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Early presentation of spastic paraparesis in individuals carrying *PSEN1* mutations: a clinical and genetic analysis

Kang-Yang Jih[1,2,3], Ting-Rong Hsu[4], Jong-Ling Fuh[1,2], Tse-Hao Lee[5], Yung-Shuan Lin[1,2], Shih-Yu Fang[1,2], Yi-Chu Liao[1,2,6*] and Yi-Chung Lee[1,2,6,7*]

Abstract

Background Mutations in the presenilin 1 gene (*PSEN1*) are well-known causes of early-onset familial Alzheimer's disease, but they can also present with atypical phenotypes such as pure spastic paraparesis. This study aims to investigate the clinical and genetic features of *PSEN1* variants in patients mainly manifested with hereditary spastic paraparesis (HSP)-like phenotypes.

Methods Mutational analysis was performed in 242 unrelated Taiwanese patients with clinically suspected HSP using a targeted resequencing panel covering the entire coding regions of *PSEN1*, along with 76 genes associated with HSP and 55 genes linked to HSP-like phenotypes.

Results Two of the 242 patients (0.8%) were found to carry the pathogenic *PSEN1* variants (p.P284S and p.F386S). In addition to the two probands, six affected family members were further identified to have the pathogenic *PSEN1* variants. Six of these eight patients (75%) presented with spastic paraparesis as their initial symptom, one suffered from cognitive decline, and another manifested with personality change. The average age of symptom onset was 40.1 ± 4.8 years. Except for one patient, cognitive decline developed in all subjects before the last follow-up. For the patient carrying the *PSEN1* p.P284S variant, amyloid deposition in bilateral lateral temporal, frontal, precuneus, and parietal regions was evident by amyloid PET, but no hippocampus atrophy was found on brain MRI. For the three patients carrying the *PSEN1* p.F386S variant, brain atrophy with dilated ventricles were noted in the patient initially presented with personality changes, but normal MRI findings in the other two patients manifested with spastic paraparesis.

Conclusions Spastic paraparesis can be the initial and isolated clinical presentation of *PSEN1* mutations. We identified eight patients from two families carrying a pathogenic *PSEN1* variant, all but one carriers have developed cognitive symptoms. *PSEN1* related spastic paraparesis usually has a later age of onset compared to other common hereditary spastic paraparesis subtypes, and the family history of early onset dementia might be obscure. Our findings

*Correspondence:
Yi-Chu Liao
yichu.liao@gmail.com
Yi-Chung Lee
ycli@vghtpe.gov.tw

Full list of author information is available at the end of the article

suggested that *PSEN1* variants are a rare cause of spastic paraparesis but should be considered especially in those with a later age of onset.

Keywords Spastic paraparesis, *PSEN1*, Alzheimer's disease, HSP

Background

Alzheimer's disease (AD) is a prevalent neurodegenerative condition and the leading cause of dementia in older adults. Autosomal dominant Alzheimer's disease (ADAD), which accounts for approximately 1% of overall AD cases, is mainly attributed to mutations in three genes: the presenilin 1 gene (*PSEN1)*, the presenilin 2 gene (*PSEN2)*, and the amyloid beta precursor protein gene (*APP)* [1, 2]. Among them, *PSEN1* mutations are the most common ones and responsible for approximately 60–70% of ADAD cases [3, 4], with over 300 disease-causing variants been reported (https://www.alzforum.org/mutations/psen-1).

PSEN1 encodes the presenilin-1 protein, which functions as the catalytic center of γ-secretase complex responsible for the cleavage of amyloid precursor protein. Its dysfunction leads to accumulation of cerebral amyloid ß, a hallmark of AD pathology [5]. Patients harboring pathogenic *PSEN1* variants usually present with memory loss and cognitive decline similar to sporadic AD, but with an average age of onset around 40 years old. Majority of them had an onset age between 30 and 60 years old [3, 6, 7]. Besides memory decline, *PSEN1* variants could manifest with various neurological syndromes. Common non- amnestic presentations include visual agnosia, aphasia, and behavioral changes, which could be identified in more than half of the *PSEN1* mutation carriers [8]. Motor symptoms are more prevalent in *PSEN1* carriers compared to non-carriers (28% versus 13%), with increased deep tendon reflex, gait disturbance, cranial nerve abnormalities and tremor being common presentations [9, 10]. Other neurological manifestations such as frontotemporal dementia, spastic paraparesis, and ataxia, despite rare, has been reported in previous literatures [11–15].

