ISSN 2449-8955 European Journal of Biological Research *Research Article*

DOI: http://dx.doi.org/10.5281/zenodo.4641962

Analysis of early onset of Alzheimer's disease genes: disease causing and risk factors

Prama Pandey, Poonam Sharma*

Department of Zoology, Gargi College, University of Delhi, Delhi, India

* Corresponding author: Phone: 011-4604-0310, E-mail: poonam.sharma@gargi.du.ac.in

Received: 18 January 2021; **Revised submission:** 21 February 2021; **Accepted:** 27 March 2021

https://jbrodka.com/index.php/ejbr

ABSTRACT: Alzheimer's disease is on the rise around the globe and is ranked sixth in the United States as the leading cause of death. It is a progressive neurodegenerative disease and the main causes of dementia. It is often characterized by symptoms such as lack of memory, agitation, restlessness, changes in personality, inability to perform everyday tasks, and impairment of speech. There are two forms of Alzheimer's disease: early onset of Alzheimer's disease occurring before 65 years of age, manifesting in 5-10% of the population, and late-onset of Alzheimer's disease manifesting after 65 years of age. In this study, the role of single nucleotide polymorphism in Alzheimer's disease using genome-wide association studies was investigated. Further, mutations underlying early onset of Alzheimer's disease were analyzed and it was found that mutations in the six genes *APP*, *PSEN1*, *PSEN2*, *MAPT*, *GRN* and *PRNP* resulted in the structural and functional protein modifications. These altered amino acids in early onset of Alzheimer's disease contribute to its pathogenesis. A single change in these genes is inherited in an autosomal dominant manner and might lead to early onset of Alzheimer's disease, however sporadic cases have also been identified.

Keywords: Alzheimer's disease; Single nucleotide polymorphism; EOAD; Amyloid; Tau.

1. INTRODUCTION

Alzheimer's disease is the leading cause of dementia. When a person younger than 65 years of age develops Alzheimer's, he is said to be suffering from Early Onset of Alzheimer's Disease (EOAD). EOAD can be of two types: Common Alzheimer disease (progresses similarly to Late Alzheimer), and Familial Alzheimer (it is controlled by a variety of genes) [1, 2]. Alzheimer disease affects the brain of an individual, the damage begins at the hippocampal region and the entorhinal region, located in the temporal lobe and responsible for memory formation. As the number of dead healthier neurons increases, the disease progresses to additional parts of the brain and the brain tissue further degenerates interfering with trivial processes of swallowing, walking, memorizing and talking etc. This loss of brain tissue is attributed to the deposition of abnormal amounts of extracellular amyloid and intracellular tau proteins [3].

These abnormal depositions are a result of single nucleotide polymorphisms (SNPs) in DNA nucleotides. SNPs causing non-synonymous mutations (missense or non-sense) lead to the production of protein products which are entirely different from the original protein in terms of charge, size and overall

effect. This modified amino acid sequence leads to improper cleavage of the APP protein, disrupted cleavage activity by PSEN 1 and 2 and hyper-phosphorylation of MAPT protein [4, 5]. These mutations ultimately lead to the pathophysiology of Alzheimer disease which includes the presence of intracellular tau filaments, extracellular beta-amyloid plaques and inflammation [6, 7]. Symptoms of EOAD include dementia – the gradual loss of cognition, memory and judgement, loss of ability to function, behavioural and personality changes, subtle memory loss at first and then worsening of memory, difficulty in recognizing people, inability to perform daily chores such as, cooking meal, doing laundry etc. restlessness, agitation and loss of communication skills [8].

2. MATERIALS AND METHODS

Genetics Home Reference (GHR), a National Library for Medicine, consisting of information about genetic diseases was used. Using GHR site Pathogenic alleles responsible for EOAD were analyzed and the function of the proteins encoded by these genes and the families they belong to were investigated and recorded.

Then, using the NCBI-gene site, transcript mutation and rsIDs were identified. NCBI-SNP database was used to study the codon change and amino acid sequence changes were identified. The data are recorded in the form tables (Table 1 and Table 2).

Table 1. Table showing genes responsible for EOAD, functions of the proteins they encode for and their protein families.

