E-ISSN: 3068-5052
Journal of Regenerative Medicine & Biology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

*Review Article*

# Amyloid Precursor Protein (APP) A673T Mutation as a Model for Developing Preventive Strategies in Alzheimer's Disease

**M González-Flores[1,2], C Soriano-Amador[1,2], P Mateos-Martínez[1,2], R González-Sastre[1,2*], V López-Alonso[2*], R Coronel[1*], I Liste[1*]**

[1]Neural Regeneration Unit, Spain

[2]Computational Biology Unit, UFIEC, Instituto de Salud Carlos III (ISCIII), Majadahonda 28220, Madrid, Spain

***Correspondence author:** Isabel Liste Noya, R Coronel and V López-Alonso Computational Biology Unit. UFIEC. Instituto de Salud Carlos III (ISCIII), Majadahonda 28220, Madrid, Spain; Email: iliste@isciii.es; rcoronel@isciii.es; victorialopez@isciii.es

Citation: González-Flores M, et al. Amyloid Precursor Protein (APP) A673T Mutation as a Model for Developing Preventive Strategies in Alzheimer's Disease. J Reg Med Biol Res. 2025;6(3):1-8.

https://doi.org/10.46889/JRMBR.2025/6304

Received Date: 18-10-2025

Accepted Date: 10-11-2025

Published Date: 17-11-2025



## Abstract

The A673T variant of the Amyloid Precursor Protein (APP), first identified in the Icelandic population, represents a paradigm-shifting discovery in Alzheimer's Disease (AD) research. This protective mutation confers significant resistance against AD onset and age-related cognitive decline by modulating APP processing and reducing Amyloid-β (Aβ) aggregation. Remarkably, A673T not only mitigates amyloidogenic effects but also counteracts several pathogenic APP mutations implicated in familial AD. Recent *in-vivo* studies using knock-in mouse models have validated its neuroprotective effects, demonstrating substantial reductions in amyloid burden and preservation of synaptic function. Given its broad implications for understanding APP physiology, AD pathogenesis and the development of novel therapeutic strategies, this review comprehensively examines the physiological role of APP, its contribution to AD pathology, the impact of disease-related mutations and the unique protective mechanisms conferred by the A673T variant.

**Keywords:** Amyloid Precursor Protein; Alzheimer's Disease; Amyloid-β; Disease-Related Mutations

## Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder and one of the most common forms of dementia, affecting approximately 50 million patients worldwide. AD is characterized by a decline in memory, language and other cognitive abilities that progressively affect the performance of daily activities in people's lives as the disease advances. This leads to great difficulties for both the person suffering from the disease and their families, in addition to representing a high economic cost. The risk of developing AD increases with age, as evidenced by the fact that the prevalence in people under 65 is 10-30%, in contrast to an incidence that doubles every 10 years after the age of 65 [1].

The causes of AD are not yet fully understood but probably are multifactorial and include a combination of age-related changes in the brain, along with lifestyle and genetic factors.

There are some genetic variants that increase the risk of developing AD or promote its development at an early age. A gene that influences the risk of developing AD is the Apolipoprotein E (APOE). This gene is involved in the production of a protein that helps transport cholesterol and other types of fats in the bloodstream. The APOE ε4 allele is the strongest genetic risk factor for late-onset sporadic AD, with individuals carrying one APOE ε4 allele having a 2-3 fold increased risk, while those carrying two ε4 alleles have a 10-12 fold increased risk [2].

In addition, AD has been linked to three causative genes that encode proteins involved in the degradation of Amyloid Precursor Protein (APP) and the formation of Aβ peptide. These genes are the APP, the Presenilin 1 (PSEN1) and the Presenilin 2 (PSEN2). Both PSEN1 and PSEN2 encode essential elements of the γ-secretase complex, which cleaves the Amyloid Precursor Protein

(APP) intramembranously. People with mutations in any of these genes have a significantly increased likelihood of developing AD between the ages of 30 and 50. Most mutations in these three genes associated with AD are autosomal dominant, have high penetrance (>85%) and result in early-onset disease [3].

Various hypotheses have been put forward to understand how AD develops. The most relevant hypotheses share a common analysis of two characteristic brain hallmarks present in this pathology, which are believed to contribute to neuronal damage and degeneration, resulting in memory loss and other symptoms associated with the disease. One of these alterations is the accumulation of extracellular β-amyloid peptide, which results in the formation of the well-known senile plaques or amyloid plaques. These are thought to interfere with synapses in neuron-neuron communication and promote cell death. The second change is the abnormal accumulation of intracellular and extracellular Tau protein. These protein accumulations correspond to neurofibrillary tangles, which block the transport of nutrients and other essential molecules into neurons and also promote toxicity in their extracellular form, thus presumably contributing to cell death [4,5].

