# CURRENT STATUS OF KNOWLEDGE ON ALZHEIMER'S DISEASE GENETICS

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**Abstract:** As the entire human being works as a perfectly balanced whole, each and every disturbance at any level brings other disturbances, like a chain reaction to superior levels, the current researches aim for the molecular aspects of any physiological disorders. It is well possible that any physiological reaction is not the cause of a disease but an effect of molecular disturbances in biochemical and genetic mechanisms responsible for a feature or behavior exhibit. The exact causes of Alzheimer's disease are mostly unknown, excepting 1 to 5% cases notably identified with obvious genetic variance. In the scientific world, there are many hypotheses that explain the occurrence of Alzheimer's disease: amyloidal hypothesis, taupathy hypothesis, cholinergic hypothesis and so on, but from all of these it seems that the molecular/genetic hypothesis is the most studied of all, because of its relevance to the true pathological mechanism. It seems that some allelic variants and mutations of genes that encode important regulatory molecules in neuronal activity may give a certain predisposition to Alzheimer's disease or to other neurodegenerative diseases, even in young individuals. One good example is the APOE gene that encodes a surface component of triglyceride reach lipoproteins. At the neuronal level, this glycoprotein has an important role in lipid distribution during nerves growth and repair. The APOE gene exists in three allele variants present in human population in different proportions (ε2, ε3, ε4) which in different combinations give to the carrier various predispositions to cholesterol and triglycerides mechanisms disorders, Levy's bodies dementia and Alzheimer's disease (ε4 allele).

## INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative pathological state which occurs mostly due to aging and exhibits varying symptoms by individual, physiological, neurological, psychical, biological and molecular conditions. This process alters one's cognitive functions of brain leading to intellectual abilities and even social behavior and individual personality loss (ADA, 2007). Alzheimer's disease is characterized by heavy behavior disorders which lead the public thinking to a misused pseudonym senile dementia, from the Latin *demens*, meaning insane or demented. This condition is the most common form of mental decline in elders (ART, 2008). It is believed that it is increasingly common because of the longer sustainability of life, much longer than average life expectancy. As every part of the body, during aging, the brain is also affected, but slower than the others. As long as the drug therapies and life styles prevents body degeneration, brain degeneration often get to be visible in elder behavior (as dementia got to be called loss of mind, or doting, associated with the brain degeneration followed by functions loss – memory, cognition, poorly developed in small children) (NIA, 2011). It is also believed that during ancient and past times, this disease was very rare, death occurring from degeneration of other organs (guts, lungs, heart, muscles), this being the explanation why Alzheimer's disease was poorly described in history (Berchtold and Cotman, 1998).

In present, Alzheimer's disease is one of the most severe neurodegenerative diseases because its cause and progression are yet to be discovered. More than that, is seems that almost all elders over 85 years old exhibit Alzheimer's disease characteristic symptoms; it is highly incurable and irreversible, unstoppable and unpredictable (Mölsä *et al.*, 1986; Brookmayer *et al*., 2007, NIA, 2007). Although the main condition that precedes the neuropsychiatric symptoms is the beta-amyloid plaques (βAP) and neurofibrillary tangles (NFT) accumulation, it is possible that the molecular mechanisms behind this process might be slightly different, in molecular terms. It is highly possible that intraneuronal and extraneuronal accumulations have different origins, as a study on differential preference for small molecules to aggregate in cellular compartments shows (Brookmeyer *et al.*, 1998). The present review aims to motivate further investigations of Alzheimer's disease genetics due to its immense complexity and importance in determining the true Alzheimer's disease's etiology so that finnaly an efficient treatment can be found.

## MOLECULAR MECHANISMS INVOLVED IN ALZHEIMER'S PATHOLOGY

Alzheimer's disease was firstly described as "presenile dementia" based on the observations made by the German psychiatrist Alois Alzheimer on a patient who exhibited a progressive loss of cognitive functions and died shortly. During autopsy, Alzheimer observed the brain using histological methods and described features as it follows: "Numerous small

milliary foci are found in the superior layers. They are determined by the storage of peculiar material in the cortex" (Maurer *et al*,. 1997). Alzheimer continued: "All in all we have to face a peculiar disease process. Such peculiar disease processes have been verified recently in considerable numbers". "Milliar foci, which are caused by deposition of a peculiar substance in the cortex" were lately defined as senile plaques and "very peculiar changes in the neurofibrils" as the helical tangles. These molecular aggregations Alzheimer observed back then remain the main explanation of pathogenesis of Alzheimer's disease even though other very important molecular, genetic and epidemiological hypotheses were expressed (Povova *et al.*, 2012). The main problem of the explanation of pathology of Alzheimer's disease still could be seen in the inability to identify key mechanisms that release pathologies observed in Alzheimer's disease.

