

## Review Article

# Early Onset Alzheimer's Disease and Oxidative Stress

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Alzheimer's disease (AD) is the most common cause of dementia in elderly adults. It is estimated that 10% of the world's population aged more than 60–65 years could currently be affected by AD, and that in the next 20 years, there could be more than 30 million people affected by this pathology. One of the great challenges in this regard is that AD is not just a scientific problem; it is associated with major psychosocial and ethical dilemmas and has a negative impact on national economies. The neurodegenerative process that occurs in AD involves a specific nervous cell dysfunction, which leads to neuronal death. Mutations in APP, PS1, and PS2 genes are causes for early onset AD. Several animal models have demonstrated that alterations in these proteins are able to induce oxidative damage, which in turn favors the development of AD. This paper provides a review of many, although not all, of the mutations present in patients with familial Alzheimer's disease and the association between some of these mutations with both oxidative damage and the development of the pathology.

## 1. Introduction

Brain requires a high consumption of oxygen to generate adenosine triphosphate (ATP). It is known that oxygen metabolism in the mitochondria, endoplasmic reticulum (ER), and peroxisomes generates oxidant agents known as free radicals [1, 2], small molecules with unpaired electron that includes the oxygen reactive species (ROS) like hydroxyl radical ( $\text{OH}^\cdot$ ), superoxide radical ( $\text{O}_2^\cdot$ ), the reactive nitrogen species (RNS), and nitric oxide ( $\text{NO}^\cdot$ ). These molecules show high reactivity with macromolecules [3] and have an important biological function as signaling molecules [4]. However the interaction of these agents and nonradical oxidants with membrane lipids, proteins, and DNA also could be conducted to cellular senescence. This oxidative damage is catalyzed by the presence of trace elements Fe, Cu or both [5].

As part of evolution, organisms have developed enzymatic and nonenzymatic antioxidants mechanism to counteract oxidative damage, which act removing free radicals, scavenging ROS/RNS or their precursors and binding trace elements [1]. The antioxidant enzymes are superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). The nonenzymatic antioxidants group is composed of the natural molecules glutathione (GSH) and the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), and compounds like ascorbic and lipoic acid, polyphenols and carotenoids dietary derived [6].

However, an imbalance of oxidants and antioxidants agents could generate oxidative stress, which results in a damage of macromolecules and disruption of reduction/oxidation (redox) signaling [7]. Mitochondrial dysfunction, excitotoxicity, and oxidative stress are common pathological

conditions of neurodegenerative diseases such as Parkinson's disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis, and Alzheimer's disease (AD) [8, 9].

AD is a disorder of the central nervous system (CNS) that results in generalized brain atrophy. Clinically, AD is characterized by the gradual and progressive loss of memory and other cognitive functions, such as the ability to solve everyday problems and emotional control [10–12]. Conventionally, AD is divided in two subtypes, depending on the age of onset: familial cases and sporadic cases. Familial AD (FAD), which accounts for only 5–10% of all AD cases, exhibit an autosomal dominant form of inherited mutation in the amyloid precursor protein gene and the presenilin 1 or 2 genes and are characterized by an age of onset prior to 55 years old (early onset AD (EOAD)). Sporadic cases account for 90–95% of all AD cases and usually present a later age of onset ( $\geq 65$  years). These cases do not show the familial aggregation associated with the early development of the disease and are known as late onset AD (LOAD). Twin studies provide insight into the relative contributions of genetic and environmental influences on AD and other types of dementia [13–15]. It has been observed that among patients who develop LOAD, approximately 40–65% present apolipoprotein E allele 4 (APOE $\epsilon$ 4) as an indirect genetic agent [16–19]. However, the presence of APOE $\epsilon$ 4 as a genetic risk factor is not enough for developing the disease [20, 21]. Histopathologically, AD is defined by the presence of two specific features: neuritic plaques (NPs) and neurofibrillary tangles (NFT) [22–24]. *In vitro* and *in vivo* data now support the notion that the accumulation of both A $\beta$ -containing senile plaques and tau-containing neurofibrillary tangles (NFTs) in the brain can directly or indirectly cause free radical-induced stress. Mutations in APP and PS can increase reactive oxygen species (ROS) production and generate mitochondrial damage which in turn favors the neurodegenerative process observed in AD. This paper reviews the general characteristics of FAD, the mutations carried by APP and PS in transgenic mouse models, and their role in oxidative damage.

