A pathogenic PSEN1 Trp165Cys mutation associated with early-onset Alzheimer’s disease

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Abstract

Background: Presenilin-1 (PSEN1) is one of the causative genes for early onset Alzheimer’s disease (EOAD). Recently, emerging studies reported several novel PSEN1 mutations among Asian. We describe a male with EOAD had a pathogenic PSEN1 mutation.

Case presentation: A 53-year-old male presented with memory decline, followed by difficulty in finding ways. Patient had positive family history, since his mother and one of his brother was also affected with dementia. Brain magnetic resonance imaging (MRI) scan showed mild degree of atrophy of bilateral hippocampus and parietal lobe. ¹⁸F-Florbetaben-PET (FBB-PET) revealed increased amyloid deposition in bilateral frontal, parietal, temporal lobe and precuneus. Whole exome analysis revealed a heterozygous, probably pathogenic PSEN1 (c.695G>T, p.W165C) mutation. Interestingly, Trp165Cys mutation is located in trans membrane (TM)-III region, which is conserved between PSEN1/PSEN2. In vitro studies revealed that PSEN1 Trp165Cys could result in disturbances in amyloid metabolism. This prediction was confirmed by structure predictions and previous in vitro studies that the p.Trp165Cys could result in decreased Aβ42/Aβ40 ratios.

Conclusion: We report a case of EOAD having a pathogenic PSEN1 (Trp165Cys) confirmed with in silico and in vitro predictions.

Keywords: Pathogenic, PSEN1, Trp165Cys, Mutation, Alzheimer’s disease

Background

Alzheimer’s disease (AD) (MIM #104300) is a neurodegenerative disease among elders, which is resulted by abnormal protein assembly inside the brain. Extracellular and intracellular amyloid beta (Aβ) and Tau protein, respectively, were associated as the main hallmarks of the disease. Early onset AD (EOAD) and late onset AD (LOAD) are the two main forms of the disease. Three genes were verified as causative factor for EOAD: amyloid precursor protein (APP) (MIM #104760) [1], presenilin 1 (PSEN1) (MIM #104331) [2], and presenilin 2 (PSEN2) (MIM #600759) [3]. Approximately 300 mutations of PSEN1, PSEN2, and APP in 635 affected individuals or families have been reported in the Dementia Mutation Database [4] (https://www.alzforum.org/mutations). Majority of mutations were observed in PSEN1 [5–7] (n = 219, 76.6%) with over 230 mutations reported as pathogenic in the Alzforum database (https://www.alzforum.org/mutations/pсен1), as compared to APP (n = 51, 17.8%), and PSEN2 (n = 16, 5.6%) [8–11].

PSEN1 protein contains nine transmembrane (TM) domains, connected with hydrophilic loop regions. As the member of γ-secretase complex, PSEN1 could function as a catalytic subunit of aspartyl protease, involved in the cleavage of C99 residue in APP protein into β-amyloid (Aβ) peptide. PSEN1 mutations may impair the γ-secretase processing, resulting in altered of Aβ production. Gain-of-function mutations could increase the amyloid processing and the ratio Aβ42/Aβ40 [12, 13]. Loss-of-function mutations may reduce protective mechanisms, such as α-secretase cleavage [14]. In addition, accumulation of amyloid peptides may also associated with the reduced Aβ42 clearance [15] and neuronal loss [15–17]. In majority of patients, disease occurred at

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40–50 years of age [18–21]. Several cases of young onset AD have been reported, where patients were less than 30–40 years of age [6, 7, 22–31]. Guerrio et al. (2010) designed an algorithm for variants in EOAD causative genes [32] on prediction of the pathogenic nature of novel mutations. Investigating patients carrying novel as well as previously known mutations along with the associated phenotypes will aid in classification of these variants and may eventually support genetic counseling [33]. In this study, we reported a pathogenic PSEN1 W165C mutation as determined by genetic testing in a Korean patient with EOAD.

Case presentation
A 53-year-old man with 13 years of education presented with progressive memory decline. At aged 50, he complained forgetfulness of meetings or details of story, and repeating the same questions. He had difficulty in orienting to date and in finding way to a new place. His past medical history revealed myocardial infarction with proper medical treatment. His Korean version of Mini-Mental Status Examination (K-MMSE) score was 21/30 and clinical dementia rating scale (CDR) score was 0.5 at three years after symptom onset. And follow-up K-MMSE score at six years after symptom onset was 19/30 and CDR score was 1. His brain MRI at three years after symptom onset revealed mild atrophy of bilateral hippocampus and parietal lobe (Fig. 1a). FBB-PET at five years after symptom onset showed increased amyloid deposition in bilateral parietal, frontal, temporal lobe and precuneus (Fig. 1b). The patient had an APOE ε2/ε3 polymorphism.