Amyloid plaques (βAP) often occur in association areas cortex and are associated with cell synapse endings. Neurofibrillary tangles (NFT) are characteristic to entorhinal cortex (median part of the temporal lobe) and affect cortico-cortical projection origin cells (Hoff, 1997). The first neurons that succumb due to NFTs are cholinergic Meynert basal nuclei, entorhinal pyramidal neurons and hippocampal neurons (Morrison *et al.*, 1997). βAP are a permanent characteristic to Alzheimer's but NFTs do not always occur, meaning that it is highly possible that βAP are also a effect or a collateral damage. βAP affect sensorial, motor and association areas, but NFTs only association one, meaning that NFTs only affect long distance interactions (Gomez-Isla *et al*., 1997). As another argument, tau protein, major NFT component, is not present in dendrites and is active primarily in the distal portions of axons where it provides microtubule stabilization but also flexibility as needed. While βAP aren't always associated with neuron death, NFTs are the main cause of Alzheimer's type degenerescence (Rapaport *et al.*, 2002). More than that, it has been shown that MAPT knock down mice are resistant to βA toxicity [idem]. So it is possible that changes occurred in tau protein pathway to be caused by βA which triggers the activation of some specific kinases and phosphorilases (Rapaport and Ferreira, 2000).

The way βA and other small peptides are formed through APP cleavage can be understood through precursor protein structure. It is consisted in several active domains situated both extracellular, intracellular and intramembranar. It is thought that the small domains growth factor-like and bind to copper ions, closely related, are the key domains in cleavage promotion. There are many APP isoforms but the brain isoform shows no specific serin protease inhibitor domain probably because the brain associated mechanism is independent to kinasic regulation (De Stooper and Annaert, 2000). Although it has been shown that βA triggers a certain type of apoptosis, through a kinase cascade mechanism, this fact is important because it says that brain isoform cannot be regulated by external specific pathways' factors.

After synthesis, APP undergoes a serie of posttranslational maturation events such as glycosylation, phosphorylation and tyrosine residue sulfonation. Proteolytic action is due to a suite of proteolytic specific enzymes: α, β and γ secretases. Both α and β secretases lead to C-terminal end cleavage partly associated with apoptosis. Next to this action, γ secretase triggers transmembrane domain cleavage in βA and βA-like fragments (De Stooper and Annaert, 2000). The amyloidogenic processes are highly associated with membrane phospholipids presence. As the γ secretase activity is conditioned by the β secretase one, only after C-terminal end was cleaved, γ secretase can be activated. More than that, γ secretase is also activated only in presence of cholesterol and apoE. That led to the theory that Alzheimer's can be triggered by high concentrations of cholesterol and low activity of apoE (inheritance of disabilited apoEε4 variant) (Vetrivel *et al.*, 2004).

Tau protein is a highly soluble microtubule-associated protein (MAP) also essential in Alzheimer's pathology, the major component of NFTs. In humans, these proteins are found mostly in neurons compared to non-neuronal cells. One of tau protein's main functions is to modulate the stability of axonal microtubules. Other nervous system MAPs may perform similar functions, as suggested by tau knockout mice that did not show abnormalities in brain development - possibly because of compensation in tau deficiency by other MAPs (Harada *et al*. 1994). Tau proteins interact with tubulin to stabilize microtubules and promote tubulin assembly into microtubules.

Tau has two ways of controlling microtubule stability: isoforms and phosphorylation. Hyperphosphorylation of the tau protein can result in the self-assembly of tangles of paired helical filaments and straight filaments, which are involved mainly in the pathogenesis of Alzheimer's disease (Alonso *et al.*, 2001). All of the six tau isoforms are present in an often hyperphosphorylated state in paired helical filaments from Alzheimer's disease brain. In other neurodegenerative diseases, the deposition of aggregates enriched in certain tau isoforms has been reported. When misfolded, this otherwise very soluble protein, it can form extremely insoluble aggregates that contribute to a number of neurodegenerative diseases (Hall, 2011; Saman and Hall, 2011).