Gene	Protein family function	Common function
APP	Proteins of this family are important for nervous system development (neuron migration, synaptogenesis, neurite outgrowth and axonal pathfinding). App proteins can function using multiple-modes, these can function as ligands via their secreted fragments or as cell surface proteins carrying signal transduction and adhesion.	All the three members of *APP* gene family, APP, APLP1, APLP2 associate with NMDA receptor and enhance its cell surface expression. NMDA receptors are important in synaptic plasticity and memory.
PSEN 1	Presenilins function in developmental signaling, apoptosis, and processing amyloid beta proteins.	They form catalytic units of gamma secretase.
PSEN 2	Same as *PSEN 1*	Same as *PSEN 1*
MAPT	Members of the family function in binding to and stabilizing microtubules.	All of them are associated with microtubules and make them stable.
GRN	All the members of the family are secreted proteins and function in cell growth and proliferation.	They might be inhibitors, stimulators or both however, all of them have a function in cell growth.
PRNP	Prion family of proteins function in early embryo-genesis.	Two proteins of the family have a neuroprotective function. However, one member of the protein family is present in the testes.

Table 2. Table showing pathogenic alleles of the genes responsible for EOAD (only some of the data is provided).

Gene	Transcript mutation	rsID	Amino acid sequence change	Effect	Medical consequence
APP	c.2150T>G c.2078T>G	rs63749964	V717G V693G	Hydrophobic valine having a longer hydrocarbon chain is replaced by hydro-phobic glycine having only a Hydrogen atom as its side chain.	Pathogenic
	c.2149G>T c.2077G>T	rs63750264	V717F V693F	Hydrophobic valine is replaced by a hydrophobic aromatic amino acid.	Pathogenic
	c.2074A>G c.1753A>G	rs63750399	I692V I585V	Hydrophobic isoleucine is replaced by hydrophobic valine whose	Pathogenic

Gene	Transcript mutation	rsID	Amino acid sequence change	Effect	Medical consequence
				hydrocarbon chain is shorter as compared to it.	
	c.2143G>A c.2071G>A	rs63750734	V715M V691M	Hydrophobic valine is replaced by hydrophobic methionine having a sulfur in its side chain.	Pathogenic
	c.2141C>T c.2069C>T	rs63750973	T714I T690I	Polar threonine is replaced by non-polar isoleucine.	Pathogenic
	c.2140A>G c.2068A>G	rs63750643	T714A T714A	Polar threonine is replaced by non-polar alanine.	Pathogenic
	c.2137G>A c.2065G>A	rs63750066	A713T A689T	Non-polar alanine is replaced by polar threonine.	Pathogenic
APP	c.2080G>A c.20G>A	rs63749810	D694N D670N	Negatively charged amino acid is replaced by polar uncharged amino acid.	Pathogenic
	c.2078A>G c.2006A>G	rs63751039	E693G E669G	Non-polar glycine is added instead of polar glutamate.	Pathogenic
	c.2077G>C c.2005G>C	rs63750579	E693Q E669Q	Non-polar glycine is replaced by polar glutamate	Pathogenic
	c.2075C>G c.2003C>G	rs63750671	A692G A668G	Non-polar alanine is replaced by non-polar glycine having only an H in its side chain.	Pathogenic
	c.2018C>T c.1946C>T	rs193922916	A673V A649V	Non-polar alanine is replaced by a non-polar valine having a longer side chain.	Pathogenic
	c.1995G>C c.1923G>C	rs63750363	E665D E643D	Positively charged glutamic acid is replaced by another positively charged aspartic acid, which has a shorter side chain.	Pathogenic
	c.236C>T c.224C>T	rs63749824	A79V A75V	Non-polar alanine is replaced by a non-polar valine having a longer side chain.	Pathogenic
	c.254T>C c.242T>C	rs63750599	L85P L81P	Non-polar amino acid is replaced by polar uncharged proline.	Pathogenic
	c.265G>T c.253G>T	rs63750815	V89L V85L	Hydrophobic valine having a longer side chain is replaced by another hydrophobic leucine having a shorter side chain.	Pathogenic
	c.275G>C c.263G>C	rs63751141	C92S C88S	Polar cysteine has a thiol is replaced by another polar amino acid serine.	Pathogenic
	c.314T>G c.302T>G	rs1057518919	F105C F101C	Aromatic amino acid is replaced by polar, uncharged cysteine.	Pathogenic
PSEN 1	c.338T>A c.326T>A	rs63751399	L113Q L109Q	Non-polar leucine is replaced by polar glutamine.	Pathogenic
	c.344A>G c.344A>G	rs63750450	Y115C	Aromatic amino acid tyrosine is replaced by a polar cysteine.	Pathogenic
	c.347C>A c.335C>A	rs63750730	T116N T112N	Polar threonine containing a hydroxyl group is replaced by polar asparagine having an amide group in its side chain.	Pathogenic
	c.360A>T c.348A>T	rs63751272	E120D E116D	Negatively charged glutamic acid is replaced by another negatively charged aspartic acid whose side chain is shorter.	Pathogenic
	c.404A>G c.392A>G	rs63751278	N135S N131S	Polar asparagine having an amide in its side chain is replaced by polar serine having a hydroxyl group.	Pathogenic
PSEN 2	c.254C>T	rs63750048	A85V	Hydrophobic alanine is replaced by hydrophobic valine having a longer side chain.	Pathogenic
	c.364A>C	rs63749851	T122P	Polar uncharged threonine is replaced by polar uncharged proline having a	Pathogenic