## 2. Neurofibrillary Tangles

NFTs are intracellular deposits of paired helical filaments (PHFs). NFT density in AD patients' brain is closely related to dementia severity [25, 26]. In these filaments, the most important molecular marker is tau, a microtubule-associated protein. The gene that encodes this protein is located on chromosome 17 [27]. In the adult human brain, six tau isoforms are produced via alternative splicing of exons 2, 3, and 10. When exon 10 is excluded, the result is a protein with three repeats of the microtubule-binding domain (3RMBD). When exon 10 is included, a fourth microtubule binding domain is added to generate four-repeat tau (4RMBD) [28–30]. Tau is a highly soluble protein that is natively unfolded and does not show an apparent secondary structure [31, 32] due to high proline and glycine content in its primary structure. However, under pathological conditions, tau tends to self-assemble into insoluble filament structures [33]. This protein is implicated in neurodegeneration in many disorders, such as AD,

progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease (PiD), Down's syndrome (DS), postencephalitic Parkinsonism, and Niemann-Pick disease [34–36]. Mutations in tau gene cause frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17) [37–40]; however, AD pathology is not related to mutations in the tau gene.

## 3. Neuritic Plaques

NPs are one of the stereotypical markers of AD; they are spherical extracellular deposits, 10–100  $\mu\text{m}$  in diameter, containing a fibrillary core surrounded by microglia, reactive astrocytes, and dystrophic neurites from degenerating neuronal processes [41]. The main component of NPs is amyloid- $\beta$  (A $\beta$ ), a 39–42 amino acids peptide [42, 43] that originates as a normal secretory product derived from amyloid precursor protein (APP) [44]. The primary function of APP remains unknown, although it has been proposed that it could participate as a growth factor in cultured fibroblasts [45], play roles in cell adhesion [46], intraneuronal calcium regulation [47], and neural plasticity [48], and act as a synapse formation regulator [49]. APP undergoes two types of proteolytic processing, resulting in the generation of two distinct classes of peptides with different biological roles [45]: (a) soluble APP ( $\alpha$ APPs) via proteolytic processing by  $\alpha$ - and  $\gamma$ -secretase and (b) amyloid- $\beta$  peptides via proteolytic processing of APP by  $\beta$ - and  $\gamma$ -secretase (Figure 1).  $\gamma$ -secretase is a protein complex consisting of presenilin 1 (PS1)/presenilin 2 (PS2), nicastrin (NCT), anterior pharynx-defective 1 (APH-1), and presenilin enhancer 2 (PEN-2) [50–53].

## 4. Amyloid- $\beta$ and Oxidative Stress

In AD, A $\beta$  peptides of 40 and 42 amino acids acquire a  $\beta$ -sheet structure, which is proaggregator and leads to the formation of dimers, oligomers, insoluble fibers, and NP formation [54, 55]. Oligomers represent the most toxic aggregation stage of A $\beta$ , because they promote excitotoxicity by interacting with glutamate receptors, endoplasmic reticulum stress, mitochondrial dysfunction, altered acetyl-cholinergic neurotransmission, inflammation, and oxidative stress [56].

The transition metals, Cu $^{2+}$ , Zn $^{2+}$ , and Fe $^{3+}$ , are altered in AD brain and they have been involved with A $\beta$  aggregation and oxidative damage [57]. In particular, A $\beta$  has three histidine residues at positions 6, 13, and 14 for metals coordination. A $\beta$  catalyses the reduction of Cu $^{2+}$  and Fe $^{3+}$  and generates H $_2$ O $_2$ , which is converted to OH $^{\bullet}$  in the presence of the metals Cu $^{1+}$  and Fe $^{2+}$ ; the generation of this reactive species leads to the formation of proapoptotic lipid peroxidation (LPO) products, such as 4-hydroxynonenal (HNE) [58, 59]. In contrast, an *in vitro* study showed that Zn $^{2+}$  quenched A $\beta$ -Cu $^{2+}$  complexes, promoting an antioxidant function [60].

Another important amyloid residue that is related with the oxidative stress is the Methionine 35 (Met $^{35}$ ). The expression of human A $\beta$  1–42 in *Caenorhabditis elegans* (*C. elegans*) promoted an increase of protein oxidation levels, compared