Although various treatments for AD have been tested, very few of them have been shown to have a beneficial effect on the course of the disease. Furthermore, the effect of these drugs is limited, as they only temporarily delay or slow down the progression of the disease, but do not stop neurodegeneration [6].

It is known that many of the mutations present in both the APP genes and the enzymes that cleave them promote cognitive decline and the development of this disease. However, a neuroprotective mutation of the APP gene variant, known as A673T, has recently been found. It was discovered in the Icelandic population and reduces BACE1 cleavage by 40%. This translates into a lower presence of Aβ peptides, therefore less aggregation and, in the long term, less cognitive decline. In this context, the present review provides an integrated overview of APP physiology, its pathological roles in AD, the impact of genetic mutations and the distinctive protective mechanisms associated with the A673T variant.

**Amyloid Precursor Protein (APP) and Its Physiological Role**

Human APP gene is located on chromosome 21 and APP protein consists in a single transmembrane domain (type I). APP is ubiquitously expressed with a large ectodomain and a short cytoplasmic region. The extracellular domain also comprises two highly conserved subdomains, E1 and E2, which, in the central nervous system, are involved in the binding of metals such as copper and zinc, as well as heparin.

APP has three main isoforms, which are generated through differential splicing. These are, first, APP695, expressed predominantly in the brain and the other two isoforms are APP751 and APP770, which are located outside the central nervous system. Despite limited knowledge about its non-pathological function, it has been recognized that it has important physiological roles, mainly in the modulation of synapses during brain development and in neuronal plasticity, memory and neuroprotection in maturity and in the aging brain. In addition to this, it is believed that it could have a function as a growth factor [7-9].

*In-vitro* studies conducted in our laboratory show that APP plays an important role in phenotypic specification of human Neural Stem Cells (hNSCs). Specifically, we have observed that transient overexpression of APP induces an early exit of cell cycle in hNSCs and directs their differentiation toward glial cells (gliogenesis) while decreasing their differentiation toward neurons (neurogenesis) [10]. Subsequent studies further elucidated the molecular mechanisms involved, revealing that APP regulates these cell differentiation processes through multiple signaling pathways as Notch, Wnt, PI3K-AKT and JAK-STAT, among others [11]. Additionally, we found that low levels of APP promote neurogenesis while decreasing gliogenesis in hNSCs (effects opposite to those observed in transient overexpression of APP), highlighting the delicate modulatory role of APP in balancing neuronal and glial cell formation in hNSCs [12]. These findings provide new insights into the role of APP during neural development and suggest possible implications of this protein that help improve our understanding of AD.

**Role of APP in Alzheimer Disease Pathogenesis**

One of the histopathological characteristics observed in the brains of patients with AD is the presence of senile or amyloid plaques, which are extracellular in nature and caused by the accumulation of Amyloid Beta peptide (Aβ). The Aβ peptide comes from the sequential proteolysis of the Amyloid Precursor Protein (APP) [16]. To understand how APP is involved in AD, it is important to consider the proteolytic processing that this protein undergoes, as biologically active fragments are produced, each of which has specific or even opposing functions. This process of APP proteolysis is mediated mainly in two ways: the non-amyloidogenic pathway and the amyloidogenic pathway. The non-amyloidogenic processing pathway produces a large soluble

ectodomain (sAPP$\alpha$) and an 83-residue membrane-associated C-terminal fragment (C83) when $\alpha$-secretase cleaves APP within the Aβ domain. Alpha-secretase activity is present in several proteases belonging to the ADAM family. The P3 peptide and the intracellular domain of APP (AICD) are formed when γ-secretase cleaves C83.

In the amyloidogenic pathway, a membrane-bound protease called β-secretase cleaves APP at the N-terminal end of the Aβ domain, resulting in a 99-residue C-terminal fragment retained in the membrane (C99) and a soluble ectodomain (sAPPβ) which is 16 amino acids shorter than sAPP$\alpha$. This means that the second fragment released by the action of γ-secretase, the beta-amyloid peptide, will be 16 amino acids longer and it is this difference that alters its molecular properties and makes it insoluble in the extracellular medium, causing it to aggregate in senile plaques. γ-secretase, a membrane-bound complex that includes presenilin as a catalytic component, cleaves C99 to release AICD and Aβ peptides. γ-secretase cleavage produces Aβ peptides with various C-terminal ends, such as Aβ1-40 (Aβ40), Aβ1-42 (Aβ42) and other minor species [17].