Gene	Transcript mutation	rsID	Amino acid sequence change	Effect	Medical consequence
				ring in its side chain.	
	c.365C>G	rs28936380	T122R	Polar uncharged amino acid is replaced by positively charged arginine.	Pathogenic
	c.389C>T	rs63750197	S130L	Polar uncharged amino acid is replaced by a non-polar amino acid.	Pathogenic
PSEN 2	c.422A>T	rs63750215	N141I	Polar uncharged amino acid amino acid is replaced by non-polar amino acid.	Pathogenic
	c.717G>A	rs63749884	M239I	Sulfur containing non-polar methionine is replaced by non-polar isoleucine.	Pathogenic
	c.1289C>T	rs63750666	T430M	Polar uncharged threonine is replaced by sulfur containing non-polar methionine.	Pathogenic
	c.1316A>C	rs63750110	D439A	Negatively charged amino acid is replaced by non-polar alanine.	Pathogenic
	c.2T>C	rs63751006	M1T	Non-polar amino acid gets replaced by a polar amino acid.	Pathogenic
	c.26C>A	rs63751243	A9D	Non-polar alanine gets replaced by polar aspartate.	Pathogenic
GRN	c.26C>T	rs63751243	A9V	Non-polar alanine is replaced by non-polar valine having a longer side chain.	Pathogenic
	c.373C>T	rs63750077	Z125Ter	Early termination fails to incorporate glutamate.	Pathogenic
	c.305C>T	rs74315401	P102L	Non-polar proline having secondary imine is replaced by a non-polar amine containing leucine.	Pathogenic
PRNP	c.385A>G	rs1799990	M129V	Non-polar amino acid containing sulphur gets replaced by a non-polar amino acid having a hydrocarbon side chain.	Pathogenic
	c.435T>G	rs80356710	Y145Ter	Early termination fails to incorporate tyrosine.	Pathogenic
	c.350C>T	rs74315402	A117V	Non-polar alanine is replaced by non-polar valine having a longer side chain	Pathogenic

3. RESULTS AND DISCUSSION

The present study illustrated that mutations in primarily three genes is responsible for early onset of Alzheimer's Disease: APP, PSEN1 and PSEN2 (Table 2).

3.1. *APP* gene

APP gene present on the long arm (q) of chromosome 21 (21q21.3) encodes for APP protein, which is a type 1 membrane protein (integral membrane protein having its amino- terminal facing the extracellular side) [9]. This protein has two domains; larger extracellular and smaller intracellular. Two cleavage events occur in these proteins: β-secretase cleavage occurs in the extracellular domain and γ-secretase cleavage which occurs in the intracellular domain. During amyloidogenic processing of APP, β-secretase or beta site cleaving enzyme (BACE) cleaves the amyloid beta-protein at its N-terminus to produce soluble amyloid protein (sAPPβ) and a 99 amino acid C-terminal residue (C99) (Fig. 1). Subsequently, γ-secretase (membrane protein) along with presenilin (catalytic component) cleaves the C99 fragment to produce an amyloid beta-

protein (Aβ) and APP intracellular domain (AICD) [10, 11]. The cleavage sites for γ-secretase are diverse and therefore, Aβ having different C-termini are produced ranging from, Aβ1- 40 (Aβ40), Aβ1- 42. The function of APP in the central nervous system is neural proliferation, migration, synaptogenesis and neural plasticity. Under normal physiological conditions, Aβ40 to Aβ42 ratio is high, that is, amyloid beta 40 is produced predominantly.

