THE BEGINNINGS OF ALZHEIMER'S DISEASE: A REVIEW ON INFLAMMATORY, MITOCHONDRIAL, GENETIC AND EPIGENETIC PATHWAYS

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Perna S., C. Bologna, P. Cavagna, L. Bernardinelli, D. Guido, G. Peroni, M. Rondanelli (2016): *The beginnings of Alzheimer's disease: a review on inflammatory, mitochondrial, genetic and epigenetic pathways.-* Genetika, Vol 48, No. 2, 515-524.
Alzheimer's Disease (AD) is the most common cause of sporadic dementia, as it affects 60% of cognitive impaired patients; it commonly affects middle and late life, and it is considered an age-related disease. Early-onset familial AD is associated with mutations of the genes encoding amyloid precursor protein (APP), presenilin 1 (PS-1), or PS-2, resulting in the overproduction of amyloid beta-protein. Epidemiological and case-control studies have led to the identification of several risk factors for sporadic AD. The most concrete genetic risk factor for AD is the epsilon4 allele of apolipoprotein E gene (APOE). In addition, several genes such as CTNNA3, GAB2, PVRL2, TOMM40, and APOC1 are known to be the risk factors that contribute to AD pathogenesis. A direct role of interaction between genetic and environmental determinants has been proposed in an epigenetic dynamic for environmental factors operating during the preconceptual, fetal and infant phases of life. Also the the association between mtDNA inherited variants and multifactorial diseases and AD has been investigated by a number of studies that, however, didn't reach a general consensus on the correlation between mtDNA haplogroups and AD
        Keywords: genetics, epigenetics, Alzheimer, dementia, mitochondrial genome, genes

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INTRODUCTION

Alzheimer's Disease (AD) is the most common cause of sporadic dementia, as it affects 60% of cognitive impaired patients; it commonly affects middle and late life, and it is considered an age-related disease. In 2010, 35.6 million people affected were estimated, and there is 7.7 million of new cases/year. The Italian situation is characterized by about a million cases, involving in the 60% people with more than 80 years. In the next 20 years there is an increasing incidence of about 50%, and cases will double in 2050 (PRINCE *et al,* 2011)

The typical symptoms are difficulties in remembering names and recent events in an early stage, together with apathy and depression. Lately other behavioral findings are expressed, like impaired judgment, disorientation, confusion, behavior changes, and difficulties in speaking, swallowing, and wandering. In the latest phase of disease, the patient is unable to communicate and to provide to its basic needing, requires constant care and in most cases dies because of systemic diseases.

There are typical hallmark abnormalities from an histopathological point of view, as deposits of the protein fragment beta-amyloid (extracellular plaques) and twisted strands of the tau protein (extracellular neurofibrillary tangles) (ALZHEIMER'S ASSOCIATION, 2012).

