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Novel presenilin 1 mutation (p.Thr-Pro116-117Ser-Thr) in a Spanish family with early-onset Alzheimer's disease

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ABSTRACT

Presenilin 1 (PSEN1) is a γ-secretase component, which is in charge of the amyloid precursor protein (APP) cleavage. APP is believed to play a central role in the pathogenesis of Alzheimer's disease (AD). PSEN1 mutations are the most important causes of familial AD, being related to the earlier onset and rapid progression of the disease. Presenilins and APP mutations represent an extraordinary opportunity to study the pathophysiology of AD. We describe the clinical and genetic study of a 37-year-old male patient with a novel mutation in PSEN1 (p.Thr-Pro116-117Ser-Thr). We have studied the pedigree of his family with a further 9 members affected, all of them with onset in their 30s. We have also described the clinical data and results of brain biopsies in 2 of them. DNA sequencing of a tissue sample from an uncle of the patient, who died of AD in the 80s, showed the same mutation as in the patient. These data and predictive analysis indicate the pathogenicity of the mutation.

1. Introduction

New advances in genetics have improved our comprehension of neuropsychiatric disorders. It has been recently communicated that the first case of Alzheimer's disease (AD), described in November 1906 by Alois Alzheimer, could have been related to a mutation in exon 6 of presenilin 1 (PSEN1) (Müller et al., 2013), although a further genetic study seems to contradict these previous results (Rupp et al., 2014).

PSEN1 is a γ-secretase catalytic component, which is in charge of the transformation of the amyloid precursor protein (APP). Presenilins have 2 highly conserved and functionally redundant isoforms, PSEN1 and PSEN2, which share 67% of its sequence (Zhang et al., 2013). The discoveries of genetic mutations linked to early-onset familial Alzheimer's disease (FAD) in PSEN1, PSEN2, and APP have increased the interest in the role of these proteins, mainly PSEN1 mutations. Globally PSEN1 mutations are responsible for 95% of autosomal dominant FAD (Hunter and Brayne, 2018), which account for approximately for 5% of all patients with AD (Cervera-Carles and Clarimón, 2016).

PSEN1 is a nine-transmembrane-domain protein with the N-terminus and a large hydrophilic loop located in the cytosol and the C-terminus with extracellular orientation (Laudon et al., 2005). The gene encoding PSEN1 is located on chromosome 14q24.2 (Larner, 2013; Sherrington et al., 1995). There have been described at least 220 (Cruts et al., 2012) or 231 (https://www.alzforum.org/mutations accessed in May 2019) pathogenic mutations in PSEN1 in FAD cases.

Presenilins and APP mutations represent an extraordinary opportunity for the study of the pathophysiology of AD. In this article, we report on the clinical and genetic study of a 37-year-old male patient with FAD associated with a yet undescribed PSEN1 mutation. We have also constructed a family pedigree including other 9 members affected.

2. Material and methods

2.1. Subjects

We report on the clinical case and genetic testing of a patient with FAD and a novel mutation in PSEN1. We have also studied the pedigree of the patient's family (Fig. 1C). Nine family members were also

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affected by dementia; all of them deceased. The dementia onset was in their 30s, and they suffered from a rapid progression of the disease. We found the clinical records of 2 uncles of the patient, both with AD and deceased in the 80s. The records included a brain biopsy pathology description. We obtained tissue samples from one of them and performed a comparative genetic study by DNA sequencing (Fig. 2).

The legal guardian of the index patient gave written informed consent for the publication of the genetic and clinical data. Most of the living family members, all without FAD, cooperated with the elaboration of the pedigree.

2.2. Cerebrospinal fluid analysis

Routine cerebrospinal fluid (CSF) cell count, protein, glucose, and protein electrophoresis assessments were performed in the subject index by standard laboratory techniques. Levels of amyloid beta 42 ($A\beta_{42}$), total tau, and phosphorylated tau were measured by enzyme immunoassay with Lumipulse G System.

2.3. Genetic testing

DNA peripheral blood extraction and automated nucleic acid purification were performed (magNA Pure robot; Roche Inc). The coding exons of PSEN1, PSEN2, and their flanking regions were analyzed by PCR and Sanger sequencing. The primers and PCR conditions were as described by Li et al. (2006). Sequencing of exons 16 and 17 of APP was performed on genomic DNA, as described by Campion et al. (1996). The obtained sequences were compared with the following reference sequences: ENST00000324501.9 for PSEN1, ENST00000366782.5 for PSEN2, and ENST00000346798.7 for APP.