A 53-year-old man (III-1, Fig. 2) visited the Seoul National University Bundang Hospital with gradually impaired cognitive function over the previous years. The proband’s family history had a strong family history of dementia, and presented several family members affected by EOAD (Fig. 2). His mother (II-2) suffered from AD with onset in her fifties and deceased. The patient was one of the 4 siblings, comprising 2 brothers and 2 sisters. His first younger brother (III-2) was also diagnosed AD deceased in his forties, and had 2 children. His second younger brother (III-5) and his two younger sisters (III-3, III-4) displayed normal cognitive function. The health condition of the rest of his family members remained unknown, since all living family members and relatives declined to provide any additional information regarding their health.

Genetic analysis of PSEN1 and structural prediction of mutant PSEN 1 protein
Methods
An in depth genetic screen was performed using a specifically expanded panel of 50 causative and risk factor genes for various neurodegenerative disorders [34]. Whole exome sequencing (WES) was performed in Novogene. Standard Sanger sequencing was carried out by BioNeer Inc. (Dajeon, Republic of Korea) [34]. Big Dye Terminator Cyclic sequencing was performed using the ABI 3730XL DNA Analyzer (Bioneer Inc., Dajeon, Republic of Korea). Sequencing data was analyzed using NCBI Blast (http://blast.ncbi.nlm.nih.gov/Blast.cgi) and the chromatograms were screened using the DNA BASER (http://www.dnabaser.com) tool. Possible novel mutations were checked in the Korean Reference Genome Database (KRGDB; http://nih.go.kr/menu.es?mid=a50303020300), which was obtained by whole genome sequencing of 622 healthy

Fig. 1 Brain functional and structural neuroimaging data of the proband at diagnosis. a. Axial FLAIR, coronal, and sagittal T1 images of brain MRI, arrows pointing at left-dominant bilateral temporal lobe atrophy. b. FDG-PET, arrows pointing at hypometabolism in left temporal cortex, right anterior temporal cortex and bilateral frontal cortex.
Korean individuals. The mutations were also screened against Broad Institute’s Genome Association Database (genome AD, http://gnomad.broadinstitute.org) and 1000 Genomes (http://www.1000genomes.org/) databases.

The possible pathogenic nature of missense variants was predicted using simple online tools, such as PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2), Sorting Intolerant from Tolerant (SIFT; http://sift.jcvi.org/), and PROVEAN (http://provean.jcvi.org) algorithms. ExPasy analysis was also performed (https://www.expasy.org/) using different parameters, such as Kyte and Doolittle hydrophobicity index, bulkiness, and polarity. Mutant and normal prion protein structures were compared by 3D modelling. Protein structures were built using the Raptor X web server (http://raptorx.uchicago.edu/), while Discovery Studio 3.5 Visualizer (Accelrys, San Diego, USA) was used to display the 3D images [35].

Results

A heterozygous G > T substitution (chr14; g.73653575: G > T) was discovered and confirmed to occur in the PSEN1 coding region using both WES and standard sequencing. This mutation caused the change from tryptophan to cysteine (c.495G > C; p.Trp165Cys) substitution, located at exon 6 of PSEN1 gene, and in transmembrane (TM) helix domain-III of the PSEN1 protein (Fig. 3).

The mutation is associated with EOAD patient with memory decline, followed by difficulty in finding ways and had a strong family history of AD; however, the specific mechanism is not functionally uncovered. The mutation was found in subject a Korean patient with EOAD and not observed in KRGDB, ExAC, and 1000genome control data sets. All in silico pathogenicity programs predicted the mutation to be deleterious. Figure 4 predicted that abnormal conformation inside the helix results in the mutated form due to an abnormal intra-or intermolecular disulfide bridge associated with the potential re-activities with metals or other compounds with thiol groups. Additionally, cysteine is not common recorded in the helix, further suggesting that this mutation might lead to abnormal conformation within the TM region. The intramolecular interactions may also change with the mutation: Trp165 has strong interaction with Ser169 (two hydrogen bonds), and forms another hydrogen bond with Val161. Cys165 changes the hydrogen bonds significantly. The interaction with Ser169 and Val169 remained, but with Ser169, only one hydrogen bond was visible. Two new interactions could be seen with Ile162 and Ile168 (Fig. 5) In addition, the mutation is localized to trans membrane-III region conserved between PSEN1/PSEN2 and expected to affect Ab42 levels. This hypothesis was previously demonstrated that PSEN1 W165C led to increase Aβ42 and decreased Aβ40, resulting in elevated Aβ42/Aβ40 ratio in gaining loss of function in presenilin [36–39].