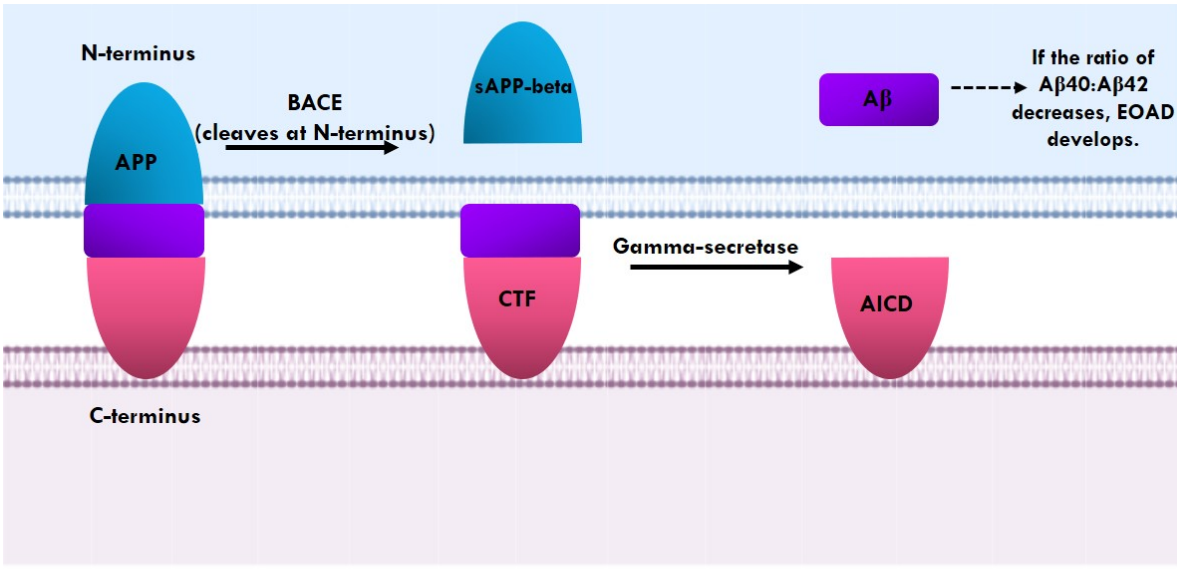

Figure 1. Amyloid processing of APP protein.

More than 25 *APP* mutations that can result in EOAD have been identified. These mutations in the *APP* gene might result in an augmented quantity of β-peptide amyloid. Another possibility can be that these mutations which modify the charge or the length of the side chain, ultimately produce a protein having a totally different conformation e.g., a longer sticky peptide which accumulates in the brain to form amyloid plaques. Hence, Aβ40 to Aβ42 ratio goes down producing Aβ42 predominantly in the cell. This form of amyloid beta- protein is neurotoxic since it leads to the formation of amyloid plaques which deposit extracellularly and lead to the death of brain tissue [4, 12, 13].

3.2. *PSEN 1 (Presenilin 1)*

This gene is present on the long arm (q) of chromosome 14 (14q24.2) *PSEN 1* gene product forms an indispensable part of γ-secretase which functions in cleaving of amyloid beta protein [14, 15]. For *PSEN 1* gene more than 62 mutations were identified. A relatively common variation positions are polar asparagine having an amide in its side chain at positions 131 and 135 is replaced by polar serine having a hydroxyl group are suspected to take place at sites which directly interact with amyloid protein for its cleavage. It is also reported that *PSEN 1* mutations result in the production of an abnormal protein called presenilin-1[16, 17]. This faulty presenilin 1 protein obstructs the role of the γ-secretase complex; hence, the production of APP is altered and excess longer, toxic amyloid-β peptides are produced [18]. These then bind together into clumps called amyloid plaques in the brain eventually leading to death of nerve cells and steady symbols and indications of EOAD.