Spastic paraparesis, although rare, has been observed in AD patients caused by *PSEN1* pathogenic variants (Fig. 1A) [16]. Spastic paraparesis generally appears alongside dementia, but in rare instances, it may precede dementia for many years or occur solely without cognitive decline [11, 17–19]. Identifying *PSEN1* mutations as the cause of spastic paraparesis can be challenging, particularly when patients exhibit no cognitive symptoms or lack a family history of dementia. The significance of *PSEN1* mutations in patients diagnosed with spastic paraparesis has not been well understood due to the lack of large-scale studies investigating the role of *PSEN1* in these patients. Early identification of patients carrying the pathogenic *PSEN1* variants is increasingly important as therapies targeting amyloid deposits have become available. Previous studies showed that nearly all individuals with pathogenic *PSEN1* variants eventually develop AD [19], making genetic diagnosis vital for early intervention.

To explore the relationship between *PSEN1* mutations and spastic paraparesis, we analyzed the clinical and genetic features of patients with *PSEN1* variants identified from a cohort of 242 unrelated Taiwanese patients with clinical diagnosis of hereditary spastic paraparesis (HSP).

Methods

Study subjects

Between 1998 and 2022, we enrolled a continuous series of 242 unrelated Taiwanese patients of Han Chinese ethnicity who were diagnosed with HSP at the Department of Neurology, Taipei Veterans General Hospital. Among these patients, 133 (55%) were male and 95 (39%) had a clear family history of HSP (72 with autosomal dominant, 19 with autosomal recessive and 4 with X-linked inheritance pattern). The other 147 patients were apparently sporadic cases. The average age at disease onset was 29.2 ± 17.7 years (0–69 years). All participants met one of the following criteria: (1) pure spastic paraparesis (2), spastic quadriparesis with earlier and more severe involvements in the lower extremities, or (3) initial presentation of spastic paraparesis followed by neurodegenerative diseases affecting multiple parts of the nervous system [20]. Comprehensive evaluations, including physical examinations, neurological examination of cranial nerves, motor and sensory systems, as well as brain and spine magnetic resonance imaging (MRIs), were conducted to exclude other etiologies. Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital.

Mutational analysis of *PSEN1*

Peripheral blood samples were collected from participants, and genomic DNA was extracted from leukocytes using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Mutation analysis of *PSEN1* was performed using a targeted resequencing panel that covered the entire coding regions of *PSEN1*, along with 76 HSP genes and 55 genes associated with HSP-like phenotype (Supplementary Table 1, Additional file 1). Sequencing was conducted on an Illumina HiSeq2500 platform, and all sequenced reads were aligned to the Human Genome