Discussions

Since four different populations have been previously described the PSEN1 Trp165 from four familial AD cases (Table 1), the 165 codon seems to be a very vulnerable site. Initially, PSEN1 Trp165Cys mutation was found in a French family, with a codon combination of TGG > TGC. Mutation was associated with strongly was positive family history, since several affected family members were identified in three generations. Age of onset ranged between 37 and 47 years in the relatives with disease. No details were available
on clinical symptoms of affected patients [36]. Second case of Trp165Cys was discovered with alternative codon exchange of TGG > TGT in an Indian family. Affected patients developed disease in their 40s, and disease phenotypes were rapid progressive disease progression and cerebral/cerebellar atrophies [37]. Our case was associated with probable EOAD case in a male patient, and his family members presented AD in their 40s. It may be difficult to find out, whether there could be a common founder between the Indian and Korean families. Since the Korea and India may be geographically isolated from each other, we suggest...
that PSEN1 Trp165Cys occur independently in these two families.

PSEN1 Trp165Cys is located in the TM-III region of PSEN1 protein. An exchange from native amino acid to Cys may increase the risk of an abnormal intramolecular disulfide bond formation with another Cys. These new S-S bonds may create novel inter- or intramolecular structures, involving in pathogenic mechanisms. The potential mechanism was displayed and revealed the Fig. 5. In addition, at the residue, another mutation to glycine (Gly, G) was previously documented in a Japanese family with young onset AD [39], suggesting that this residue may be critical for PSEN1 function. Interestingly, the mutation is located to TM-III region conserved between PSEN1/PSEN2 and expected to affect Ab42 levels. This prediction was previously demonstrated that PSEN1 Trp165Cys resulted in increased Aβ42 and decreased Aβ40, respectively. It could lead to elevated Aβ42/Aβ40 ratio in gaining loss of function in

Table 1 Clinical findings in the published at codon 165 of PSEN1

| Country       | Campion et al., 1999 [36] | Wallon et al., 2012 [38] | Higuchi et al., 2000 [39] | Syama et al., 2018 [37] | This study |
|---------------|--------------------------|--------------------------|--------------------------|--------------------------|------------|
| Mutation      | France                   | Japan                    | India                    | Trp165Cys                | Trp165Cys  |
| Codon change  | TGG to TGC               | TGG to GGG               | TGG to TGT               | TGG to TGT               | TGG to TGT |
| Familiar      | Yes                      | Yes                      | Yes                      | Yes                      | Yes        |
| Age at onset (year) | 37–47                   | 34–38                    | 45                       | 50                       |
| ApoE genotype | ε3/ε3                    | NA                       | NA                       | ε2/ε3                    |
| Clinical signs and symptoms | EOAD                    | EOAD                     | EOAD                     | EOAD                     |
| Brain Imaging (MRI, CT) | NA                      | NA                       | MRI: indicated diffuse cerebral and cerebellar atrophy in one case. | MRI: indicated diffuse cerebral and cerebellar atrophy in one case. | MRI: indicated diffuse cerebral and cerebellar atrophy in one case. |
| Functional data | ↑Aβ42 and ↓Aβ40 in vitro; elevated Aβ42/Aβ40 ratio | No functional data | ↑Aβ42 and ↓Aβ40 production in vitro; elevated Aβ42/Aβ40 ratio | ↑Aβ42 and ↓Aβ40 production in vitro; elevated Aβ42/Aβ40 ratio | ↑Aβ42 and ↓Aβ40 production in vitro; elevated Aβ42/Aβ40 ratio. |
presentin [36–39], verifying as a pathogenic mutation, involved in EOAD. This mutation was associated with rapid progression of disease, since the duration from the first clinical symptoms to the death ranged 4–10 years. Earlier onset of disease (37–47 years) was observed in a French family, but there was no information on the clinical symptoms in this family (Table 1).