The Aβ42 peptide, one of the main products of the amyloidogenic pathway of APP processing, is known for its high aggregation propensity and its central role in the pathogenesis of Alzheimer's disease. Its hydrophobic structure and tendency to form neurotoxic oligomers make it a key agent in synaptic dysfunction and neurodegeneration. Under physiological conditions, Aβ42 coexists with Aβ40, but even small variations in the ratio between these two species can drastically alter the balance between soluble and insoluble peptide forms, promoting the formation of fibrillar aggregates and amyloid plaques. In our laboratory, we have studied the effects of Aβ peptides (in its different conformations) on hNSCs. Firstly, we demonstrated that monomeric Aβ42 and Aβ40 peptides exert distinct but complementary effects on hNSCs. Specifically, monomeric Aβ42 promotes proliferation and gliogenesis, whereas monomeric Aβ40 enhances neurogenesis [13,14]. These findings highlight a differential role for the two major amyloid species in regulating stem cell fate decisions. Subsequently, we found that aggregated Aβ42 species affect hNSCs in different ways compared to monomeric peptides, with oligomeric and fibrillar Aβ42 showing variable influences on cell viability, differentiation and proliferation [15]. This comparative approach underscores the complexity of Aβ peptide biology in hNSCs and suggests that both peptide conformation and species critically modulate their functional outcomes.

In addition, there are other less common and lesser-known APP processing pathways because research on them is still very recent. These are known as the δ pathway, the η pathway, meprin-β cleavage and Caspase cleavage [9].

**APP Mutations and Their Impact in AD**

Mutations in the APP gene have been identified as a cause of familial early-onset Alzheimer's disease and to a lesser extent, in late-onset cases. Dominant mutations are mainly located in exons 16 and 17, near the β- and γ-secretase cleavage sites, promoting the amyloidogenic pathway and altering Aβ production. Most of these mutations affect APP processing. Additionally, APP locus duplications and two recessive mutations (pathogenic in the homozygous state) have also been reported [18].

The V717I (London) mutation was the first APP mutation linked to Familial Alzheimer's Disease (FAD) and remains the most common APP mutation in FAD [19]. Located within the transmembrane domain near the γ-secretase cleavage site, this mutation specifically increases Aβ42 production without significantly affecting Aβ40 levels, thereby elevating the Aβ42/Aβ40 ratio. The mutation alters the initial γ-secretase cleavage site, resulting in enhanced generation of both Aβ42 and Aβ38 peptides and affects intracellular APP trafficking within neurons.

The double mutation K670N/M671L (Swedish) dramatically increases overall Aβ generation by enhancing both Aβ40 and Aβ42 levels compared to wild-type APP [20]. The V716F (Indiana) mutation increases the Aβ42/Aβ40 ratio and is associated with very early disease onset (mean 42 years) and particularly severe pathology [21]. In contrast, the T714A (Iranian) mutation reduces total Aβ42 output while maintaining elevated Aβ42/Aβ40 ratio and is associated with atypical clinical features including prolonged prodromal amnesia [22]. Mutations at residue 693 also profoundly influence aggregation: the E693G (Arctic) mutation promotes protofibril assembly through an alternative pathogenic mechanism, accelerating formation of β-amyloid protofibrils without significantly increasing total Aβ production [23]. The E693Δ (Osaka) deletion represents a unique recessive mutation that accelerates Aβ oligomerization but inhibits fibril formation, causing disease only in homozygous carriers through intraneuronal accumulation of toxic oligomers and associated GABAergic dysfunction [24].

The D678N (Tottori) mutation, located immediately adjacent to the β-secretase cleavage site in exon 16, disrupts normal APP proteolysis and results in the production of mutant Aβ peptides (Asn7-Aβ) with altered properties [25]. The A673V mutation exhibits recessive inheritance and intensifies both amyloidogenic processing and Aβ aggregation, shifting APP metabolism

toward enhanced β-amyloid production while demonstrating that co-expression with wild-type Aβ creates unstable mixed aggregates that protect heterozygous carriers [26]. APP locus duplications raise APP gene dosage and drive Aβ overproduction , further validating the dose-dependent contribution of APP to AD pathogenesis and often presenting with additional clinical features such as seizures and cerebral amyloid angiopathy [27].

**Protective Variant of Alzheimer's Disease: APP A673T**

Given the central role that APP appears to play in the pathophysiology of AD, the identification of genetic variants with a protective effect, those capable of delaying the onset of the disease or reducing the risk of developing it, represents a significant opportunity to guide the design of new therapeutic strategies that prevent its onset or slow its progression [28,29].