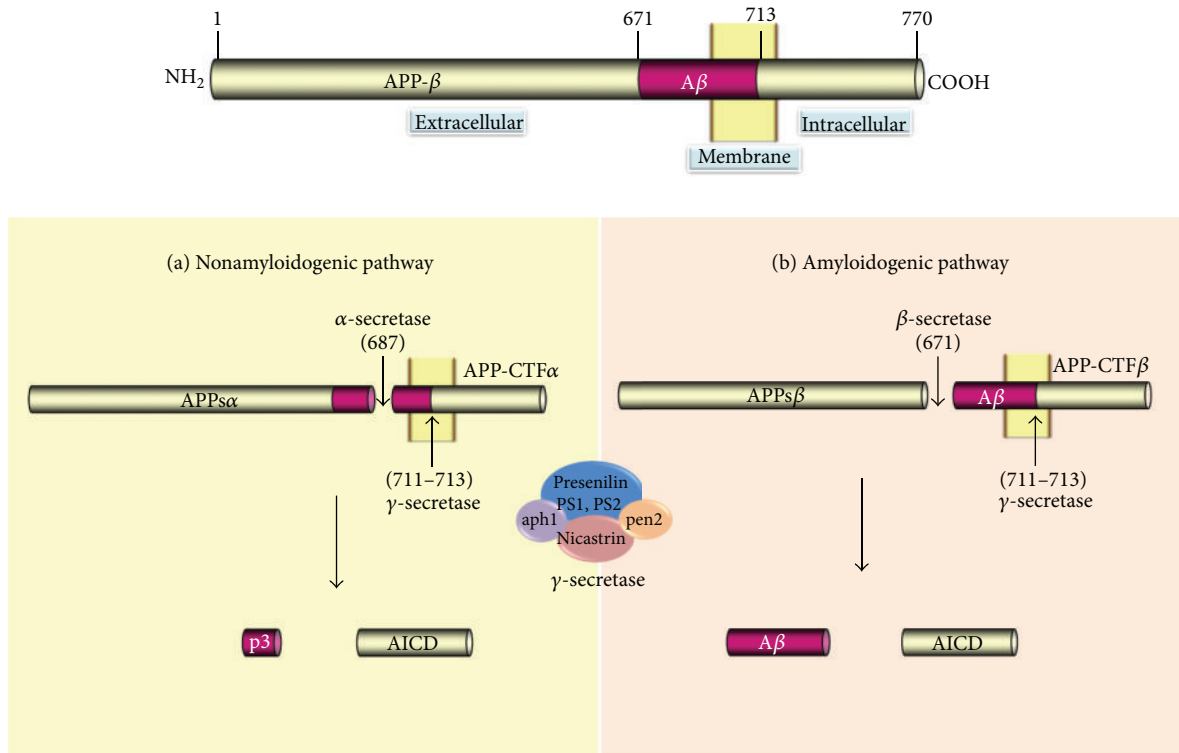


FIGURE 1: APP $\beta$  processing. the APP is an integral membrane protein and is sequentially processed by the three proteases  $\alpha$ -,  $\beta$ -, and  $\gamma$ -secretase. The nonamyloidogenic pathway involves the  $\alpha$ -secretase, which made the cut at the middle portion of the fragment corresponding to the amyloid sequence, preventing the amyloid peptides generation. The amyloidogenic pathway involves  $\beta$ -secretase, leading to the formation of C-terminal fragments (CTFs) that are subsequently cleaved by the “ $\gamma$ -secretase-complex” which is responsible for the formation of A $\beta$  (40 or 42 amino acids in length) and the A $\beta$ PP intracellular domain peptide (AICD) of 58 or 56 amino acids.

with the *C. elegans* transgenic line CL3115 that express a substitution of Met<sup>35</sup> by a Cysteine (replacement of the S atom in Met by CH<sub>2</sub>) [61]. In addition, the J20 transgenic mouse with human APP containing Swedish (KM670/671NL) and Indiana (V717F) mutations present elevated A $\beta$  deposition and increased oxidative stress in the brain around 5–7 months old. Introduction of M631L mutation to APP (corresponding to the Met<sup>35</sup> residue of A $\beta$ ) in J20 mouse resulted in no oxidative stress in brain at 9 months old [62]. The mechanism of Met<sup>35</sup> leading oxidative damage involves the A $\beta$  binding to Cu<sup>2+</sup>; this reaction generates H<sub>2</sub>O<sub>2</sub> that could cause the oxidative modification of the sulphur atom of Met<sup>35</sup> generating sulphuryl free radical. This species favors ROS formation in the lipid bilayer, promoting LPO and membrane protein oxidation [63]. It has been documented that the induction of methionine-sulfoxide reductase prevents the oxidation of Met<sup>35</sup> residue, suggesting that this enzyme could be a therapeutic target in order to decrease the oxidative activity of A $\beta$  aggregates [64]. Despite this, A $\beta$  would promote oxidative stress through other indirect mechanisms. The A $\beta$  accumulation in parenchyma and blood vessels causes microglial migration and promotes acute and chronic inflammatory responses against the aggregates, thus inducing the production of proinflammatory cytokines, prostaglandins,

NO, and ROS, which eventually could promote neuronal death [65]. Also, A $\beta$  oligomers activate the N-methyl-D-aspartate receptor (NMDA-R), leading to a rapid influx of calcium, which promote ROS generation from the NADPH oxidase. These effects are counteracted by memantine, an open channel NMDA-R antagonist prescribed as a memory-preserving drug for AD patients [66, 67]. Finally, the A $\beta$  accumulation in the mitochondria is conducted to morphological alterations, and also a functional impairment including a decrease of ATP, increasing ROS generation, and breaking membrane potential that leads to cellular apoptosis [68, 69].