GENETICS PATHWAYS

While the single etiological events that lead to AD have not been clearly resolved, it is now generally accepted that genetic factors clearly play a major role in AD by an age-dependent dichotomous model (TANZI, 1999). On one hand, early-onset (<65) familial AD (EOFAD) is caused by defects in any of three different genes: the amyloid β protein precursor (APP) on chromosome 21 (GOATE *et al.,*1999) the presenilin 1 (PSEN1) on chromosome 14, (SHERRINGTON *et al.,*1995) and the presenilin 2 (PSEN2) on chromosome 1 (ROGAEV *et al.,* 2002; LEVY-LAHAD, *et al.,*1995). These mutations are rare and highly penetrant in early-onset familial AD, they are transmitted in an autosomal dominant fashion and have contributed greatly to our current knowledge of the pathogenesis of AD, as they result in specific phenotypic profiles to patients with dementia: the amyloidogenic pathology associated with APP, PSEN1, andPSEN2 (SELKOE and PDLISNY, 2009). Mutations in the tau gene (MAPT) with taupathy, progranulin gene (PGRN) and charged multi-vesicular body protein 2B gene (CHMP2B) and alfa synucleolin gene are associated with other or concomitant forms of dementia as the autosomal dominant form of frontotemporal dementia (FTD) (SPILLANTINI *et al.*, 1998; CRUTS *et al.*, 2006), the Lewy body dementia (LBD) (TSUANG *et al.*, 2004; HARDING *et al.*, 2004) and parkinson disease dementia PDD (POLYMEROPOULOS *et al.*, 1997; ZARRANZ *et al.*, 2004). More complex is the characterization of genetic risk factors for late-onset AD (LOAD). (LOAD) represented by sporadic forms not familiar forms and load age> 65, o which represents the vast majority of all AD cases (HOENICKA, 2006). Despite more than 500 association studies have been performed on candidate genes (in case control or family-based studies with different ethnic populations) and GWAS, genome wide analysis, our actual knowledge is based on a group of about 200 genes that have been tested and probed to associate significatively with AD patients (BERTRAM *et al.*, 2007) . Among susceptibility genes the apolipoprotein E (APOE) gene (19q13.2) (AD2) is the most prevalent risk factor for AD especially in those subjects harboring the APOE-4 allele (SAUNDERS *et al.*, 1993; STRITTMATTER *et al.*, 1993) whereas carriers of APO E-2 allele might be protected against dementia (CORDER *et al.*, 1994). In contrast to other association base findings in AD, the risk factor APOE-4 has been consistently replicated in a large number of studies across many ethnic groups, between

approximately 3 and 15 for heterozygous and homozygous carriers, respectively, of the E4 allele (BERTRAM *et al.*, 2007).

APOE-related pathogenic mechanism are also associated with brain aging and with neuropathological hallmarks of AD. Unlike the mutations in the known EOFAD genes, APOE-ε4 is neither necessary nor sufficient to cause AD but operates as a genetic risk modifier. Carriers of the APE-4 genotype show different conditions in biochemical and clinical markers as higher blood pressure and LDL-cholesterol levels, reduced blood histamine levels in brain, brain hemodynamics atrophy markedly increased, faster cognitive deterioration, and the age at onset is 5−10 years earlier in approximately 80% of AD cases harboring the APOE-4/4 genotype by decreasing the age of onset in a dose-dependent manner (CACABELOS *et al.*, 2012). The results of various researches show nevertheless a not constant effect of APOE genotypes among different ethnic groups: African sub-Saharan population, African American, other population of West African ancestry and Hispanics show a weal and inconsistent association with AD. There is a robust association between APOE genotype and AD in Europeans and south Asians (KALARIA *et al.*, 2008; FARRER *et al.*, 1997). Besides APOE gene more genetic factors are indubitably involved in AD and act as risk factors in other association base findings. Till recently the findings of this gene were not consistently replicated in a large samples or results of association studies demonstrated controversial (BERTRAM *et al.*, 2007). In the last four years nevertheless new important discoveries from large scale GWAS have put in evidence more important polymorphic genes as Clu PICALM CR1 (HAROLD *et al.*, 2009; CARRASQUILLO *et al.*, 2010).

BIN1, MS4A, CD2AP, CD33, ABCA7 EPHA1 from the NIA-ADGC (OLIVERAS-LÓPEZ *et al.*, 2013) even associate with episodic memory performances (BARRAL *et al.*, 2012).

These discoveries show new directions in AD research and underscored the role of oxidative stress, chronic inflammation, immune system, lipid and cholesterol metabolism, synapse and molecular trafficking, as relevant genomic pathways and subject of further investigations (GUERRIERO *et al.*, 2015; VENTURINI *et al.*, 2015).

Newly discovered genes appear to act not in an isolated manner but in a pattern of interconnection: The meta-analysis of Jun *et al.* (JUN *et al.*, 2010) from 12 different studies, including white, African American, Israeli-Arab, and Caribbean Hispanic individuals has confirmed that CR1 PICALM and CLU are AD susceptibility loci in European ancestry populations, but also that genotypes at PICALM confer risk predominantly inAPOE-4-positive subjects. Thus, APOE and PICALM synergistically interact (JUN *et al.,* 2010). In addiction the work of RAJ *et al.* (2012) showed that PICALM, BIN1, CD2AP, and EPHA1 are interconnected through multiple interacting proteins and appear to have coordinated evidence of selection in the same human population, suggesting that they may be involved in the execution of a shared molecular function (RAJ *et al.,* 2012).