## GENES INVOLVED IN ALZHEIMER'S PATHOLOGY

Regarding the effects and the course of the molecular mechanisms discussed, the genes involved in Alzheimer's pathology are to be described according to the encoded product's role. Therefore there are genes that encode the substrate proteins (APP or tau protein), the enzymes that cut them (PSEN1 and PSEN2 as domains of the γ secretase complex) or other genes that encode for proteins or receptors encountered alongside (APOE, TREM2). Thus the genes involved directly in Alzheimer's pathology are generically called deterministic genes and their mutations cause early onset

Alzheimer’s disease, a dominant autosomal inherited Alzheimer’s type, familial and extremely rare. The other genes involved in Alzheimer’s pathology but not directly are called risk factors and their mutations cause a vulnerability of their carrier to developing Alzheimer’s pathology. Whether they have deficits in cholesterol metabolism, whether ‘brain maintenance cells’ get a disability in ‘cleaning’, risk factors give the opportunity to certain mechanisms to be disturbed and the effects to disseminate like a chain reaction until they reach the mechanisms involved in Alzheimer’s pathology.

APP and PSEN1 and 2 genes

APP and PSEN genes are involved directly in Alzheimer’s pathology by being the main genes that encode the substrate and the enzymes that lead to the main product of which accumulation cause plaques and Alzheimer’s symptoms: the amyloid precursor protein’s gene and the presenilin 1 and 2 genes, key domains of the γ secretase complex.

APP gene, a highly conserved ancestral gene, is localized on the 21$^{st}$ chromosome’s long arm encodes the protein that by its cleavage leads to amyloid synthesis – a membrane protein classified as a endogenous ligand (Yoshikai *et al.*, 1990; Sarkar and Tharp, 2013). Along its 18 exons, it carries coding informations regarding the structure and the functions of APP and more importantly, its variants arose by alternative splicing of the transcript (Lamb *et al*., 1993). In human, alternative splicing of APP gene transcript is tissue characteristic arising certain protein isoforms specific to brain, medulla and other tissues. It is believed that certain changes in isoforms proportions lead to Alzheimer’s disease (Zheng and Koo, 2006). It also seems that APP binds to surface proteins in order to regulate cell adhesivity. Studies show that in brain APP regulates neuron migration during early ontogenesis.

In spite of its high gene sequence conservation, it has been shown that the amino acids sequence of the intramembrane domain is highly variable (Goate *et al.*, 1991). The mutations which occur in βA generating domain and other important APP domains cause familial Alzheimer’s disease characterized by highly dense and thick amyloid plaques (Murrell *et al.*, 1991). The mutations in the regulating or intronic gene sequences are associated with high amounts of APP and βA synthesized (Chartier-Harlin *et al.*, 1991).

The most common APP gene mutation is a substitution that leads to protein structure change (Val717Ile) (Talarico *et al.*, 2010) and it is associated with early onset Alzheimer’s disease. Some mutations cause an aberrant protein synthesis, longer and highly adhesive. When the high amounts of normal or aberrant APP are being cleaved and excreted outside the cells, they accumulate and block mostly synaptic gaps. Also a highly toxic protein fragment can appear that can trigger an apoptotic mechanism.

Nevertheless it has been shown that there can appear protective mutations. It is the case of the A673T mutation, a substitution contiguous to β secretase cleavage site that cause a decrease by 40% of in vitro βA formation (Citron *et al.*, 1992).

It has been proven that any variation in transcription promoting sequences can alter gene expression and therefore alter the normal mechanisms which can give a susceptibility to many neurodegenerative diseases. These promoter sequences are located in the immediate vicinity of the main regulation sequence and of the upstream 5’ region.