The mechanisms of A $\beta$  to generate oxidative stress take a high impact on the fast progression of EOAD, because all germline mutations are conducted to an increase of A $\beta$  production and aggregation. Immunotherapy with anti-A $\beta$  antibodies has been tested in transgenic mouse model, resulting in a prevention of synaptotoxicity of A $\beta$  aggregates [70].

## 5. Early Onset Alzheimer’s Disease

FAD or EOAD accounts for less than 10% of cases and is associated with mutations in proteins such as PS1, PS2, and APP.

TABLE 1: Amyloid precursor protein mutations.

Mutation	Phenotype	Age of onset	References
E665D	AD, but may not be pathogenic		Peacock et al., 1994 [141]
KM670/671NL (Swedish)	AD	52 (44–59)	Mullan et al., 1992 [81]
H677R	AD	55 (55–56)	Janssen et al., 2003 [142]
D678N (Tottori)	FAD	60	Wakutani et al., 2004 [143]
E693Δ	AD		Tomiyama et al., 2008 [144]
D694N (Iowa)	AD or cerebral hemorrhage	69	Grabowski et al., 2001 [83]
A713T	AD, but may not be pathogenic	59	Carter et al., 1992 [145]
T714A (Iranian)	AD	52 (40–60)	Pasalar et al., 2002 [146]
T714I (Austrian)	Affects $\gamma$ -secretase cleavage directly, 11X increase in $A\beta(42)/A\beta(40)$ ratio <i>in vitro</i> .		Kumar-Singh et al. [147]
V715A (German)	AD	47	De Jonghe et al., 2001; [148] Cruts et al., 2003 [149]
V715M (French)	AD	52 (40–60)	Ancolio et al., 1999 [150]
I716T	AD	55	Terrini et al., 2002 [151]
I716V (Florida)	AD	55	Eckman et al., 1997 [82]
V717F (Indiana)	AD	47 (42–52)	Murrell et al., 1991 [77]
V717G	AD	55 (45–62)	Chartier-Harlin et al., 1991 [72]
V717I (London)	AD	55 (50–60)	Goate et al., 1991 [74]
T719P	AD	46	Ghidoni et al., 2009 [152]
L723P (Australian)	AD	56 (45–60)	Kwok et al., 2000 [153]

These mutations are closely related to the early onset of the disease, with a high penetrance being observed among mutation carriers [71–79]. Currently, more than 200 distinct disease-causing mutations have been identified across these genes, which exhibit an autosomal dominant disease-transmission pattern.

## 6. APP Mutations

APP is a type I integral membrane glycoprotein that resembles a signal-transduction receptor [44] (Figure 2). The APP gene has been mapped to chromosome 21q21 and consists of 18 exons. Alternative splicing generates several isoforms of this gene, which are designated according to amino acid length: APP563, APP695, APP714, APP751, and APP770. In the CNS, the only isoforms present are APP695, APP714, APP751, and APP770, with APP695 being mainly expressed in neurons. To date, approximately 36 different missense mutations in the APP gene have been identified among 85 families (Table 1). Most of these mutations are located in exons 16–17, in the transmembrane domain, where the sites recognized by the  $\alpha$ -,  $\beta$ -, and  $\gamma$ -secretases are found (Figure 2(b)). These mutations alter the processing of the protein and cause the accumulation of  $A\beta(42)$  fragments by decreasing  $A\beta(40)$  peptide levels or increasing  $A\beta(42)$  production [74, 78].

Mutations in APP linked to EOAD include the Dutch (E693Q) [80], London (V717I) [74], Indiana (V717F) [77], Swedish (K670N/M671L) [81], Florida (I716V) [82], Iowa (D694N) [83], and Arctic (E693G) [84] mutations. The major

mutations in APP include the Swedish double mutation (APPSW, APPK670N, and M671L) and the London mutation (V717I). In 1991, Goate et al. identified a missense mutation in the gene encoding APP that segregates with AD. This mutation is located in exon 17 in part of the sequence encoding the  $A\beta$  peptide and leads to a valine to isoleucine change at amino acid 717 (V717I) [74], corresponding to the transmembrane domain near the  $\gamma$ -secretase cleavage site. The Swedish mutation, which is located just outside the N-terminus of the  $A\beta$  domain of APP, favors  $\beta$ -secretase cleavage and it is associated with increased levels and deposition of  $A\beta(42)$  in the brains of AD patients [85, 86].