We also used the following protein variant effect-prediction tools: PolyPhen2 (Adzhubei et al., 2010); SIFT (Ng and Henikoff, 2003); PROVEAN (Choi et al., 2012); Mutation Taster 2 (Schwarz et al., 2014); Mutation Assessor (Reva et al., 2011), and PredictSNP, a consensus classifier for prediction of disease-related mutations (Bendl et al., 2014).

3. Results

3.1. Index patient clinical description

A 37-year-old male patient, with a history of thalassemia minor and migraine without aura, was admitted in the Psychiatry ward after having been found half-naked and disorientated in the street. He had been previously studied by Neurology 8 years ago. He had no other relevant medical history, including substance misuse.

In the first clinical examination, he was conscious, disoriented to time and partially to place. He obeyed simple commands, but his cognitive impairment did not allow a complete examination. The neurological examination only elicited mild bradykinesia and symmetric hyperreflexia in the 4 limbs. He walked with tendency to swerve to the left side. No other motor or sensory problems were

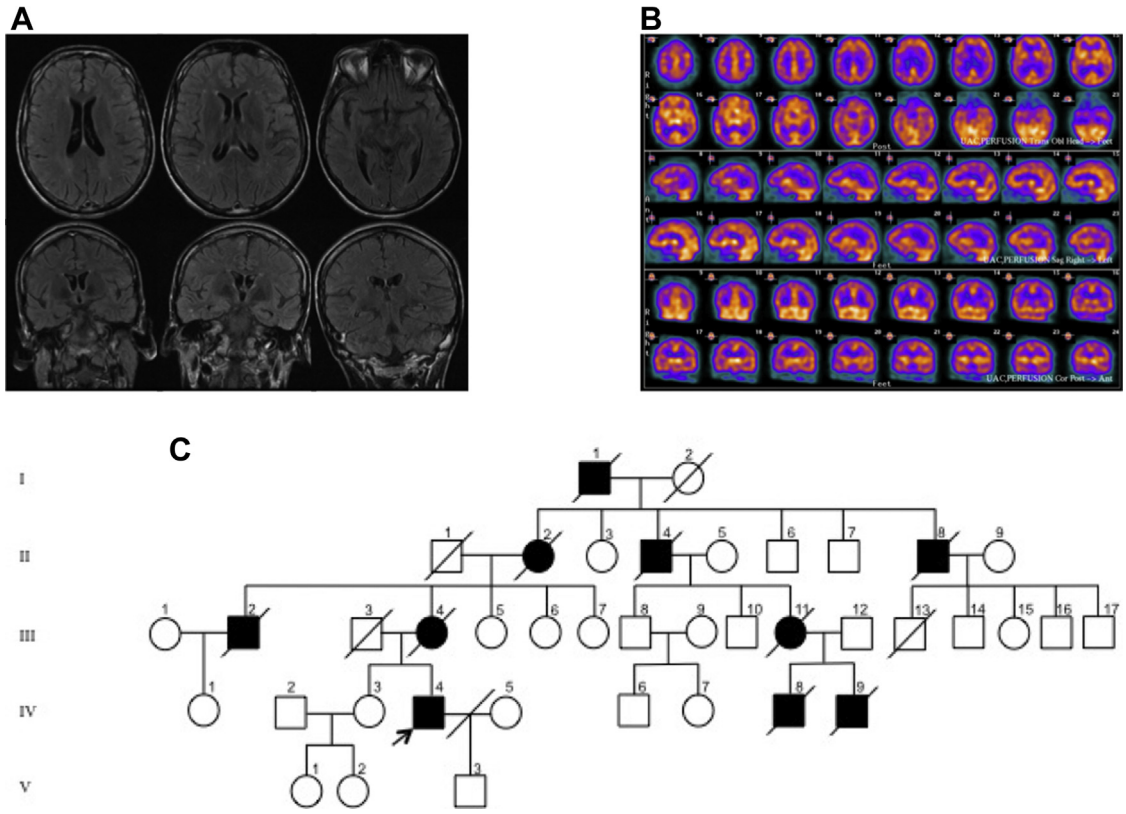