The PSEN genes encode two important proteins, presenilin 1 and presenilin 2 – components of the secretasic complex, and have a remarkable sequence similarity. They are localized on the 14$^{th}$ and 1$^{st}$ chromosomes, respectively. Studies show that both nitrogenous base gene sequence and amino acids expression product successions are very similar for both PSEN1 and PSEN2. Also, the splicing mechanism, functions, structure but not regulating sequence, are almost identical. Each gene is consisted of 13 exons of which 10 encode the proteins’ sequences. Regulating sequences are consisted by the first three exons of the PSEN1 gene and the last three of PSEN2. By the fact that intron-exon jonctions are also almost virtually identical, it is believed that these two genes derive from the same ancestral gene which was duplicated during evolution and speciation, equivalent to *Coenorhabditis elaegans* sel-12 gene (Smialowska and Baumeister, 2006).

It seems that the presenilins are major component of the nine region transmembrane domain γ secretasic complex. On the other hand, it has been shown that they interact with an intramembrane domain involved in calcium ions homeostasis which regulates the neurotransmitter releasing mechanism on presynaptic level [idem]. These proteins function are highly dependent on a phosphorylation mechanism acetylcholine dependent for presenilin 1. The way that they interact with the apoptosis pathway is yet to be revealed (Smialowska and Baumeister, 2006).

PSEN1 and 2 gene expression is important for neurons and glia. PSEN1 is equally expressed in all body tissues but PSEN2 expresses tissue dependent (brain, heart, and pancreas). Both gene expression products are stored in neuron soma and dendrites (Spasic *et al.*, 2006).

There have been described over 40 PSEN1 mutations and only two PSEN2 mutations all of which are missense mutations of highly conserved residues. There is one exception, a 9$^{th}$ exon splicing site PSEN1 mutation which cause an amino acid substitution correlated in young with paraplegia (S290C). No other mutation has been shown to neither alter nor block presenilin cell processing and it has been postulated that not the presenilins blockage undergoes Alzheimer’s occurrence but the aberrant N-terminal and C-terminal faulty cleavage fragments increase γ secretasic complex action and amyloid synthesis. More than that some say that because there are no records of nonsense or frame shift mutations it is highly possible that these genes might not be determinant for Alzheimer’s. A more relevant explanation is that the mutations might alter presenilins functions or that the aberrant protein product might block the wild-type protein functions through a dominant-negative mechanism (Brouwers *et al.*, 2008).

Tau protein gene (MAPT gene)

Tau protein is encoded by MAPT (microtubule-associated protein tau) gene. As it is called, this protein is important in neurons' cytoskeleton integrity as the main microtubules component. This gene is expressed in neuron nucleus and then the protein is carried to axons where it exhibits its functions. MAPT gene is localized on the 17$^{th}$ chromosome and by its expression leads to six protein isoforms synthesis through three exons alternative splicing. Because of the phosphorylation activation mechanism, it is thought that any error occurred both in MAPT gene and enzymes involved in this pathway can cause tau protein instability or isoforms proportion disturbance. However only some errors can lead to an Alzheimer's disease predisposition but all of them lead to neurological or neurodegenerative pathologies (Avila *et al.*, 2004).

It is known that MAPT gene has two haplotypes, H1 and H2, in which it seems that the gene is expressed in reverse order. The H2 haplogroup is common only to Europeans and populations with European inheritance. The H1 haplogroup is associated with a high probability of neurodegenerative diseases occurrence such as dementia and Alzheimer's disease (Shaw-Smith *et al.*, 2006).

Tau protein gene variations and tau protein disorders are mostly specific to frontotemporal dementia with Parkinsonism rather than Alzheimer's. There isn't yet an explanation of this fact but it is thought that MAPT mutations are associated with progranulin gene mutations to cause pathological conditions. MAPT mutations do not cause familial AD, but can certainly cause frontotemporal dementia (FTD). The pathogenic mutations, either exonic or intronic, generally alter the relative production of tau isoforms and can lead to disturbances in microtubule assembly mechanisms or tau protein adhesivity.

There have been described three MAPT gene mutations. The R5H mutation, a missense single nucleotide substitution alongside 1$^{st}$ exon of the gene, reduces tau protein's ability to promote microtubule assembly that leads to neuronal loss in the frontal and temporal lobes, tau protein deposits in glia and aberrant insoluble tau protein synthesis. This mutation is characteristic to frontotemporal dementia (Hayashi *et al*., 2002). The non-coding 10$^{th}$ intron C>T mutation has no pathological implications found yet for both FDT not AD (De Silva, 2009). K280del 10$^{th}$ exon mutation causes a three nucleotide deletion but has an unclear pathogenicity for AD and FDT. The K280del variant inhibits 10$^{th}$ exon inclusion and leads to unusual tau transcripts. It also has been shown that it reduces the ability of tau protein to promote microtubule assembly. These effects cause variable pathogenicity, mainly severe atrophy of the frontal and temporal cortex and alternatively, tangles, neuritic amyloid plaques, Lewy bodies, or atherosclerosis (Roks *et al.*, 1999; Rizzu *et al.*, 1999). The latter mutation is very rare and associated with early onset Alzheimer's. There are no animal models for none of these three mutations.