## 7. APP Mutations and Oxidative Stress

The presence of APP mutations in EOAD leads to increased levels of  $A\beta$ , which may result in mitochondrial dysfunction and augmented ROS levels, thus increasing oxidative damage. A role of  $A\beta$  causing mitochondrial dysfunction has been extensively reported. It is known that  $A\beta$  is able to decrease mitochondrial complexes I and IV activity, leading to electron transport chain and oxidative phosphorylation dysfunction, which in turn causes adenosine triphosphate (ATP) depletion [87, 88]. Additionally,  $A\beta$  stimulates mitochondrial permeability transition pore opening, thus disturbing mitochondrial ion balance [89].  $A\beta$  has been also linked with mitochondrial dynamics dysfunction [90]. All this mitochondrial alterations might in turn lead to an increase in ROS production and consequently enhance oxidative stress.

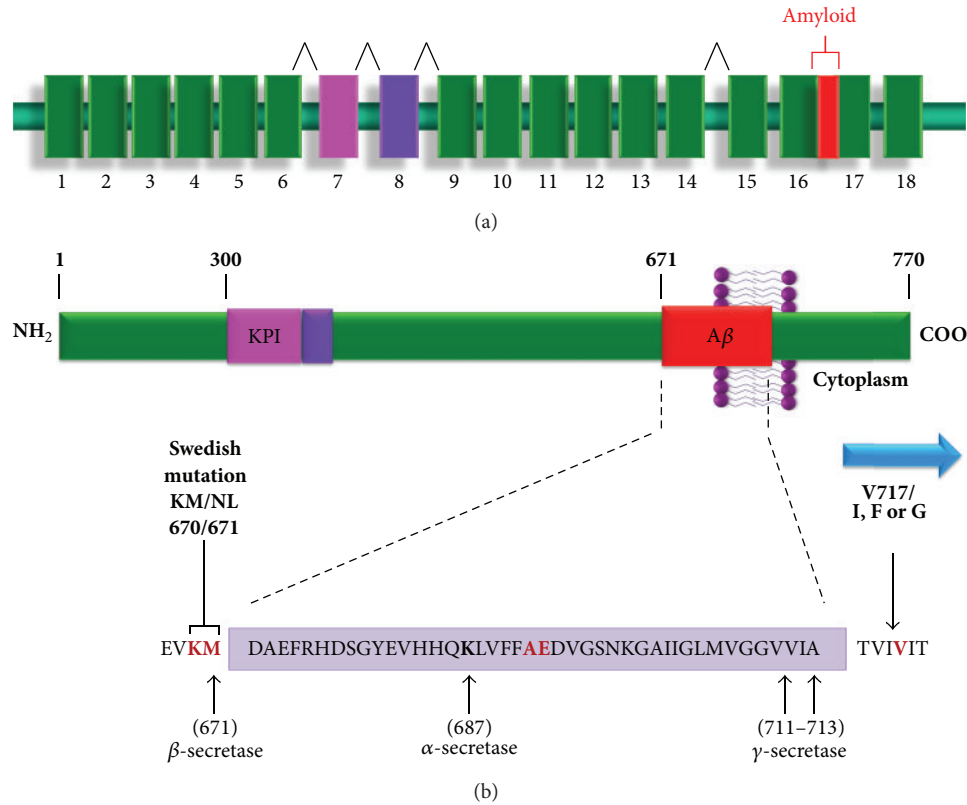


FIGURE 2: Human APP gene structure. (a) The APP gene consisting of 18 exons is located on chromosome 21 (21q21.2-3) and is alternatively spliced into several products, named according to their length in amino acids (i.e., APP695, APP714, APP751, APP770, and APP563) that are expressed differentially by tissue type. The region encoding the amyloid sequence comprises part of exons 16 and 17 (red box). (b) APP is a member of a family of conserved type I membrane proteins and consists of a large extracellular domain, a hydrophobic transmembrane domain, and a short cytoplasmic carboxyl terminus. Some isoforms contain a domain homologous to the Kunitz-type serine protease inhibitors (KPI) in the extracellular sequences (pink box). Amyloid sequence contains 40- and 43-amino-acid residues that extend from the ectodomain into the transmembrane domain of the protein. The  $A\beta$  sequence lies partially outside the cell membrane (amino acids 1-17 of  $A\beta$ ) and the some identified mutations in the protein are indicated in bold.

Transgenic animal models that overexpress mutant APP have been useful in the assessment of the oxidative damage that occurs when  $A\beta$  levels increase. This was observed in isolated mitochondria taken from transgenic mice expressing a double Swedish/London mutation of APP. The results showed both very marked mitochondrial dysfunction and reduced ATP-levels in adult APP mice. These alterations were present after three months, at which point amyloid intracellular levels were noted to have increased, while no extracellular  $A\beta$  deposits were present. Mitochondrial dysfunction was associated with higher levels of ROS, with a decreased Bcl-xL/Bax ratio and a reduction of mitochondrial complex IV activity. There is evidence that oxidative stress might cause an upregulation of Bax [91]. This increase in the activity of Bax and other proapoptotic members of the Bcl-2 family could be playing a role in enhancing the massive neuronal loss observed in AD patients. [92].