3.3. *PSEN 2 (Presenilin 2)*

This gene is present on the long arm (q) of chromosome 1 (1q42.13) [19]. *PSEN 2* gene product is also a prime component of γ-secretase along with PSEN1. Presenilin 2 is involved in the amyloid precursor protein processing in the brain. Presenilin 2 is reported to break amyloid precursor protein into smaller peptides; soluble amyloid precursor protein (sAPP) and amyloid beta peptide. Mutations, where a polar uncharged amino acid like asparagine is replaced by a non-polar isoleucine amino acid alters the activity of γ-secretase in the region of protein which interacts with amyloid protein to cleave it, causing impaired amyloid precursor protein processing and overproduction of amyloid beta peptide. Consequently, this results in deposition of amyloid plaques and neurons' death. All these mutations lead to inappropriate cleaving amyloid protein and produce Aβ42 in excessive amounts, as a consequence of which extracellular plaques get deposited [17, 19, 20].

3.4. *MAPT*

Microtubule associated protein Tau *(MAPT)* gene present on the long arm(q) of chromosome 17 (17q21) encodes for tau protein [21]. Tau protein interacts with tubulin proteins and helps in their assembly into microtubules. Microtubule assembly by tau, which is a phosphoprotein is dependent upon the level of phosphorylation. Under normal physiological conditions, an adult human brain has 2-3 moles of phosphate/ mole of tau protein. However, during Alzheimer's tau protein gets 3-4 times hyper-phosphorylated as compared to its normal levels; it is during this state that tau proteins detach from microtubules and attach to form tangled threads inside neurons [22]. Inside neurons, there are 6 isoforms of this protein, three of these isoforms have 3 repeating segments in microtubule-binding domain whereas rest 3 proteins have 4 repeating segments in the microtubule-binding domain. Neurons have a 1:1 ratio of 3-repeats isoforms and 4-repeats isoforms, this ratio is crucial in maintaining normal cellular function. *MAPT* gene can therefore act as a potent risk factor for development of EOAD [23, 24].

3.5. *GRN*

GRN gene is present on the long arm (q) of chromosome 17, somewhere around the *MAPT* gene. *GRN* gene is responsible for providing instructions to encode the progranulin protein (PGRN) [25]. The progranulins can be further cleaved into their active forms granulins (GRN) in seven different ways. GRN is a secreted protein, therefore it establishes its function outside the cell, it is responsible for cell-cell signalling, acts as a growth factor, helps in cell proliferation and wound repair. Loss of function mutations in one of the heterozygous combination of alleles leads to haploinsufficient gene product of a single allele in a diploid locus and is unable to generate threshold level of gene products [26]. As a result, such haploinsufficient individuals only have half the functional progranulin protein and hence, only half the functional granulins. It has been suspected that deficiency in this protein leads to the build-up of TDP-43 (TAR DNA binding protein). TDP-43 forms aggregate inside the nucleus, disrupts cellular functions and leads to cell death [27, 28, 29].

3.6. *PRNP*

Prnp gene, present on chromosome 20 encodes for prion proteins (PrP) the proposed functions of this gene are neuroprotection, buffering of copper and zinc ions in the synaptic cleft, myelin sheath maintenance in PNS, it also prevents the formation of reactive oxygen species (ROS) formed as a result of copper-mediated redox reactions, these also have important roles during embryogenesis, recent studies also suggest its role in spatial learning and memory formation [30]. PrP is a cell surface protein and a key player in prion disease [31]. This disease usually results from misfolding of prion proteins and their aggregation, further stimulating

misfolding in normal native proteins. This misfolding, characterized by various pathogenic mutations resulting either from substitution or early termination (Table 2) changes expected side chain of amino acids which interrupts the overall charge on the protein. This mutated protein is a major contributor to neurodegenerative diseases. It is also speculated that A β protein interacts with PrP receptor on the cell surface and causes a reduction in long-term potentiation (LTP) which is characteristic of Alzheimer's [32, 33].