GENES IN THE IMMUNE INFLAMMATORY PATHWAY

Recent GWAS analysis has underscore the role of newly discovered genes in the immune inflammatory pathway to AD: CR1, CD33, MS4A4E MS4A6A.

CR1: function appears linked to innate and adaptive immunity as it and plays an important role in the regulation of the complement cascade and clearance of immune complexes, particularly hose opsonised by complement components C3b and C4b (KHERA *et al.*, 2009) CR1 may pay a dual role in AD pathogenesis as it is involved in the clearance of Aβ and it has been reported in neuroinflammation, which is a prominent feature in AD (CHREHAN *et al.*, 2011).

CD33.This gene encodes a protein that act as a transmembrane receptor containing immunoglobulin domains, expressed on cells of myeloid lineage that binds extracellular sialylated glycans. (GARNACHE-OTTU *et al.*, 2005; CAO and CROCKER, 2011).

In the immune response, CD33 should act as an inhibitory receptor upon ligand induced tyrosine phosphorylation by recruiting cytoplasmic phosphatase(s) via their SH2 domain(s) that block signal transduction through dephosphorylation of signaling molecules. CD33 also induces apoptosis in acute myeloid leukemia (in vitro) (CROCKER *et al.*, 2008). CD33 has primarily been studied in peripheral immune system where appears to inhibit proliferation of myeloid cells; It is expressed on myeloid progenitors and monocytes and also in the brain (VON GUNTEN and BOCHNER, 2008).

MS4A4E MS4A6A. They encode proteins with multiple membrane-spanning domains that were initially identified by their homology to CD20, a B-lymphocyte cell surface molecule. (ISHIBASHI *et al.*, 2001). The functional products of these are considered receptors integral to membrane; the MS4A4A gene is expressed in myeloid cells and monocytes and has holmology to CD20 gene, for this is believed to act with an immune-related function, as possibly other members of this protein family (LIANG and TEDDER, 2001).

There are other pathways that have been highlighted by GWAS analysis: for example lipid metabolism and cholesterol that is strongly supported by the APO E gene and by many others newly discovered genetic factors as CLU, ABCA7, and ACE, SORL1.

Endocytosis and trafficking -synaptic cell membrane that is underscored by genetic factors as BIN1, PICALM and CD2AP. These pathways are not strongly linked to the amyloid hypothesis that has driven so much recent thinking and open up avenues for intensive research with regard to the potential for therapeutic intervention (JONES *et al.,* 2010; MORGAN, 2011).

EPIGENETICS PATHWAYS

The total heritability of the more common non Mendelian form of AD has been established in the work of GATZ *et al.*, (2006) using the largest population -based twin study. Results show that it is still very high, with estimates ranging from 60 to almost 80% in the best fitting model, leaving the remainder to environmental factors (GATZ *et al.,* 2006). This work shows in particular a strong probandwise concordance for twins couples in dementia and AD. This concordance is higher in monozygotic men (44% tot dementia 45% AD) in monozygotic women (58% tot dementia, 61% AD), weaker in dizygotic men (25% tot dementia, 19% AD) and women (45% tot dementia, 41% AD). More over the same genetic factors appears to be influential for both men and women. These values confirmed the importance of genetic factors that previous twin studies have put in evidence (RAIHA *et al.,* 1996; BERGEM *et al.,* 1997) and in particular by the Duke Twins Study of Memory in Aging with values of concordance of about 40% for AD monozygotic twins and 20 % for dyzigotic twins, and some twin pairs, in which the one twin remains unaffected even 19 years after the onset of Alzheimer's disease in the other twin (PLASSMAN *et al.,* 2006). Twin studies demonstrate a high but not perfect concordance as a result of genetic homology, and that a large part of differences between twins is to be explained by a complex interaction between genetic and environmental factors, that eventually results in the pathology.