Isoprostanes (iPs) are specific and sensitive markers of *in vivo* lipid peroxidation (LPO). Tg2576 mice, which develop  $A\beta$  brain deposits due to the overexpression of a transgene with a double Swedish mutation (APP<sup>swe</sup>), were used to

determine levels of iPs and LPO. Urine, plasma, and brain tissues were collected from both Tg2576 and wild-type (WT) animals at different ages, starting at four months old and continuing until eighteen months old. The results showed that, compared with WT mice, iP levels increased at eight months old in Tg2576 mice and preceded the onset of  $A\beta$  deposition in the CNS [93]. It has been shown that LPO products, such as HNE are diffusible and highly reactive with other biomolecules and thus are neurotoxic. The results obtained in this AD model are coincident with previous reports that show that HNE levels are increased in the AD brain [94].

In this way, superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities are found to increase in cortical tissue, while the level of nitric oxide and reactive nitrogen species showed peak values around nine months old [95]. These results might suggest that in the Tg2576 mouse model, LPO and the elevation of antioxidants precede amyloid plaque formation. Notably, the ages at which these oxidative stress peaks occur are coincident with the ages at which these mice begin to present impaired cognitive performance

with respect to control mice, leaving open the possibility that oxidative stress could account for cognitive impairment in this model.

It has also been observed that mitochondrial  $A\beta$  accumulation increased around four months-old (before plaque formation) in transgenic APP mice expressing both APP V717/F and the APP Swedish mutation, suggesting an intracellular  $A\beta$  toxicity cascade [96].

Another FAD mouse model features Thy1-APP751SL mice, which are made transgenic by the 751 amino acid form of APP are used with the Swedish and London mutations under the control of the promoter Thy1. These mice overexpress APP and develop both high levels of  $A\beta$  and plaque formation at six months old. HNE levels were significantly higher in twelve months old animals, while the overexpression of APP led to reduced Cu/Zn-SOD activity at three and twelve months of age and had a more pronounced effect on twelve months old animals [97, 98].

## 8. Presenilin Mutation

Most FAD cases are associated with mutations in PS1 or PS2 [71, 76, 99]. These mutations are autosomal dominant and highly penetrant. Presenilins are expressed in several tissues and in the brain, but they are expressed mainly in neurons [75]. Presenilins localize in the endoplasmic reticulum (ER), Golgi apparatus, endosomes, lysosomes, phagosomes, plasma membranes, and mitochondria [100–102]. These proteins undergo endoproteolytic processes, generating stable N- and C-terminal fragments (NTF and CTF, resp.). These fragments interact with other proteins to form a macromolecular complex with  $\gamma$ -secretase activity, which is responsible for the intramembranal proteolysis of APP and other proteins [51, 85, 103–106]. Both PS1 and PS2 possess the conserved aspartate residues required for  $\gamma$ -secretase activity [107]. In addition to this function, presenilins directly or indirectly regulate the trafficking and metabolism of select membrane proteins in neurons [108]. Studies in several models have shown that presenilins play roles in synaptic function [109, 110], learning and memory [111], neuronal survival in the adult brain, regulation of calcium homeostasis [112, 113], and presynaptic neurotransmitter release [114]. PS1 function loss has been reported to inhibit normal migratory neuronal trajectories during neurodevelopment [115]. Mutations in PS1 and PS2 induce  $A\beta$  overproduction, apparently by increasing  $\gamma$ -secretase activity [116–120], which is the final step in amyloid peptide formation. Although transgenic mice with a single mutation in either PS1 or PS2 do not form plaques, they exhibit a number of pathological features, including age-related neuronal and synaptic loss as well as vascular pathology.

## 9. Presenilin 1

The PS1 gene is located on chromosome 14q24.2 and comprises 12 exons. The open reading frame is encoded in exons 3–12 and generates 467 amino acids length protein.