4. CONCLUSIONS

Early Onset of Alzheimer's Disease (EOAD) is inherited in an autosomal dominant fashion. The five primary genes found responsible for the condition are *APP, PSEN1 and PSEN2, GRN* and *PRNP*. Mutations in these genes, which are all located on the long arm of chromosomes are responsible for the deposition of the extracellular amyloid plaques. Mutations in another gene *MAPT*, generates intracellular tau tangles and hence indirectly leads to EOAD. Mutations in *GRN* gene lead to the development of aggregations inside the nucleus and the misfolding of prion protein as a result of mutations in *PRNP* as well as the interaction of amyloid-beta with prion protein are also speculated to be the major contributors. All these manifestations of the respective genes ultimately lead to the shrinkage of brain tissue and consequently, claiming the patient's life. Death of the person primarily occurs because normal physiological functions such as breathing, swallowing etc. get impaired. The SNPs in these genes lead to misfolded proteins as few of these contribute to the incorporation of wrong amino acid, such as replacing a hydrophobic, non-polar amino acid with a hydrophilic, polar amino acid alters the charge on the side chain which can alter the normal protein function by changing the overall conformation of the protein. Such SNPs in *APP* gene are suspected to cause improper cleavage of amyloid protein by γ-secretase and presenilins. SNPs in *PSEN 1* and *2* impair the function of presenilins which in turn impairs the cleavage activity of γ-secretase. The MAPT gene on the contrary gets hyper-phosphorylated due to mutations in genes encoding for kinases and phosphatases. Haploinsufficient product obtained due to mutated *GRN* leads to aggregation of TDP-43. PrP protein on the other hand gets misfolded, it further transmits this state to native proteins and is speculated to interact with amyloid-beta protein. Investigation of these SNPs as a risk factor to better understand their detrimental effect is of great relevance not only for their role as biomarkers but also as these provide insight into the process of EOAD progression These above-identified SNPs can prove beneficial in developing gene therapeutic procedures specific to Alzheimer's. Further study and validation of the identified SNPs will be required to determine their clinical value and use for translation research as novel targets.

Authors' Contributions: Both authors contributed equally to this work. Both authors read and approved the final manuscript.

Conflict of Interest: The authors have no conflict of interest to declare.

Acknowledgment: This work was supported by DBT STAR College grant and Gargi College, University of Delhi.

REFERENCES

1. Early-Onset of Alzheimer's Disease, John Hopkins Medicine https://www.hopkinsmedicine.org/health/conditions-and-diseases/alzheimers-disease/earlyonset-alzheimer-disease
2. Tellechea P, Pujol N, Esteve-Belloch P, Echeveste B, García-Eulate MR, Arbizu J, Riverol M. Early- and late-onset Alzheimer disease: Are they the same entity? Enfermedad de Alzheimer de inicio precoz y de inicio tardío: ¿son la misma entidad? Neurologia. 2018; 33(4): 244-253.