Fig. 1. Brain structural neuroimaging images and family pedigree of the index patient at diagnosis. (A) MRI of the proband. Axial and coronal FLAIR MRI series. (B) Brain SPECT scan of proband. (C) Family tree of index patient (IV4, black arrow). Cases described by family members: I1 deceased at 32 years; II2 deceased at 34 years; II4 deceased at 36 years; II8 deceased at 37 years; III4 deceased at 42 years (mother of proband). Cases with clinical description (medical records): III2 deceased at 48 years. Diagnosed of AD through a brain biopsy in a report of neurosurgery from 1984. Same mutation as the index patient from DNA sequencing (view text); III11 deceased at 35 years. Diagnosed of AD through the pathology study from a brain biopsy at death in 1986 (view text); IV4 patient index; IV8 deceased at 38 years. Diagnosed of probable AD in the clinical report from 2012 (view text); IV9 deceased at 36 years. Diagnosed of probable AD in the clinical report from 2012 (view text). Abbreviations: MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; AD Alzheimer's disease.

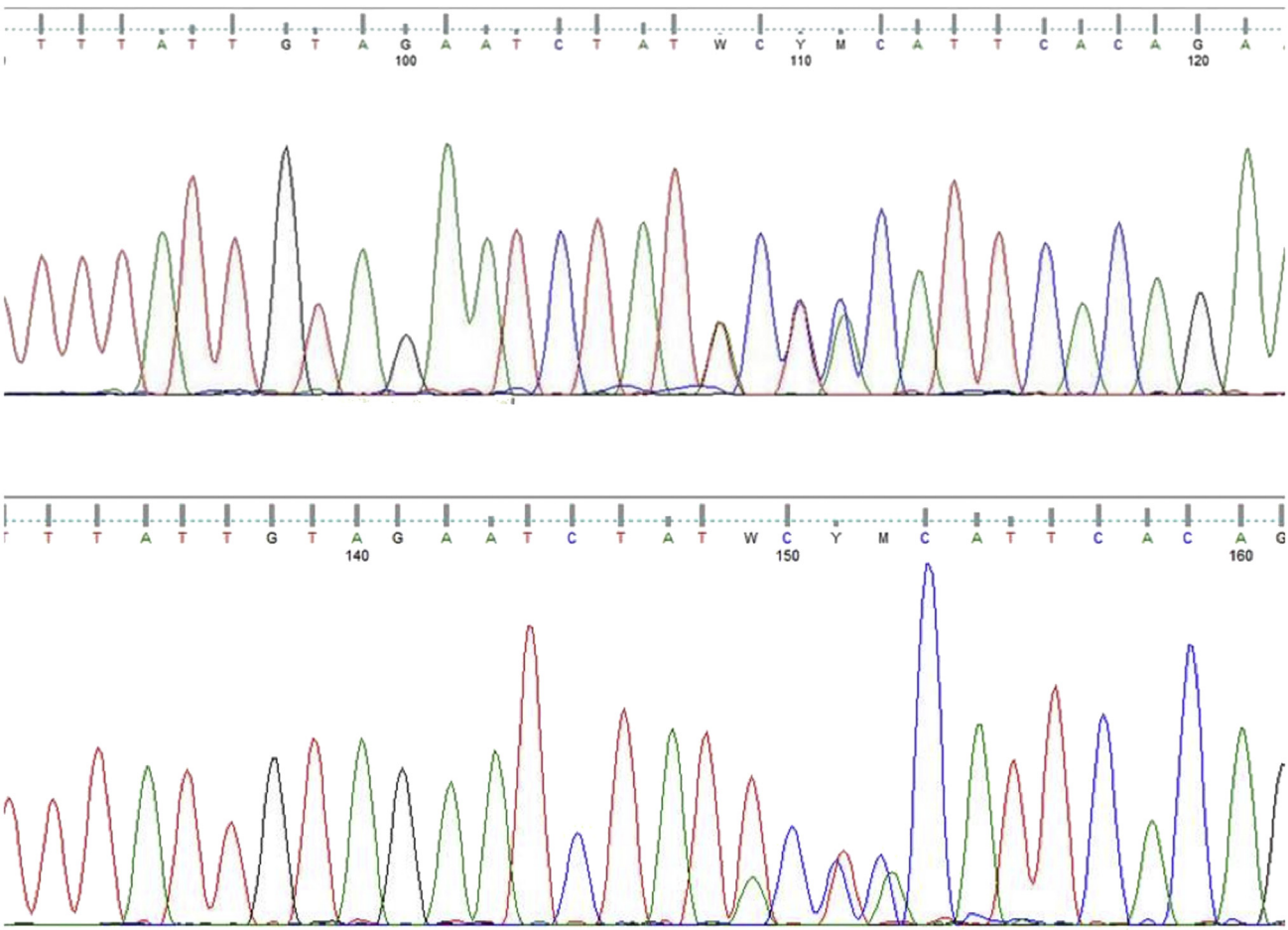

Fig. 2. Two DNA sequences of exon 5 of the presenilin 1 gene with the same mutation; top: patient index (IV4; Fig. 1C) and bottom: patient's uncle (III2; Fig. 1C).