**Discovery, Genetic Characteristics and Population Distribution**

To this end, a whole-genome sequencing study was conducted in 2012 on a cohort of 1,795 Icelanders with the aim of identifying new variants of the APP gene associated with a reduced risk of AD. The most relevant finding was the identification of a single nucleotide polymorphism (rs63750847, c.2017G>A,) present at position 673 of the gene, which causes the substitution of alanine for threonine (A673T, p.Ala673Thr), located adjacent to the β- secretase cleavage site and within the β-amyloid peptide sequence (position 2 of Aβ).

This rare variant, also known as the "Icelandic mutation," was detected mainly in control individuals and not in patients with AD and is currently one of the few known protective variants against late-onset AD [30].

At the population level, the frequency of the A673T variant shows marked geographical variation, being significantly more prevalent in Nordic populations: Finland (0.51%), Iceland (0.45%), Sweden (0.42%), Norway (0.21%) and Denmark (0.014%) [30,31]. In contrast, it is extremely rare in non-Nordic populations, being virtually absent in Asians and uncommon in the white North American population, where the mutation appears to be limited to certain races or ethnic groups [32-34].

The A673T variant was observed more frequently in elderly individuals (≥85 years) who also had higher cognitive performance than non-carriers. This finding suggests that the variant may play an important role in protecting against late-onset AD and mitigating age-related cognitive decline [30]. Furthermore, it has been proposed that A673T could contribute to prolonging longevity, as carriers were 50% more likely to reach 85 years of age compared to non-carriers. This evidence has been supported by a study by Kero, et al., which described a 104.8-year-old female A673T carrier with a low burden of β-amyloid pathology, probably attributed to concomitant hippocampal sclerosis [35]. The A673T allele also confers protection against cognitive decline in elderly individuals without Alzheimer's disease, the two could be mediated by the same or similar mechanisms or pathways. Previous research shows the A673T variant provides equal protection in both APOE ε4 carriers and non-carriers [36,37].

**Protective Molecular Mechanism of A673T**

The protective effect of A673T appears to be directly related to its proximity to the site of BACE1 (β-secretase) cleavage and its ability to reduce activity, shifting amyloidogenic APP processing toward the non-amyloidogenic pathway (Fig. 1). Early *in-vitro* assays conducted by Jonsson, et al., demonstrated that HEK293T cells transfected with the human APP-A673T variant had significantly reduced levels of the soluble fragment of APP processed by β-secretase (sAPPβ) relative to the fragment processed by $\alpha$-secretase (sAPP$\alpha$). In addition, the levels of Aβ40 and Aβ42 in the supernatants decreased by approximately 40% compared to cells transfected with wild-type APP, suggesting that A673T modulates BACE1 activity by reducing the generation of amyloidogenic peptides [30]. These results were subsequently replicated *in-vitro* in different experimental models. In primary mouse cortical neurons transfected with A673T-carrying cDNA and in isogenic neurons derived from human iPSCs expressing this variant, a consistent reduction in extracellular levels of Aβ40 and Aβ42 was observed [36,38]. Similarly, *in-vivo* studies demonstrated a 28% reduction in plasma levels of Aβ40 and Aβ42 in individuals carrying A673T compared to non-carriers [39]. Likewise, decreased levels of sAPPβ and Aβ42 (9% and 26% less, respectively) were detected in Cerebrospinal Fluid (CSF), along with a tendency toward a reduction in Aβ40. Proteomic analyses based on mass spectrometry also identified alterations in the regulation of proteins and phosphopeptides, suggesting that this variant could also reduce Tau phosphorylation [40].

Considering the protective effect associated with the A673T variant, recent studies have also explored its interaction with pathogenic APP mutations associated with AD. Guyon, et al., demonstrated that A673T can reduce Aβ40 and Aβ42 levels in the presence of certain causal mutations. In SH-SY5Y cells transfected with cDNA combining A673T with any of the 29 APP

mutations analyzed, a significant reduction in Aβ40 was observed in 10 variants and in Aβ42 in 14 of them [41]. In 2D and 3D human neuronal models, A673T also succeeded in decreasing sAPPβ levels even in the presence of two pathogenic APP mutations [40]. The protective effect *in-vivo* has also been proven in murine models of AD. In a line of APPG-F- A673T Knock-In (KI) mice carrying the Arctic and Beyreuther/Iberian mutations, the presence of A673T significantly reduced the amyloid burden in the cortex and hippocampus and plasma Aβ42 levels tended to be lower compared to animals without the variant [42]. In primary mouse cortical neurons and HEK293 cells transfected with human APP A673T, Aβ40 and Aβ42 production was reduced by approximately 35-40% compared to wild-type APP. Isogenic human iPSC-derived neurons expressing APP at endogenous levels confirmed that A673T reduces BACE1-mediated processing and β-CTF production. Critically, mutant A2T oligomers bind with significantly lower affinity to synaptic puncta compared to wild- type Aβ oligomers, representing a distinct protective mechanism since soluble oligomer binding to synapses initiates Alzheimer's-related toxicity [42].