In particular analysis of function and degeneration of brain obtained by MRI voxel appear to show a different action of genes and environment on the manifestation of AD pathology.

The work of JARVENPAA *et al.* (2004) showed that in monozygotic twins pairs discordant for AD, the affected twins has mesial temporal hippocampal areas altered by the disease while the neocortical areas result less degenerated. Neocortical areas are indeed considered less influenced by environmental factors and twins difference in brain mesiotemporal areas appear the results of action of non-genetic factors (THOMPSON *et al.,* 2001). These results are correlated in the work of FRISONI *et al.* (2005) with the type EOD or LOAD of Alzheimer's disease: in patients EOD, where it is believed that the genetic determinants are stronger neocortical areas have altered, whereas in patients LOAD are the areas mesiotemporal to present more alterations, as a possible result of interaction with effects environment. A direct role of interaction between genetic and environmental determinants has been proposed in a epigenetic dynamic for environmental factors operating during the preconceptual, fetal and infant phases of life (GLUCKMAN and HANSON, 2004). This events would have been a LEARN (latent early life associated regulation) alteration affecting the expression of genes associated with later manifest condition (LAHIRI *et al.,* 2007). The pathological manifestations in AD patients may have proceeding initiating events occurred in early stages of brain development. In particular a direct role for metal exposition has been proposed for animal models and human studies. The environmental exposure of rats to the metal Pb from birth to postnatal day 20 showed a delayed over-expression of APP an elevation of its amyloidogenic Aß product in old age (BASHA *et al.,* 2005). The exposure to metal lead of infantile cynomologous monkeys (Macaca fascicularis) underlighted a clear correlation to Alzheimer's disease like pathology, with amyloid plaques and elevated expression of amyloid pathway genes (APP BACE1 SP1), in aged individuals (WU *et al.,* 2008).

Moreover both APP and BACE 1 gene promoters in the amyloid pathway are rich in CpG dinucleotides and GC box elements, making them a subject to epigenetic reprogramming and transcriptional regulation via DNA methylation parhways (LAHIRI *et al.,* 2007).

The possibility that developmental exposure to Pb could result in the formation of AD pathology in humans is further supported by findings in a patient that survived from severe Pb toxicity at 2 years of age, but died of severe mental deterioration with senile plaques and NFT (neufibrillar tangles) at the age of 42 (NIKLOWITZ and MANDYBUR, 1975).

MITOCHONDRIAL PATHWAYS

Given the fundamental contribution of the mitochondrial genome (mtDNA) for the respiratory chain, the association between mtDNA inherited variants and multifactorial diseases and AD has been investigated by a number of studies that, however, didn't reach a general consensus on the correlation between mtDNA haplogroups and AD (ELSON *et al.,* 2006). Mitochondrial respiratory chain (MRC) impairment has been in fact detected in brain, muscle, fibroblasts and platelets of Alzheimer's patients, indicating a possible involvement of mitochondrial DNA (mtDNA) in the aetiology of the disease (GRAZINA *et al.,* 2006; COSKUN *et al.,* 2004). mtDNA mutations through heteroplasmic transmission might modify age of onset of the disease, conferring phenotypic heterogeneity and contributing to the neurodegenerative process, probably due to an impairment of MRC and/or translation mechanisms (LIN *et al.,* 2002). Moreover an interaction between APOE polymorphism and mtDNA inherited variability in the genetic susceptibility to sporadic AD has been proposed (CARRIERI *et al.,* 2001).