detected. There were no other extrapyramidal signs, myoclonus, spastic paraparesis, or gait disorders. The patient showed difficulties with tandem gait and mild disequilibrium, but there were no other cerebellar signs as dysmetria, limb or truncal ataxia, intention tremor, or nystagmus. He had visual hallucinations, as he tried to catch an inexistent cat in the room. The remaining higher mental functions showed reduced spontaneous speech, severe nomination deficits, severely impaired recent memory, and significant visuospatial and praxis deficits. The Mini–Mental State Examination showed a score of 16/30. Most of the errors were produced on the items of orientation to time, delayed recall, 2 objects naming, and copy of intersecting pentagons.

His only sister was 11 months younger and apparently unaffected. She reported that the patient had been suffering progressive cognitive impairment during the previous 2 years, without functional repercussions until the last 3 months. She also acknowledged a similar clinical presentation in other family members. His mother died at the age of 42 years, with a similarly degenerative dementia process. She had a history of cocaine and heroine misuse, which started 4 or 5 years after the patient's birth. His father died 8 years before the patient's admission, and he was diagnosed with the same substance misuse and schizophrenia. The patient had a healthy 10-year-old child.

Other family members have suffered similar symptoms with onset on their 30s (Fig. 1C). The clinical records from 4 of them were available and will be described below.

Hemogram showed polyglobulia, microcytosis, and hypochromicity. The rest of the blood test results for renal function, liver enzymes, thyroid hormones, proteinogram, copper, ceruloplasmin, vitamin b12, folic acid, and serum amyloid A showed normal values. Serological testing discarded HIV, HBV, HCV, syphilis, Brucella, and Lyme disease. Lumbar puncture yielded normal values of glucose, proteins, and leukocytes. CSF showed a decreased $A\beta_{42}$ level (492 pg/mL; normal values 576–1012 pg/mL), increased total tau (405 pg/mL; normal values 47–225 pg/mL), and phosphorylated tau (114 pg/mL; normal values <61 pg/mL). 14-3-3 protein was undetectable. CSF serology testing was negative for syphilis, Brucella, and Borrelia. Cerebral magnetic resonance imaging only showed nonspecific white matter juxtacortical lesions and nonspecific diffuse cortical atrophy (Fig. 1A). Brain single-photon emission computed tomography imaging showed frontoparietal hypoperfusion, mainly on the right hemisphere (Fig. 1B). Electroencephalogram and electromyogram studies were normal.

3.2. Genetic analysis

A genetic study of a DNA peripheral blood sample (magNA Pure robot; Roche Inc) was carried out. The study revealed a c.346_349delinsTCTA mutation in PSEN1 gene located in chromosome 14. This mutation causes the substitution of 2 consecutive amino acid residues Thr-Pro in 116 and 117 positions by Ser and Thr, respectively (p.Thr116_Pro117delinsSerThr).

With the intention of better clarifying the effects of this multiple mutation, protein variant effect-prediction tools were used, with the following results—PolyPhen2, SIFT, and PROVEAN: deleterious

or pathogenic effect; Mutation Taster 2: variant of uncertain significance, and Mutation Assessor: medium. Finally, PredictSNP predicts that p.Thr116Ser is a neutral mutation and p.Pro117Thr is a pathogenic mutation.

No mutations were found in the PSEN2 and APP genes.

We also made a DNA sequence analysis in a brain tissue sample from an uncle's proband (III2; Fig. 1C). This study showed the same mutation found in the proband (Fig. 2).

3.3. Clinical description of other family members

We have a description of 9 family members with FAD. In the first and second generation, we only had descriptions provided by family members. All of them initiated the disease in their 30s, with a rapid progression. We also had a clinical description of 4 other members (Fig. 1C).

3.3.1. III2

The clinical reports from 1984 showed a male patient with severe cognitive impairment affecting memory, language, praxis, and visuospatial function. The presence of spastic paraparesis was notable. A CT scan showed severe cortical and subcortical atrophy. The genotypic study from this age (there was not PSEN1, PSEN2, and APP genetic study available) was reported as "normal." A brain biopsy showed neurofibrillary tangles and neuritic plaques, compatible with AD. The symptoms started in his 30s, and he passed away aged 48. The current genetic analysis showed the same genetic mutation as the proband (Fig. 2).