Given the accumulated evidence linking A673T to a reduced risk of AD, gene editing strategies are also being explored to introduce this variant in a controlled manner. Tremblay, et al., developed a prime editing-based approach using a modified Cas9, through which they successfully inserted the A673T mutation into HEK293T cells [43]. Although the technique showed promising editing rates, the generation of unwanted adjacent mutations and the inability to accurately quantify insertion efficiency require further studies to assess its functional impact [41,43]. In contrast to the Aβ42 peptide, the Aβ42 modified by the A2T exhibits structural and biophysical properties that significantly reduce its aggregation capacity. Molecular dynamics studies have shown that the substitution of alanine with threonine at position 2 introduces a hydroxyl group capable of forming additional hydrogen bonds with the aqueous environment, increasing the solubility of the peptide and reducing hydrophobic interchain interactions. This results in decreased oligomer stability and a reduction in the formation of high-molecular weight toxic species typical of Aβ [42]. The N-terminal region of A2T frequently engages in electrostatic contacts with residues K16 and E22, further destabilizing pathogenic dimer interfaces. Overall, A673T decreases dimer stability, lowers aggregation potential and shifts oligomer distributions toward smaller assemblies (dimers, tetramers, hexamers) rather than neurotoxic dodecamers [44,45]. Taken together, these findings reinforce the hypothesis that the A673T variant could be a key tool for developing therapeutic strategies aimed at modulating Aβ production and mitigating or preventing the progression of AD. However, although the reduction in Aβ peptides partially explains its protective effect, the underlying molecular mechanisms are not yet fully understood. Enzymatic assays have shown that A673T does not alter the binding affinity of peptide substrates to BACE1, although it does reduce their processing rate [36]. On the other hand, unchanged levels of C99 relative to sAPPβ suggest that this variant may also modulate γ-secretase-mediated processing [38,46]. Future studies using models derived from induced pluripotent stem cells (hiPSCs) from A673T carriers could contribute to elucidating these molecular pathways more precisely [47,48].

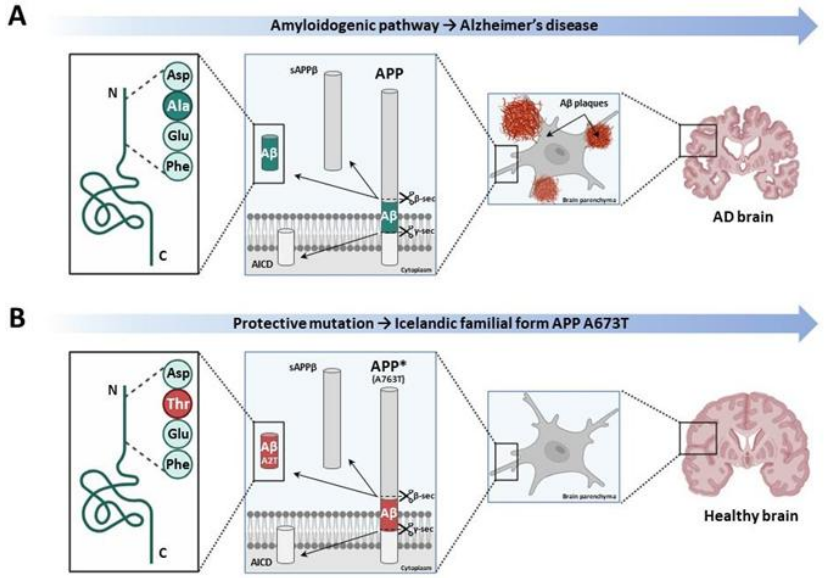


**Figure 1:** Amyloidogenic pathway in Alzheimer's disease and the protective effect of the APP A673T variant. (A) In the amyloidogenic pathway, native APP is processed to generate amyloid β (Aβ) peptides, which accumulate to form plaques leading to the neurodegeneration characteristic of Alzheimer's disease (AD). (B) The Icelandic protective mutation APP.

