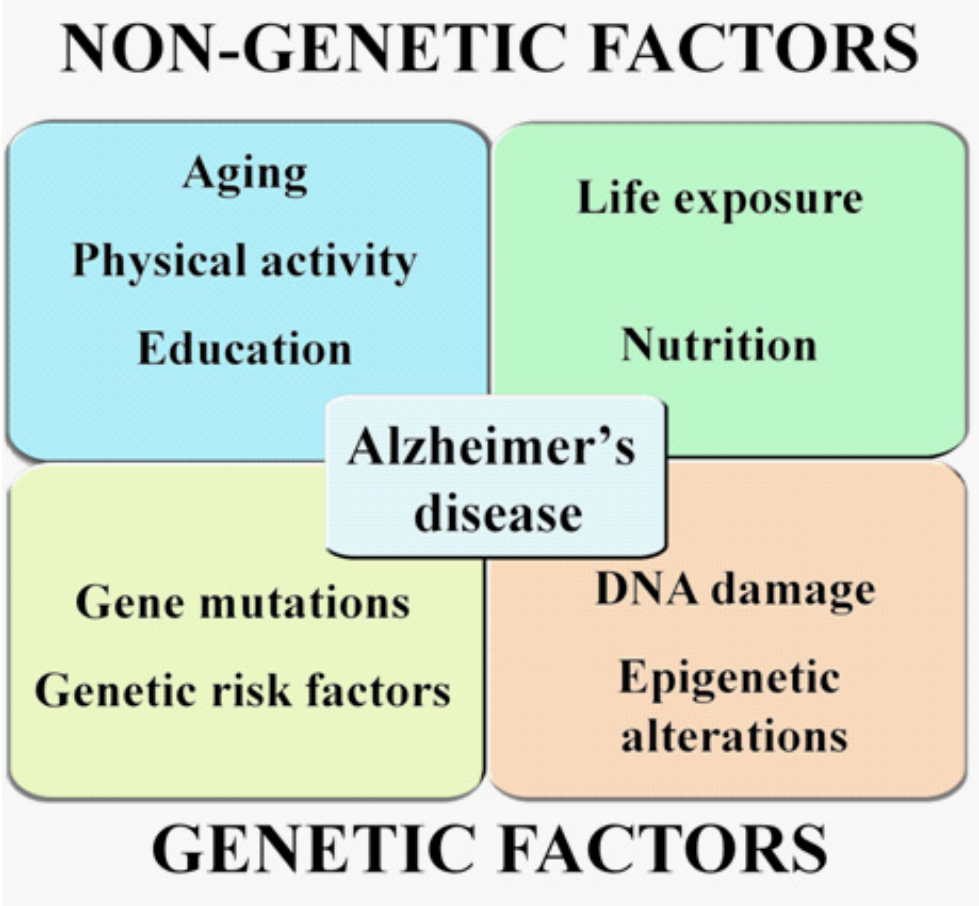

Figure 1: The complex etiology of Alzheimer's disease. A schematic overview of genetic and non-genetic risk factors that can contribute to the development of the disease.

Studies have found that this allele is correlated with an increased number of amyloid plaques in the brain tissue of AD affected subjects [23].

APOE e4 allele carriers have an increased risk of developing Alzheimer disease but not all of them will develop the disease, all not all AD patients have the APOE e4 allele. In addition, according to recent data, ApoE could be a major gene with semi-dominant inheritance [24].

In the last years collaborative international studies (Genome Wide Studies, GWA) have significantly advanced the knowledge in LOAD susceptibility genes. In 2009 at least nine novel genetic risk factors were uncovered [25,26] among which CLU, CR1, PICALM, BIN1, EPHA1 were detected in independent GWA studies and confirmed in replication analyses [27]. Successively GWA studies continued in order to expand the list of genetic variation associated to the risk of developing sporadic AD [28]. These loci are in or near novel AD genes including CD33, EPHA1, MS4A4/MS4A6, ABCA7, CD2AP, SORL1, HLA-DRB5/DRB1, PTK2B, SLC24A4-RIN3, INPP5D,

MEF2C, NME8, ZCWPW1, CELF1, FERMT2, CASS4, and TRIP4 but each has small effects on AD risk [29]. The identification of these loci has lead to study new biological pathways previously unsuspected in the pathophysiology of AD.