## RISK FACTORS GENES

Apolipoprotein E gene

APOE gene is localized on the 19$^{th}$ chromosome in a gene cluster with APOC1 and APOC2. Consisting in four exons and three introns, APOE gene expression is regulated by cholesterol, fatty acids and glucose homeostasis hepatic receptors and peroxisomal proliferating receptor (Chawla *et al.*, 1999). The most important aspect to Alzheimer's is that APOE is a three allele polymorphic gene: APOEε2 (cys112, cys158), APOEε3 (cys112, arg158) and APOEε4 (arg112, arg158). These minor differences in protein structure can slightly change apolipoprotein E functions and abilities.

The ε2 allele has a lower than 7% frequencies and the APOEε2 protein variant exhibits certain deficiencies regarding surface receptors binding. It seems that homozygote ε2 individuals exhibit lower alimentary fats metabolizing capacity; therefore they have a higher risk for atherosclerosis. The ε3 allele is considered the neuter genotype and the most frequent (79%). In contrast, ε4 allele has an intermediate frequency (14%) and the worst fenotypical impact. The carriers exhibit high risk to develop Alzheimer's disease, but also atherosclerosis, multiple sclerosis, fast telomere shortage and others. There is not a valuable explanation of the so high impact mechanism. The only explanation has been found to the increased allele frequency in spite its aggressive effects is that this allele promotes high levels of vitamin D to carriers (Eisenberg *et al.*, 2010).

It has been shown that the ε4 allele inheritance is an autosomal dominant manner of Alzheimer's disease inherited risk development. More than that it seems that the age of early Alzheimer's symptoms occurrence lowers as the ε4 allele is more present. However, it has been shown that ε4 APOE allele inheritance is an insufficient risk for disease development. More than that, APOEε4 has been associated with other neurodegenerative disorders so APOE might pay a common role in neuronal response to injury (Murrell *et al.*, 1991).

TREM2 gene

TREM2 gene encodes an important cellular receptor protein (triggering receptor expressed on myeloid cells 2). It is localized on the 6$^{th}$ chromosome and its homozygous state mutant can cause rare forms of dementia especially Alzheimer's. The R47H exon 2 mutation generates a substitution which also causes an amino acid substitution. As

TREM2 exhibits a anti-inflammatory function in brain cells, this mutation interferes with the local leukocytes' ability to find and destroy amyloid plaques (Jonsson *et al*., 2012; Lambert, 2013). This mutation has been reported present to many Alzheimer's patients older than 85.

In addition to these genes, it is considered that the Alzheimer's genetics spectrum is consisted in at least 10 other genes involved directly or triggering vulnerabilities that lead to Alzheimer's development. The molecular mechanisms from which βAP and NFT accrue are still partly unknown, but are intensely studied through medicine and psychiatry, analytical and clinical biochemistry, molecular genetics, proteomics, genomics, biostatistics and biomodeling techniques using both human subject and animal models.

## CONCLUSIONS

In conclusion, Alzheimer's disease can be considered a highly complex disease that exhibits symptoms in all organisms' levels from behavioral changes to subcellular discrepancies. It has been shown that besides external factors that lead to Alzheimer's development such as life style, alimentary habits or prolonged life sustainability there are certain internal factors uncontrollable but predictable. Alzheimer's genetics, roughly overlooked, seems to pay an important role in understanding this complex disease. As every visible effect has a molecular background, even emotions, memories, thoughts and feeling, it is highly possible that pathologies has molecular causes too. There are many genes and molecular factors involved in Alzheimer's development worth to be discussed and considered as starting points in Alzheimer's pathology, so it would be helpful to consider the molecular level in further Alzheimer's disease and other neurodegenerative diseases research.

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