A673T alters APP processing, reducing Aβ generation and preventing amyloid plaque formation, which is associated with a healthy brain.

**Conclusion and Future Approaches**

After reviewing all the information, it is concluded that, although much progress has been made in understanding Alzheimer's disease, no curative or disease-modifying treatments have yet been developed. Therefore, it is essential to continue developing multidimensional therapeutic approaches to advance toward solutions that can offer real improvements in the progression of the disease. APP represents a promising target for compounds that modulate its processing. Strategies that mimic the protective mechanism of the A673T variant may offer new therapeutic opportunities. Although no clinical trials have directly targeted A673T, ongoing gene-editing studies and small-molecule screening approaches are expected to exploit its beneficial effects for Alzheimer's disease prevention and treatment development. Future studies using models derived from induced pluripotent stem cells (hiPSCs) from A673T carriers could contribute to elucidating these molecular pathways more precisely, establishing the foundation for developing more effective therapeutic interventions against Alzheimer's disease. It could be thought that the Aβ42-A2T peptide would aggregate more slowly and might form less stable and less neurotoxic structures. Thus, studying the A2T peptide and its molecular interactions with processing enzymes and other neuronal proteins represents a promising avenue to better understand the protective mechanisms of the A673T mutation and its therapeutic potential in Alzheimer's disease prevention.

**Conflict of Interest**

The authors declare no conflicts of interest.

**Acknowledgement**

This study was supported by the Grant PID2021-126715OB-I00 funded by MCIN/AEI/ 10.13039/501100011033 and "ERDF A way of making Europe", by the Grant of Instituto de Salud Carlos III (ISCIII) PI22CIII/00055 and by the Grant PI25/00008 funded by Instituto de Salud Carlos III (ISCIII). PEJ2018-004965 grant to R.G.S. funded by AEI; and the ISCIII- PFIS contract FI23CIII/00003 to P.M.M. The authors also thank to BioPlat plataform of ISCIII (https://www.isciiibiobanksbiomodels.es/centros/bioplat/).

**References**

1. Zhang XX, Tian Y, Wang ZT, Ma YH, Tan L, Yu JT. The epidemiology of alzheimer's disease modifiable risk factors and prevention. J Prev Alzheimers Dis. 2021;8(3):313-21.
2. Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: Pathobiology and targeting strategies. Nat Rev Neurol. 2019;15(9):501-18.
3. Lanoiselee HM, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, et al. APP, PSEN1 and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med. 2017;14(3):e1002270.
4. Roda AR, Serra-Mir G, Montoliu-Gaya L, Tiessler L, Villegas S. Amyloid-beta peptide and tau protein crosstalk in Alzheimer's disease. Neural Regen Res. 2022;17(8):1666-74.
5. Hardy JA, Higgins GA. Alzheimer's disease: The amyloid cascade hypothesis. Science. 1992;256(5054):184-5.
6. Frisoni GB, Aho E, Brayne C, Ciccarelli O, Dubois B, Fox NC, et al. Alzheimer's disease outlook: controversies and future directions. Lancet. 2025;406(10510):1424-42.
7. Galanis C, Fellenz M, Becker D, Bold C, Lichtenthaler SF, Muller UC, et al. Amyloid- beta mediates homeostatic synaptic plasticity. J Neurosci. 2021;41(24):5157-72.
8. Muller UC, Deller T. Editorial: The Physiological Functions of the APP Gene Family. Front Mol Neurosci. 2017;10:334.
9. Muller UC, Deller T, Korte M. Not just amyloid: Physiological functions of the amyloid precursor protein family. Nat Rev Neurosci. 2017;18(5):281-98.
10. Coronel R, Lachgar M, Bernabeu-Zornoza A, Palmer C, Dominguez-Alvaro M, Revilla A, et al. Neuronal and glial differentiation of human neural stem cells is regulated by Amyloid Precursor Protein (APP) levels. Mol Neurobiol. 2019;56(2):1248-61.
11. Coronel R, Bernabeu-Zornoza A, Palmer C, Gonzalez-Sastre R, Rosca A, Mateos- Martinez P, et al. Amyloid Precursor Protein (APP) regulates gliogenesis and neurogenesis of human neural stem cells by several signaling pathways. Int J Mol Sci. 2023;24(16).
12. Coronel R, Lopez-Alonso V, Gallego MI, Liste I. Low levels of Amyloid Precursor Protein (APP) promote neurogenesis and