3.3.2. III11

We had a clinical report from 1984 and a pathological study report from 1986. This female patient also showed similar deficits as III2, with spastic paraparesis too. In the brain biopsy, she also presented neurofibrillary tangles and neuritic plaques. She died at the age of 35. It was not possible to perform genetic testing because of the lack of availability of the sample.

3.3.3. IV8 and IV9

We had 2 brief clinical reports from 2 siblings, descendants from III11, dated 2012. The presence of ataxic gait and myoclonus was remarkable. Both patients were diagnosed with FAD.

4. Discussion

We have found a yet undescribed PSEN1 missense mutation, in a member of a Spanish family with a clear autosomal dominant pattern of early dementia. Two other members were affected by early-onset AD, confirmed through pathological study of brain biopsy. One of them was genetically tested, and he presented the same PSEN1 mutation as the proband (Fig. 2). This mutation consists of the substitution of ACCC nucleotides in 346–349 positions of PSEN1 gene, for TCTA nucleotides (c.346-349ACCC>TCTA). The mutation causes the replacement of 2 consecutive amino acid residues Thr-Pro, in 116 and 117 positions by Ser-Thr in Exon 5 of PSEN1, respectively. No mutations were found in PSEN2 or APP. The mutation c.346_349delinsTCTA is neither found in Exome Aggregation Consortium (EXaC) nor 1000 Genomes Project (1000G) and is located in a highly conserved region between PSEN1 and PSEN2.

Our mutation is located in the central position of the first hydrophilic loop (HL-I loop) of PSEN1 and could alter the loop orientation. The database about PSEN1 mutations (https://www.alzforum.org) includes 3 mutations at codon 116 (La Bella et al., 2004; Mann et al., 2001; Romero et al., 1999) and 4 at codon 117 (Anheim et al., 2007; Dowjat et al., 2004; Wisniewski et al., 1998; Zekanowski et al., 2003), all of them pathogenic. None of these mutations includes p.Thr116Ser or p.Pro117Thr, as our case does. Other pathogenic mutations at the HL-I loop have been described, responsible for FAD at following codons: 4 at 105, one at 113, one 113_114 insertion, 3 at 115, 4 at 120, and one at 123.

The mechanisms underlying in the Notch and APP processing by γ-secretase are largely elusive at the moment, but the HL-I loop of PSEN1 is a highly conserved region and might be essential for the functioning of γ-secretase (Ryan et al., 2016), contributing as an extracellular pocket to allosteric regulation of the proteolytic reaction (Takeo et al., 2014). Nevertheless, the open debate remains about how PSEN1 mutations affect the activity of γ-secretase and APP cleavage (De Strooper et al., 1998; McGeer and McGeer, 2013; Svedružić et al., 2015; Xia et al., 2015). An in vitro analysis study of 138 distinct PSEN1 mutations causing FAD showed that 90% of mutations decreased the production of both $A\beta_{42}$ and $A\beta_{40}$. The vast majority of them had an increased $A\beta_{42}/A\beta_{40}$ ratio (Sun et al., 2017). Underlying pathogenic mechanisms involved in presenilin mutations may be more complex than initially thought (Xia et al., 2015). In our case, we found low levels of $A\beta_{42}$ in CSF, but we could not get the $A\beta_{40}$ levels.

Although Sun et al. (Sun et al., 2017) found no correlation between $A\beta_{42}/A\beta_{40}$ ratio and age at onset, a subsequent study shows a significant inverse correlation (Tang and Kepp, 2018). The age at onset of the disease seems to keep some correlation with the kind of mutation. In a meta-analysis of 387 pedigrees of autosomal dominant AD including 1307 affected and 176 mutations, authors found a significantly earlier age at onset in PSEN1 mutations than APP or PSEN2 mutations (Ryman et al., 2014). Moreover, mutations involving exon 4 and 5 are related to younger age at onset. It has been suggested that mutations before codon 200 are associated with earlier onset (Ryan et al., 2016). P.Pro117Leu, p.Pro117Arg, p.Pro117Ser, and p.Pro117Ala mutations were described in families with an onset of the disease around the 30s (Anheim et al., 2007; Dowjat et al., 2004; Wisniewski et al., 1998; Zekanowski et al., 2003), but the onset in p.Thr116Ile and p.Thr116Asn mutations seems to happen later, around the 40s (La Bella et al., 2004; Romero et al., 1999; Sutovsky et al., 2018). In our case, age at onset was quite uniform in affected members, with the beginning of all cases in the 30s and rapid disease progression.