PS1 is an integral membrane protein with eight transmembrane domains and a hydrophilic domain between domains 6 and 7. To date, more than 185 mutations in PS1 have been described in 405 families (<http://www.molgen.ua.ac.be/ADmutations/>), all of which are related to a disease onset at younger ages than sporadic AD cases [121, 122]. Although mutations are found throughout the protein, most are located in the transmembrane region (Figure 3). As shown by Shen et al. in 1997, PS1-knockout mice are not viable, and the results obtained in this study showed that PS1 is required for proper formation of the axial skeleton and for normal neurogenesis in mice and that it plays an important role in neuronal viability in specific brain subregions [123]. Selective expression of mutant PS1 in mice causes a gain of deleterious function that increases the amount of  $A\beta_{42}$  in the brain [73]. This effect was detectable as early as 2–4 months old, and different PS1 mutations were found to have differential effects on  $A\beta$  generation [71, 124]. Transgenic mice carrying the M233T/L235P knock-in (KI) mutations in PS1 and human APP show extensive neuronal loss (>50%) in the CA1/2 hippocampal pyramidal cell layer at 10 months old, which is correlated with intraneuronal amyloid accumulation, strong reactive astrogliosis, and neuronal loss [125]. Likewise, it has been reported that transient intraneuronal amyloid accumulation is correlated with neuronal loss in the frontal cortex of APP/PS1KI mice, rather than extracellular plaque pathology [126]. Breyhan and coworkers demonstrated that intraneuronal accumulation of  $A\beta$  peptides, together with oligomeric and fibrillary accumulation species, coincided with 30% of neuronal loss in the CA1 region, 18% of hippocampus atrophy and a severe reduction of synaptic plasticity [127]. In addition to its role in  $\gamma$ -secretase activity, PS1 appears to modulate glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) activity and the release of kinesin-I from membrane-bound organelles at sites of vesicle delivery and membrane insertion. These findings suggest that mutations in PS1 may compromise neuronal function, affecting GSK-3 $\beta$  activity and kinesin-I-based motility, thus, leading to neurodegeneration [128].

## 10. Presenilin 2

The PS2 gene is located on chromosome 1q42.13 and comprises 12 exons, only 10 of which are translated to generate a protein with a length of 448 amino acid residues. This protein exhibits 9 transmembrane domains and displays tissue-specific alternative splicing [129] (Figure 4). PS2 mutations are very rare, and only 13 mutations have been described among 22 families (<http://www.molgen.ua.ac.be/ADmutations/>). In the CNS, PS1 is found mainly in neurons. PS1 is expressed at higher levels during development than PS2, although in the adult brain, PS1 and PS2 are expressed at relatively similar levels and with a similar distribution. Unlike PS1, PS2-knockout mice are viable and exhibit at most a mild pulmonary phenotype [130]. Transgenic mice expressing a mutant form of PS2 (N141I) showed hyperactivity followed by hypoactivity in an open field test as well as lower expression of c-Fos and higher expression of the gamma-aminobutyric acid A receptor subunit alpha 1 in the cortex,