3. Alzheimer's Disease fact sheet, National Institute on Aging https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet
4. Dai M, Zheng H, Zeng L, Zhang Y. The genes associated with early-onset Alzheimer's disease. Oncotarget. 2018; 9: 15132-15143.
5. Roks G, Dermaut B, Heutink P, Julliams A, Backhovens H, Van de Broeck M, et al. Mutation screening of the tau gene in patients with early-onset Alzheimer's disease. Neurosci Lett. 1999; 277(2):137-139.
6. de Paula VJR, Guimarães FM, Diniz BS, Forlenza OV. Neurobiological pathways to Alzheimer's disease: Amyloid-beta, TAU protein or both? Dement Neuropsychol. 2009; 3(3): 188-194.
7. Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res. 2018; 7: 1161.
8. National Institute of Health, U.S Department of Health and Human Services https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet
9. Zhang Yw, Thompson R, Zhang H, Xu H. APP processing in Alzheimer's disease. Mol Brain. 2011; 4: 3.
10. Brouwers N, Sleegers K, Van Broeckhoven C. Molecular genetics of Alzheimer's disease: an update. Ann Med. 2008; 40(8): 562-83.
11. Dai M, Zheng H, Zeng L, Zhang Y. The genes associated with early-onset Alzheimer's disease. Oncotarget. 2018; 9: 15132-15143.
12. Deng L, Haynes PA, Wu Y, Amirkhani A, Kamath KS, Wu JX, et al. Amyloid-beta peptide neurotoxicity in human neuronal cells is associated with modulation of insulin-like growth factor transport, lysosomal machinery and extracellular matrix receptor interactions. Neural Regen Res. 2020; 15(11): 2131-2142.
13. Tcw J, Goate AM. Genetics of β-Amyloid Precursor Protein in Alzheimer's Disease. Cold Spring Harb Perspect Med. 2017; 7(6): a024539.
14. Bekris LM, Yu CE, Bird TD, Tsuang DW. Genetics of Alzheimer disease. J Geriatr Psychiatry Neurol. 2010; 23(4): 213-227.
15. Chen GF, Xu TH, Yan Y, Zhou YR, Jiang Y, Melcher K, Xu HE. Amyloid beta: structure, biology and structure-based therapeutic development. Acta Pharmacol Sin. 2017; 38(9): 1205-1235.
16. De Strooper B. Loss-of-function presenilin mutations in Alzheimer disease. Talking Point on the role of presenilin mutations in Alzheimer disease. EMBO Rep. 2007; 8(2): 141-146.
17. Giri M, Zhang M, Lü Y. Genes associated with Alzheimer's disease: an overview and current status. Clin Interv Aging. 2016; 11: 665-681.
18. Zhang S, Zhang M, Cai F, Song W. Biological function of Presenilin and its role in AD pathogenesis. Transl Neurodegener. 2013; 2: 15.
19. Cai Y, An SS, Kim S. Mutations in presenilin 2 and its implications in Alzheimer's disease and other dementia-associated disorders. Clin Interv Aging. 2015; 10: 1163-1172.
20. Giau VV, Bagyinszky E, Youn YC, An SSA, Kim S. *APP, PSEN1*, and *PSEN2* Mutations in Asian Patients with Early-Onset Alzheimer Disease. Int J Mol Sci. 2019; 20(19): 4757.
21. Jun G, Ibrahim-Verbaas CA, Vronskaya M, Lambert JC, Chung J, Naj AC, et al. A novel Alzheimer disease locus located near the gene encoding tau protein. Mol Psychiatry. 2016; 21(1):108-117.
22. Alonso AD, Cohen LS, Corbo C, Morozova V, ElIdrissi A, Phillips G, Kleiman FE. Hyperphosphorylation of Tau Associates with changes in Its function beyond microtubule stability. Front Cell Neurosci. 2018; 12: 338.
23. Iqbal K, Liu F, Gong CX, Grundke-Iqbal I. Tau in Alzheimer disease and related tauopathies. Curr Alzheimer Res. 2010; 7(8): 656-664.

24. Kar S, Fan J, Smith MJ, Goedert M, Amos LA. Repeat motifs of tau bind to the insides of microtubules in the absence of taxol. EMBO. 2003; 22(1): 70-77.
25. Townley RA, Boeve BF, Benarroch EE. Progranulin: Functions and neurologic correlations. Neurology. 2018; 90(3): 118-125.
26. Nicholson AM, Finch NA, Almeida M, Perkerson RB, van Blitterswijk M, Wojtas A, et al. Prosaposin is a regulator of progranulin levels and oligomerization. Nat Commun. 2016; 7: 11992.
27. GRN-related frontotemporal lobar degeneration, Genetics Home Reference.
28. Mukherjee O, Wang J, Gitcho, M, Chakraverty S, Taylor-Reinwald L, Shears S, et al. Molecular characterization of novel progranulin (GRN) mutations in frontotemporal dementia. Human mutation. 2008; 29(4): 512-521.
29. Arrant AE, Roth, JR, Boyle NR, Kashyap SN, Hoffmann MQ, Murchison CF, et al. Impaired β-glucocerebrosidase activity and processing in frontotemporal dementia due to progranulin mutations. Acta Neuropathol Commun. 2019; 7: 218.
30. Bernardi L, Bruni AC. Mutations in Prion Protein Gene: Pathogenic Mechanisms in C-Terminal vs. N-Terminal Domain, a Review. Int J Mol Sci. 2019; 20(14): 3606.
31. Wulf, MA, Senatore A, Aguzzi A. The biological function of the cellular prion protein: an update. BMC Biol. 2017; 15: 34.
32. PRNP gene, Genetics Home Reference.
33. Bagyinszky E, Kang MJ, Pyun J, Giau VV, An SSA, Kim S. Early-onset Alzheimer's disease patient with prion *(PRNP)* p. Val180Ile mutation. Neuropsychiatr Dis Treat. 2019; 15: 2003-2013.