The main part of these genes encode for proteins that play a role in the regulation of the clearance of immune complexes and of synaptic vesicle recycling. In addition to extracellular amyloid beta plaque deposition, neurofibrillar tangles (NFTs) are the second feature of AD brain. They are produced by abnormally hyperphophoritated tau protein (encoded by microtubule associated protein tau, MAPT gene) [30]. The tau insoluble fibrils acquired a toxic role compromising the axonal transport and contributing to synaptic degeneration [31].

Recent works have shown that a genetic variant in TREM2 gene (triggering receptor expressed on myeloid cells) could increase susceptibility to LOAD [32,33] causing accumulation of macrophages in the brain around amyloid beta plaques and failing to clear them [34]. On the contrary, another study indicate an opposite effects of TREM 2 variant [35] contributing to the more efficient cleaning of the pathologic plaques.

Thus, the question is how important is the role of these genetic risk factors in the prediction of LOAD. None of the novel risk factor showed in the GWA studies have the same impact of ApoE e4, whose odd ratio was estimated more than 3.50 respect to the other genes of 1.1-1.3 [36]. Despite the evidence of ApoE, the relevance of common genetic variations identified by GWA studies is very limited,partially due to the small relative risk associated to the variants and partially due to the failure of functional correlation of the new polymorphisms with the disease biological toxic mechanisms.

Thus, the interest of the researchers in the identification of potential risk factors is to use this information for developing interventions to prevent or delay the onset of dementia as well as identifying special high-risk populations who could be targeted in clinical trials.

EPIGENETICS

Given that AD is characterized by a complex etiology, it cannot be explained only by genetic factors [Figure 1].

Some studies have suggested that the majority of AD cases is maybe due to interactions between genetic and environmental factors leading to an increasingly emerging research area: the study of epigenetics [37]. The epigenetic modifications, such as DNA methylation and chromatin remodeling, are induced by environmental exposure during life and could explain the development of neurodegeneration. The individual lifestyle and the aging processes have been accepted as important epigenetic modulator and, consequently, as modifier of the risk to develop complex diseases. Some studies have investigated a possible epigenetic implication in typical AD processes, such as Aβ peptide deposition. The most epigenetic process studied in AD is the DNA methylation that occurs through a covalent addition of a methyl group on cytosine

located in CpG island (cluster of cytosine-guanidine dinucleotides) to form 5-methylcytosine (5mC). Predominantly, CpG island are found in gene promoter regions and their methylation is involved in gene expression, causing gene silencing or gene inactivation [38]. In particular, the relationship between alteration of DNA methylation and the AD development has been analyzed, with contrasting results [39-41]. In fact, the epigenetic studies are strongly dependent on experimental approaches, samples analyzed and techniques used. The majority of these studies are based on cell lines or human post-mortem tissue, sometimes using restricted samples number. The first study deals to epigenetic regulation in one of AD genes (APP) was done in 1990 [42]. Since then, the DNA methylation of the APP promoter was studied in different brain area (frontal cortex, temporal cortex, parietal cortex and hippocampus) [42-45]. All these studies have demonstrated a hypomethylation in the promoter of APP and no differences were found in the analyzed brain area. Similarly, the promoter of PSEN1 is regulated by DNA methylation and in AD patients resulted to be hypometylated [46]. The hypomethylation induces an over-expression of the protein and, consequently, an imbalance of Aβ production [47]; however, it has not been observed in specific brain area, such as frontal cortex and hippocampus [44,45]. For this reason, up to now, it is not yet clear if an altered DNA methylation pattern in LOAD brain tissue could play a key role in Aβ processing [46]. Moreover, conflicting results were obtained also in peripheral blood respect to the several postmortem analyses. In particular, the promoters of APP and PSEN1 genes resulted strongly hypomethylated but, contrary to brain tissue, at the peripheral level the DNA methylation in AD patients was significantly increased with respect to the methylation observed in controls [48].

The other important epigenetic mechanism, the histone modification, has been less studied in AD and, as for DNA methylation, the obtained results are conflicting. Different studies revealed, in AD post mortem brain samples, that histone acetylation levels could be lower, equal and higher with respect to healthy subjects [49-52].

Therefore, although promising, the contrasting results and the still undeveloped approaches make the epigenetic studies inconclusive and need to be increased.

GENETIC COUNSELING

The growing of the new and faster genetic technologies focuses the attention on the management of the information about genetic testing. To date, in Italy, no standards and consensus guidelines are available for genetic counseling in the field of dementia, in particular for familial AD cases.