decrease gliogenesis in human neural stem cells. Int J Mol Sci. 2023;24(19).
13. Bernabeu-Zornoza A, Coronel R, Palmer C, Calero M, Martinez-Serrano A, Cano E, et al. Abeta42 peptide promotes proliferation and gliogenesis in human neural stem cells. Mol Neurobiol. 2019;56(6):4023-36.
14. Bernabeu-Zornoza A, Coronel R, Palmer C, Martin A, Lopez-Alonso V, Liste I. Neurogenesis is increased in human neural stem cells by Abeta40 peptide. Int J Mol Sci. 2022;23(10).
15. Bernabeu-Zornoza A, Coronel R, Palmer C, Lopez-Alonso V, Liste I. Oligomeric and fibrillar species of Abeta42 diversely affect human neural stem cells. Int J Mol Sci. 2021;22(17).
16. Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. The amyloid-beta pathway in Alzheimer's Disease. Mol Psychiatry. 2021;26(10):5481-503.
17. Kaminsky YG, Marlatt MW, Smith MA, Kosenko EA. Subcellular and metabolic examination of amyloid-beta peptides in Alzheimer disease pathogenesis: Evidence for Abeta(25-35). Exp Neurol. 2010;221(1):26-37.
18. Seto M, Weiner RL, Dumitrescu L, Hohman TJ. Protective genes and pathways in Alzheimer's disease: Moving towards precision interventions. Mol Neurodegener. 2021;16(1):29.
19. De Jonghe C, Esselens C, Kumar-Singh S, Craessaerts K, Serneels S, Checler F, et al. Pathogenic APP mutations near the gamma-secretase cleavage site differentially affect Abeta secretion and APP C-terminal fragment stability. Hum Mol Genet. 2001;10(16):1665- 71.
20. Haass C, Lemere CA, Capell A, Citron M, Seubert P, Schenk D, et al. The Swedish mutation causes early-onset Alzheimer's disease by beta-secretase cleavage within the secretory pathway. Nat Med. 1995;1(12):1291-6.
21. Suzuki N, Cheung TT, Cai XD, Odaka A, Otvos L, Jr., Eckman C, et al. An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants. Science. 1994;264(5163):1336-40.
22. Pasalar P, Najmabadi H, Noorian AR, Moghimi B, Jannati A, Soltanzadeh A, et al. An Iranian family with Alzheimer's disease caused by a novel APP mutation (Thr714Ala). Neurology. 2002;58(10):1574-5.
23. Nilsberth C, Westlind-Danielsson A, Eckman CB, Condron MM, Axelman K, Forsell C, et al. The 'Arctic' APP mutation (E693G) causes Alzheimer's disease by enhanced Abeta protofibril formation. Nat Neurosci. 2001;4(9):887-93.
24. Tomiyama T, Nagata T, Shimada H, Teraoka R, Fukushima A, Kanemitsu H, et al. A new amyloid beta variant favoring oligomerization in Alzheimer's-type dementia. Ann Neurol. 2008;63(3):377-87.
25. Wakutani Y, Watanabe K, Adachi Y, Wada-Isoe K, Urakami K, Ninomiya H, et al. Novel amyloid precursor protein gene missense mutation (D678N) in probable familial Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2004;75(7):1039-42.
26. Giaccone G, Morbin M, Moda F, Botta M, Mazzoleni G, Uggetti A, et al. Neuropathology of the recessive A673V APP mutation: Alzheimer disease with distinctive features. Acta Neuropathol. 2010;120(6):803-12.
27. Sleegers K, Brouwers N, Gijselinck I, Theuns J, Goossens D, Wauters J, et al. APP duplication is sufficient to cause early onset Alzheimer's dementia with cerebral amyloid angiopathy. Brain. 2006;129(11):2977-83.
28. Andrews SJ, Fulton-Howard B, Goate A. Protective variants in Alzheimer's disease. Curr Genet Med Rep. 2019;7(1):1-12.
29. Owens LV, Benedetto A, Dawson N, Gaffney CJ, Parkin ET. Gene therapy-mediated enhancement of protective protein expression for the treatment of Alzheimer's disease. Brain Res. 2021;1753:147264.
30. Jonsson T, Atwal JK, Steinberg S, Snaedal J, Jonsson PV, Bjornsson S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature. 2012;488(7409):96-9.
31. Mengel-From J, Jeune B, Pentti T, McGue M, Christensen K, Christiansen L. The APP A673T frequency differs between Nordic countries. Neurobiol Aging. 2015;36(10):2909 e1-4.
32. Bamne MN, Demirci FY, Berman S, Snitz BE, Rosenthal SL, Wang X, et al. Investigation of an amyloid precursor protein protective mutation (A673T) in a North American case-control sample of late-onset Alzheimer's disease. Neurobiol Aging. 2014;35(7):1779 e15-6.
33. Liu YW, He YH, Zhang YX, Cai WW, Yang LQ, Xu LY, et al. Absence of A673T variant in APP gene indicates an alternative protective mechanism contributing to longevity in Chinese individuals. Neurobiol Aging. 2014;35(4):935 e11-2.
34. Wang LS, Naj AC, Graham RR, Crane PK, Kunkle BW, Cruchaga C, et al. Rarity of the Alzheimer disease-protective APP A673T variant in the United States. JAMA Neurol. 2015;72(2):209-16.
35. Kero M, Paetau A, Polvikoski T, Tanskanen M, Sulkava R, Jansson L, et al. Amyloid precursor protein (APP) A673T mutation in the elderly Finnish population. Neurobiol Aging. 2013;34(5):1518 e1-3.
36. Maloney JA, Bainbridge T, Gustafson A, Zhang S, Kyauk R, Steiner P, et al. Molecular mechanisms of Alzheimer disease protection by the A673T allele of amyloid precursor protein. J Biol Chem. 2014;289(45):30990-1000.