Several pathogenic PSEN genes are found to cluster within the predicted α-helical TMs. Among other TMs, TM3 has been identified as one of the critical site in PSEN1, where several familiar AD (FAD) mutations were found. Recently, more than twenty mutations associated with FAD have been reported in TM-III of PSEN1 [36, 40–50] (Fig. 6), and several of them were associated with EOAD (Table 2). Among these mutations, the PSEN1 Trp165Cys mutation is of particular interest because it may be associated with disease early onset. Moreover, the Trp165Cys mutation could cause increase in the Aβ42/Aβ total ratio [36–39], similarly to other FAD-associated PSEN1 H163R [51], H163Y [52], L166P [53], I167del [54], S170F [31] S170P [40], L174del [44], L173W [36] and L174M [45] mutations.

In our case, the PSEN1 p.Trp165Cys variant has been identified in a patient with early onset of age (50s years at diagnosis), suggesting that disease phenotype may be the result of amino acid substitution in this conservative residue. Furthermore, the amino acid position 165, located in the TM-III of PSEN1 indicated a significant phylogenetic conservation among vertebrates, and in homologous proteins such as PSEN2, suggesting that the position is of functional significance. Importantly, the patient’s mother and his brother were also affected by AD that is likely to involve autosomal dominant AD.

Guerrio et al. (2010) designed an algorithm on mutations on PSENs, which may be helpful in prediction on their pathogenic nature [32]. PSEN1 Trp165Cys may be a definitely pathogenic mutation. The Korean case of PSEN1 Trp165Cys may be associated with positive family history of disease, since the mother and one of the brother of patient was affected with AD. This is the third case of Trp165Cys, described all around the world, and EOAD was observed in all cases of AD. All of these findings suggested that Trp165 may be an important in PSEN1, since it bound two pathogenic mutations, Trp165Cys and Trp165Gly [36–38]. Functional studies, performed by Sun et al. (2016) revealed that mutation may impair the gamma secretase activity, resulting in elevated amyloid beta 42 production [55]. Our findings confirmed the significance of PSEN1 Trp165Cys in EOAD.
| Mutation | Clinical data | Age of Onset (Year) | Family History | Functional Studies | Reference |
|----------|---------------|---------------------|----------------|-------------------|------------|
| H163P   | FLAIR, showing bilateral hippocampal, temporal lobe atrophy, and paraventricular hyperintensity. PET, revealing moderate-to-severe hypometabolism in the diffuse cortical area. Immunohistochemical stain revealed expression of amyloid beta in the senile plaque. | 34 | No | ↑Aβ42/Aβ40 ratio; ↑Aβ42; Aβ40. | [18] Kim et al., 2012 |
| H163R   | Data are limited, but neuropathology consistent with AD has been observed in at least one case. | 42–47 | Yes | ↓Aβ42/Aβ total ratio in COS-1 cells; ↓Aβ42 and Aβ40 production in vitro. Involving γ-secretase- neurexin processing. | [51] Martin et al., 1995; |
| H163Y   | Typical AD neuropathology (one case); decreased glucose metabolism in presymptomatic mutation carriers, especially in the thalamus. Widespread brain amyloid (PiB-PET) and shrunken hippocampi. | 47 | Yes | ↓CSF Aβ42 and Aβ38 levels. ↑Aβ42/Aβ total ratio when expressed in COS-1 cells, and ↑Aβ42 production | [52] Clark et al., 1995 |
| A164V   | MRI revealed atrophy in brain involved anterior temporal lobe, and the hippocampus. | 45–50 | Yes | Possibly damaging via in silico. | [19] Roeber et al., 2015 |
| W165C (G > C) | Not available | | | | |
| W165C (G > T) | EOAD, a severe form of atrophies and rapid deterioration in cerebral and cerebellar | 45 | Yes | ↑Aβ42/Aβ ratio; ↑Aβ42, Aβ40, and AICD↓ cleavage of Notch and N-cadherin. | [37] Syama et al., 2018 |
| W165G   | Not available | 34–38 | Yes | Not available | [9] Higuchi et al., 2000 |
| L166H   | MRI: hippocampal atrophy and cortical atrophy. SPECT: bilateral hypometabolism in the parietal and frontal lobes. | 30 | Yes | Not available | [26] Pantieri et al., 2005 |
| L166P   | numerous Aβ-positive neuritic and cotton-wool plaques; abundant Aβ-positive amyloid cores in the cerebellar cortex. | 32–34 | Yes | Not available | [27] Ezquerra et al., 2000 |
| L166R   | MRI revealed cortical atrophy; PET revealed parietal hypoperfusion. | 42–50 | Yes | Possibly damaging by in silico | [20] Sassi et al., 2014 |
| L166V   | SPECT indicated temporoparietal hypoperfusion. Advanced plaques and tangles. | 40–46 | Yes | Predicted possibly damaging in silico | [21] Knight et al., 2007 |
| L166del | MRI strongly revealed symmetrical cerebral atrophy. | 38–46 | Yes | Pathogenic by in silico | [54] Jiao et al., 2014 |
| I168del | Not available | | Yes | Pathogenic by in silico | [9] Janssen et al., 2003 |
| I168T   | Neuropathology consistent with AD. | 86–94 | Yes | Pathogenic by in silico | [20] Sassi et al., 2014 |
| S169del (ΔS169, Ser169del, ΔS170) | MRI revealed cerebral atrophy involvement of the ventricles and widening of the sulci. | 40 | Yes | Not available | [28] Guo et al., 2010 |
| S169L   | Aβ deposition in the cerebellum and white matter | 33–37 | Yes | Not available | [29] Taddei et al, 1998 |
| S169P   | Numerous plaques and neurofibrillary tangles could be seen in brain of the case. | 35 | Yes | Not available | [30] Ezquerra et al, 1999 |
| S170F   | Much Lewy bodies in the substantia nigra and had severe | 27 | Yes | ↑Aβ42 and Aβ40, altering the ratio. | [31] Snider et al., 2005 |
| Mutation | Clinical data | Age of Onset (Year) | Pathogenic by in silico | Functional Studies |
|----------|---------------|---------------------|------------------------|--------------------|
| S170P    | MRI shown hypointensity, globus pallidus, and substantia nigra as well as frontotemporal cortical atrophy bilaterally, and 18F-DG PET hypometabolism in striatal and posterior cingulate. | 25 Yes | ↑ Aβ42; ↑ Aβ42:Aβ40 ratio | Carecchio et al., 2017 |
| L171P    | Not available | 36–40 Yes | Not available | ↑ Aβ42 than cells |
| L173F (G>C) | MRI revealed severe nigrostriatal dopaminergic deficit and posterior cingulate atrophy. SPECT indicated hypoperfusion of the posterior cingulate gyri and other cortical areas. | 40–42 Yes | ↑ Aβ42/Aβ40 ratio | Jin et al., 2012 |
| L174del  | MRI shown slight temporal lobe atrophy. | 24–29 Yes | Not available | ↑ Aβ42, and ↓ Aβ40, and ↑ Aβ42/Aβ40 ratio |
| L174M    | Neuropathology consistent with AD and CAA associated with AD and GA, associated | 53 Yes | Not available | Tedde et al., 2003 |
| L174R    | EOAD | 46–56 Yes | Not available | ↑ Aβ40, and ↑ Aβ42/Aβ40 ratio |
| F175L    | Much abundant amyloid plaques and neurofibrillary tangles in the cortex. | Not available | Not available | Kasuga et al., 2009 |
| F175S    | Not available | Not available | Not available | F175L |
| S178P    | Not available | Not available | Not available | S178P |
Conclusions
We confirm that PSEN1 p.Trp165Cys may be commonly associated with EOAD. Our findings were consistent with the previously reported cases of this mutation, and supported the hypothesis that PSs contribute the identification of at risk relatives who may be potential candidates for clinical trials.