The clinical phenotype in this family is fairly uniform. The available medical records from 4 family members showed typical AD cognitive impairment and other disorders, mainly ataxia and spastic paraparesis. The proband did not have these last symptoms, but it could depend on the stage of the disease. P.Pro117Ser and p.Pro117Leu mutations have been related to the presence of myoclonus (Dowjat et al., 2004). We only found this symptom described in the clinical records of the patient's cousin. However, despite efforts to link specific mutations with characteristic phenotypes, a correlation between the clinical presentation and the kind of mutation or change of one specific amino acid does not seem to exist (Gómez-Tortosa et al., 2010; Larner, 2013). Some clinical variability among family members who share the same mutation is observed, although core symptoms remain similar. Excluding the possibility of finding cases at different stages of the disease and taking into account that few reports show enough clinical information to establish reliable genotype-phenotype correlation, it seems to be logical to think that clinical phenotypes are too unspecific to suggest an absolute correlation with underlying pathogenic mechanisms. Neither the histopathological profile in cases with the same PSEN1 mutations or the amount of $A\beta_{42}$ deposited as plaques is uniform, although some mutations seem to be more aggressive than others (Mann et al., 2001).

Following the algorithm proposed by Guerreiro et al. (Guerreiro et al., 2010) and modified by Hsu et al. (Hsu et al., 2018), our double mutation should be classified as definitely pathogenic because it fits

all the criteria: (1) segregation in 3 or more cases in a family, given that the proband and his maternal uncle carry the mutation and are affected by young-onset AD, as well as the proband's mother, who as a mandatory carrier was also affected; (2) mutation affects a conserved region between PSEN1 and PSEN2; (3) other mutations have been described in the same residue; (4) mutation is located in the first helix loop; and (5) Aβ levels are altered.

In silico analysis also described the mutation as pathogenic. However, PredictSNP suggested that p.Thr116Ser could be a neutral mutation and confirmed p.Pro117Thr as a pathogenic mutation. Most tools used in prediction analysis show 65%–80% of accuracy (Richards et al., 2015), and although American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards suggest full concordance among multiple algorithms, they do not specify the amount or which algorithms should be used (Richards et al., 2015). There is poor concordance among algorithms, mainly in variants classified as benign, depending on the combinations of algorithms used (Ghosh et al., 2017), which highlights the problems associated with strictly following the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines.

The double mutation that we have described affects 2 highly conserved PSEN1 contiguous residues, in which the other pathogenic mutations have been described. Coexpression of the 2 mutations could imply additive effects and cause a higher disturbance in γ-secretase functioning (Citron et al., 1998; Leutner et al., 2000).

As limitations, we may point out that we did not have reliable data about the onset of symptoms of AD in most of the affected family members. In those cases without clinical records, we only had the descriptions made by the relatives. In the rest of the cases, age at onset did not figure in the clinical reports. However, age at symptom onset is in most cases a variable difficult to define. We also had no data about apolipoprotein E (APOE) status from proband and family members, nor $A\beta_{42}/A\beta_{40}$ ratio. Finally, as already mentioned, it is not entirely clear whether every single mutation in itself or the simultaneous presence of 2 mutations in our patient has resulted in an early-onset FAD phenotype, but the most plausible situation is that both contiguous substitutions constitute one single mutated undescribed allele. In vitro functional analysis could better explain this question.

5. Conclusions

We have described a novel PSEN1 gene mutation in 2 members of a Spanish family with autosomal dominant AD, beginning in their 30s and with a rapid progression of the disease. The clinical records of the proband and 4 other family members have also been reported, as well as the description of brain biopsy pathological study of 2 of them. This mutation causes the replacement of 2 consecutive amino acid residues Thr-Pro, in 116 and 117 positions by Ser-Thr in PSEN1 (p.Thr-Pro116-117Ser-Thr). Different pathogenic mutations have also been described in the same positions. The mutation is probably pathogenic as referred to the algorithms and prediction tools used. However, future in vitro functional analysis could clarify even more the role of p.Thr116SSer substitution in this double mutation.

Disclosure

The authors declare that they have no conflict of interest.

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