More specifically It has been proposed that LOAD or sporadic Alzheimer's disease (SAD) can be caused by defects in mitochondrial oxidative phosphorylation (OXPHOS) (NUNOMURA *et al.,* 2006). Structurally abnormal mitochondria have been observed in AD brains,

(CASTELLANI *et al.,* 2001) and deficiencies in mitochondrial OXPHOS enzymes, such as cytocrome c oxidase, have been repeatedly reported in the brains and other tissues of AD patients (BOSETTI *et al.,* 2002; COTTREL *et al.,* 2002). Defects in OXPHOS inhibit ATP production, but also increase mitochondrial reactive oxygen species (ROS) production, which, in turn, can damage the mitochondrial genome (mtDNA). Thus, this hypothesis on AD pathogenesis claims that mitochondrial impairment may result from accumulated mtDNA damage that accompanies normal aging, amplified by disease-specific factors (NUNOMURA *et al.,* 2006; GIBSON *et al.,* 1998).

Genetic variation in the hPreP gene PITRM1 might contribute to mitochondrial dysfunction in AD: the human presequence protease (hPreP) was recently shown to be the major mitochondrial Aβ-degrading enzyme, and genetic variation in the hPreP gene PITRM1 has been investigated by PINHO *et al.* (2010). Results underscore the role of hPreP (A525D) variant, corresponding to rs1224893, that shows only 20–30% of the wild-type activity. Recent data suggest the possible contribution of heme deficiency to the progressive derangement of mitochondria in the AD brain: In the study of VITALI *et al.* (2009) cytochrome c oxidase COX 15 and COX 10 mRNA were not equally distributed in the brain of AD patients and controls. Other studies on mitochondrial haplogroups show association between AD patiens and specific genetic polymorphism: in japanese AD patients the work of TAKASAKI (2009) put in evidence an association with AD disease with haplogroups G2, B4c1 and N9b1; SANTORO *et al.* (2010) found that sub-haplogroup H5 is a risk factor for AD, particularly in females, independently of the APOE genotype.

CONCLUSION

Identification of risk factors for AD would contribute to the understanding of AD pathogenesis and thus, help in the development of preventive methods, also in consideration of the fact that an effective drug therapy is lacking today. A number of susceptibility genes, epigenetic factors and environmental factors may all contribute to the development of the disease.

Early-onset familial AD is associated with mutations of the genes encoding amyloid precursor protein (APP), presenilin 1 (PS-1), or PS-2, resulting in the overproduction of amyloid beta-protein. Epidemiological and case-control studies have led to the identification of several risk factors for sporadic AD. The most concrete genetic risk factor for AD is the epsilon4 allele of apolipoprotein E gene (APOE). In addition, several genes such as CTNNA3, GAB2, PVRL2, TOMM40, and APOC1 are known to be the risk factors that contribute to AD pathogenesis.

Research advances in AD help us understand the complex genetic and epigenetic makeup and environmental interactions, as well as their effects on the natural history of dementia.

Finally, the evidence that supports a critical role of mitochondria in neurodegenerative diseases and AD in particular is compelling.

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POČETAK ALZHAJMEROVE BOLESTI: PREGLED INFLAMATORNIH, MITOHONDRIJALNIH, GENETIČKIH I EPIGENETIČKIH PUTEVA

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Izvod

Alzhajmerova bolest (AD) smatra se kao bolest vezana za starosno doba. Rani početak porodične pojave AD je vezana sa mutacijom gena koji kodiraju amiloidne prekursore proteina (APP), presenilina 1 (PS-1), ili PS-2, što kao rezultat izaziva prekomernu sintezu amiloidnog beta proteina. Epidemiološka ispitivanja koja su uključivala i slučajeve kontrole su dovela do identifikacije nekoliko faktora rizika za sporadični slučaj AD. Najkritičniji faktor rizika za pojavu AD je epsilon4 alel gena E koji kodira apolipoprotein (APOE). Najkritičniji genetički faktor rizika za AD epsilon4 alel E gena kao i nekoliko gena kao što su CTNNA3, GAB2, PVRL2, TOMM40, i APOC1, poznati kao faktori rizika za AD patogenezu. Takođe, nasleđena asocijacija između mitohondrijalne DNK i multifaktorijalnih bolesti i AD je bila ispitivana u brojnim studijama koje, međutim nisu dostigle generalni koncensus o korelaciji haplogrupa mitohondrijalne DNK i AD.