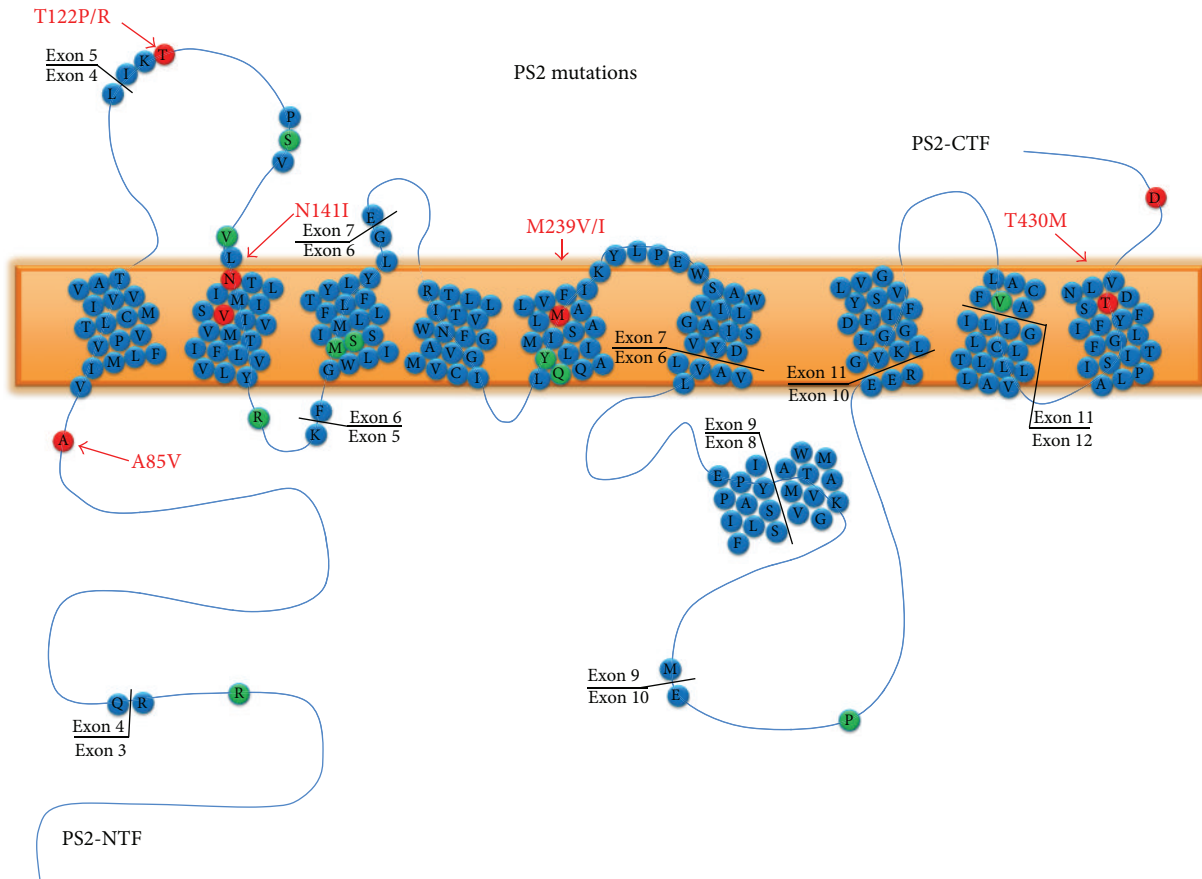


FIGURE 4: Schematic representation of Presenilin 1. The PS2 gene is located on chromosome 1q42.13 and comprises 12 exons, of which only 10 are translated to generate a protein with a length of 448 amino acid residues. This protein exhibits 9 transmembrane domains and displays tissue-specific alternative splicing; major mutations found in the protein are identified.

Using Tg2576 mice, Sung et al. demonstrated that vitamin E treatment was able to reduce oxidative stress, LPO, and  $A\beta$  burden when the treatment began at age of 5-month-old, but not when the treatment began at age of 14-month-old, again suggesting an early involvement of oxidative stress in this pathology [136]. Similar results were found by Cole and Frautschy in the same mouse model, testing the effects of docosahexanoic acid. Treatment with this antioxidant was able to reduce oxidative stress, dendritic loss,  $A\beta$  deposition, and improved cognitive performance in these mice [137]. Contrasting results were found by Siedlak et al. [138] who did not find differences between  $\alpha$ -lipoic acid-treated Tg2576 mice and placebo-treated mice with respect to  $A\beta$  burden and cognitive performance, despite a significant decrease in oxidative stress.

Dragicevic et al. also found an effect of antioxidant therapy in transgenic APP/PS1 mice. They observed that treatment with melatonin in these mice reduced mitochondrial  $A\beta$  levels and reestablished mitochondrial respiratory rates and ATP levels in hippocampus, cortex, and striatum [139].

Additionally, Mcmanus et al. reported that treatment with the antioxidant MitoQ (mitoquinone mesylate) was effective in the prevention of cognitive impairment, oxidative

stress,  $A\beta$  deposition, astrogliosis, synaptic loss, and caspase activation in 3xTg-AD mice, which express the Swedish mutation and also show tau-related pathology as observed in AD patients [140]. These results apparently show a beneficial effect of antioxidant therapy in the treatment of FAD, although it is important to consider that clinical trials performed in LOAD patients have shown only a very modest effect in memory and cognition improvement and disease progression delay. Clinical trials testing the effect of antioxidants specifically in FAD patients have not been conducted yet, to the extent of our knowledge, but considering the amyloidogenic genetic background of these patients and the more aggressive nature of this AD form, the results may be not very promising.

### 13. Conclusions

EOAD is characterized for the presence of mutations in the APP, PS1, and PS2 genes. These mutations confer an increase of  $A\beta$  production and its posterior accumulation, which generates a series of molecular events that lead to a neurodegenerative process. Amyloid has the ability to interact with several different receptor types, including the



frizzled, insulin, NMDA, and NGF receptors, which trigger events that lead to neuronal death. Most of the transgenic models expressing APP and PS human mutations show high levels of oxidative damage, suggesting that oxidative stress may be an early event in the development of the pathology and has an important role on the fast progression of EOAD compared with LOAD. Moreover, this oxidative damage can increase the synthesis and aggregation of A $\beta$ , which represents a vicious circle that favors peptide toxicity and neurodegeneration. In this sense, it has been suggested as several numbers of therapeutic approaches. The principal strategies include to antioxidants agents, NMDAR antagonists, and the A $\beta$ -immunotherapy. All of these strategies focus on the decrease of A $\beta$  oxidative activity and the toxic effects of aggregates. Therapeutic strategies could delay neurodegeneration, improving the quality of life of EOAD patients for a while, but the genetic background imposes the amyloidosis. In these AD cases, gene therapy may be the best strategy.

## Disclosure

The authors declare that this review was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interests.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of the article.

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