Abbreviations
AD: Alzheimer’s disease; APP: Amyloid precursor protein; AB: β-amyloid; CDR: clinical dementia rating scale; EOAD: Early-onset Alzheimer’s disease; FDG-PET: Fluorodeoxyglucose-potin emission tomography; KRGDB: Korean Reference Genome Database; MNMSE: Minimale state examination; MRI: Magnetic resonance imaging; PolyPhen2: Polymorphism phenotyping v2; PS1: Presenilin-1; PSEN1: Presenilin 1; PSEN2: Presenilin 2; SIFT: Sorting intolerant from tolerant; TM-III: Transmembrane segment III; WES: Whole exome sequencing

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Authors’ contributions
VVG and EB: drafting the manuscript for content and doing genetic analysis. EV: preparing the samples and revising the manuscript. JMP and JS: verifying the MRI/PET results. JPM and JS: verifying the MRI/PET results. JPM: interpreting the clinical data and revising the manuscript. VWG and EVA: predicting presenilin 1 protein structure. SYK: analysis or interpretation of data, doing study supervision, obtaining funding. VWG and SSA: drafting/revising the manuscript and interpretation of clinical data. All authors read and approved the final manuscript.

Available data and materials
Not applicable.

Ethics approval and consent to participate
This study was conducted with approval from the Institutional Review Board of Seoul National University College of Medicine & Neuropsychiatric Behavior Center, Seoul National University Bundang Hospital (B-1302/192–006).

Consent for Publication
Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare that there are no competing of interests.

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