37. Khani M, Akcimen F, Grant SM, Akerman SC, Lee PS, Faghri F, et al. Biobank-scale characterization of Alzheimer's disease and related dementias identifies potential disease- causing variants, risk factors and genetic modifiers across diverse ancestries. medRxiv. 2024.
38. Benilova I, Gallardo R, Ungureanu AA, Castillo Cano V, Snellinx A, Ramakers M, et al. The Alzheimer disease protective mutation A2T modulates kinetic and thermodynamic properties of amyloid-beta (Abeta) aggregation. J Biol Chem. 2014;289(45):30977-89.
39. Martiskainen H, Herukka SK, Stancakova A, Paananen J, Soininen H, Kuusisto J, et al. Decreased plasma beta-amyloid in the Alzheimer's disease APP A673T variant carriers. Ann Neurol. 2017;82(1):128-32.
40. Wittrahm R, Takalo M, Kuulasmaa T, Makinen PM, Makinen P, Koncarevic S, et al. Protective Alzheimer's disease-associated APP A673T variant predominantly decreases sAPPbeta levels in cerebrospinal fluid and 2D/3D cell culture models. Neurobiol Dis. 2023;182:106140.
41. Guyon A, Rousseau J, Begin FG, Bertin T, Lamothe G, Tremblay JP. Base editing strategy for insertion of the A673T mutation in the APP gene to prevent the development of AD *in-vitro*. Mol Ther Nucleic Acids. 2021;24:253-63.
42. Shimohama S, Fujioka R, Mihira N, Sekiguchi M, Sartori L, Joho D, et al. The icelandic mutation (APP-A673T) is protective against amyloid pathology *in-vivo*. J Neurosci. 2024;44(47).
43. Tremblay G, Rousseau J, Mbakam CH, Tremblay JP. Insertion of the icelandic mutation (A673T) by prime editing: A potential preventive treatment for familial and sporadic Alzheimer's disease. CRISPR J. 2022;5(1):109-22.
44. Coskuner-Weber O, Uversky VN. Insights into the molecular mechanisms of Alzheimer's and Parkinson's diseases with molecular simulations: understanding the roles of artificial and pathological missense mutations in intrinsically disordered proteins related to pathology. Int J Mol Sci. 2018;19(2).
45. Das P, Murray B, Belfort G. Alzheimer's protective A2T mutation changes the conformational landscape of the Abeta(1)(4)(2) monomer differently than does the A2V mutation. Biophys J. 2015;108(3):738-47.
46. Kokawa A, Ishihara S, Fujiwara H, Nobuhara M, Iwata M, Ihara Y, et al. The A673T mutation in the amyloid precursor protein reduces the production of beta-amyloid protein from its beta-carboxyl terminal fragment in cells. Acta Neuropathol Commun. 2015;3:66.
47. Lehtonen S, Hoytylainen I, Voutilainen J, Sonninen TM, Kuusisto J, Laakso M, et al. Generation of a human induced pluripotent stem cell line from a patient with a rare A673T variant in amyloid precursor protein gene that reduces the risk for Alzheimer's disease. Stem Cell Res. 2018;30:96-9.
48. Rolova T, Wu YC, Koskuvi M, Voutilainen J, Sonninen TM, Kuusisto J, et al. Generation of a human induced pluripotent stem cell line (UEFi003-A) carrying heterozygous A673T variant in amyloid precursor protein associated with a reduced risk of Alzheimer's disease. Stem Cell Res. 2020;48:101968.