The genetic tests have important ethical, social, legal and psychological implications not only for the single patients but also for the whole family. In fact the identification of a genetic mutation in a patient could present the possibility that other consanguineous family members could be carriers and possible future patients [53-56]. Thus, genetic testing is recommended to be offered only after a proper genetic counseling procedure [57] and, up to now,following the protocol established for Huntington's disease is recommended [58].

The mail goal of the genetic counseling in AD is to help patients and their relatives to understand the clinical implications of the genetic variants that could be identified by the DNA test. The counselor has to be able to explain clearly the disease with the hereditary consequences and should provide the right information about the decision to undergo the genetic analyses.

The genetic counseling protocol makes a distinction if subjects are symptomatic or at-risk relatives [59]. The genetic test for symptomatic patients has the purpose to confirm the clinical diagnosis, the procedure contemplates two tests–consultations, one pre-test and one post-test the blood collection and then three follow up. Obviously the number of meetings can be modified according to the patient requests and needs. For predictive genetic test in at- risk relatives, the protocol provides two consultations pre-test, evaluating the psychological aspects that a potential identification of a genetic dominant mutation could represents; after the visit for the blood sample collection, post-test meetings are planned either after one week than in the three following months [59]. Genetic analyses has ethical, social and psychological implications for patients and their families so it's recommended that so delicate information has to be managed by an expert team of specialists, including neurologists psychiatrists and geneticists.

NEW APPROACHES FOR STUDY: CONSORTIA AND INNOVATIVE MOLECULAR MODELS TO STUDY AD

In 2011, four of the largest AD research Consortia — the Alzheimer's Disease Genetics Consortium (ADGC), the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), the European Alzheimer Disease Initiative (EADI), the Genetic and Environmental Research in Alzheimer Disease (GERAD) consortium- created thefirst international collaboration on Alzheimer's disease genetics. In particular the partnership called IGAP (international genomics of Alzheimer's disease) was finalized to discover and map the genes involved in Alzheimer's disease.

Several Universities from Europe and United States are involved and share abundant information on common database including clinical, neuroimaging and genetic data of several thousands of subjects.

DIAN (Dominantly Inherited Alzheimer Network) [60] is another international research partnership of scientists who are interested in understand better the genetic and pathogenic processes in Familial Alzheimer's disease forms. The mail goal is to provide clues useful also to decode other dementias and develop future clinical and pharmacological treatments.

Funded by a grant from the National Institute on Aging, DIAN currently involves fifteen outstanding research institutions in the United States, Australia, Europe, Asia and South America.

Induced pluripotent stem cell (iPSC) technology can provide novel opportunities to study cellular mechanisms and provide therapeutic strategies against Alzheimer's diseases [61].

In 2011 Yagi and colleagues [62] demonstrated that human somatic cell could be reprogrammed tocreate a neuronal model of ADalso carrying PSEN1 and PSEN2 gene mutations. They generated iPSCs from fibroblasts of FAD patients with mutations in PSEN1 (A246E) and PSEN2 (N141I), and characterized the differentiation of these cells into neurons. They found that FAD-iPSC-derived differentiated neurons increased toxic amyloid β secretion, recapitulating the molecular pathogenesis of mutant presenilins. Moreover, the secretion of toxic amyloid β peptide from these neurons sharply responds to γ-secretase inhibitors and modulators, indicating their potentiality to identify and validate new candidate drugs. These data demonstrate that the FAD-iPSC-derived neuron is a valid model of AD and provides an innovative strategy for the study of the disease.

FUTURE PERSPECTIVE

The genetic approach, in particular genomic, epigenomic, transcriptomic, proteomic, and metabolomics, together with the environmental factors and concomitant pathologies are determinant for AD progression and the efficacy of drugs treatments [63-65].

Genetic factors are potentially involved in pharmacogenomics of AD, including candidate genes associated with disease pathogenesis (*APP, PSEN1, PSEN2, MAPT, APOE*) and genes associated with the mechanism of drugs action and metabolism [66].

The most confirmed gene in AD pharmacogenetics is the Apolipoprotein E (*APOE)* gene.

In fact several studies have provided evidence that *APOE* polymorphisms may influence the therapeutic response to anti-dementia drugs [67].

Taking advantage also from genetic studies, the main goal for the research in the future will be:

1) to understand the pathogenesis of AD, 2) to characterize biomarkers for an early identification of pre-symptomatic subjects, 3) to develop preventive strategies to stop the disease progression in asymptomatic patients 4) to identify specific neuronal targets susceptible of therapeutic intervention, 5) to get pharmacogenomic and pharmacoepigenomic strategies for drug development.

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