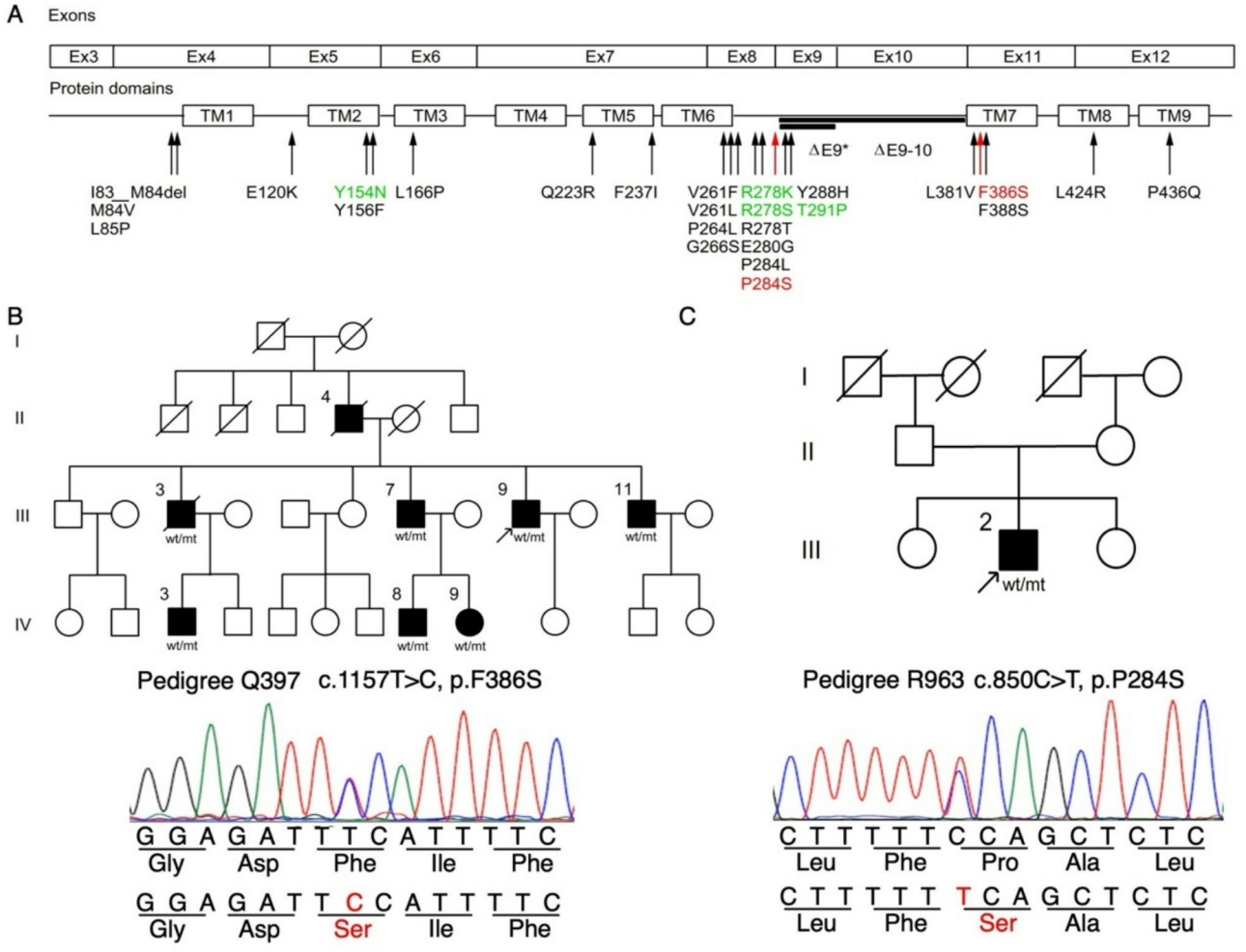

Fig. 1 *PSEN1* variants associated with spastic paraparesis. **(A)** A diagram displays *PSEN1* variants associated with spastic paraparesis. The four variants associated with spastic paraparesis as the initial manifestation in previous studies were labeled in green. The two variants identified in this cohort are labeled in red. **(B and C)** Genetic analysis of the families with *PSEN1*-related spastic paraparesis in the present study. Pedigrees of the two families harboring the heterozygous *PSEN1* c.1157T > C (p.F386S) and c.850 C > T (p.P284S) variants, respectively. Sanger sequencing traces shown below the pedigrees confirmed the heterozygous *PSEN1* c.1157T > C (p.F386S) and c.850 C > T (p.P284S) variants in patients Q397 (proband, arrowhead) and R963 (proband, arrowhead).The "mt" represents a variant *PSEN1* allele, and the "wt" refers to a wild-type allele. Open symbol, unaffected; filled symbol, affected; symbol with a diagonal line, deceased; square, males; circle, females; arrow, the proband

version 38 (hg38/GRCh38). The reference coding sequence for *PSEN1*, NM_000021.4, was used to annotate variants. Identified *PSEN1* pathogenic variants were confirmed by Sanger sequencing. For each identified variant, allele frequency was initially examined using the Genome Aggregation Database (gnomAD v4.1.0; http://gnomad.broadinstitute.org) and the Taiwan Biobank database (taiwanview.twbiobank.org.tw/search) [21], which contains whole genome sequences from 1517 healthy Taiwanese individuals. Patients with rare variants, defined as being absent in the Taiwanese Biobank control genomes, were selected for further analysis. Bioinformatics tools, including PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/index.shtml) and CADD (https://cadd.gs.washington.edu/), were utilized to assess the pathogenicity of the identified variants.

Clinical evaluations and neuroimaging studies

The probands and their families underwent comprehensive history taking and neurological examinations. Brain MRI, including T1- and T2- weighted images without gadolinium enhancement, were performed. Additionally, 18 F-florbetaben amyloid positron emission tomography (PET) scans were conducted using the Discovery MI DR PET/CT scanners (GE Healthcare, Chicago, IL, USA). The Amyloid PET images were acquired 90 min after the injection of 300 ± 30 MBq 18 F-florbetaben, with a 20-minute imaging duration. The brain amyloid plaque load (BAPL) scoring system was used to evaluate

the amyloid burden in the tested patients [22]. Cognitive function were assessed using Mini-Mental State Examination (MMSE) [23] and Cognitive Abilities Screening Instrument (CASI) [24]. The cutoff values for the MMSE and CASI examinations to differentiate individuals with or without dementia were adapted from previous studies [25, 26].

Results

Mutation analysis

In our cohort of 242 unrelated spastic paraparesis patients, we identified four heterozygous missense variants in *PSEN1* in four index patients: c.584A>G (p.Y195C), c.850C>T (p.P284S), c.835A>G (p.N279D), and c.1157T>C (p.F386S). These variants were absent in the 1517 control genomes from the Taiwan Biobank database. The c.850C>T (p.P284S) and c.1157T>C (p.F386S) variants have been previously reported as pathogenic mutations in literatures [3, 27]. However, pathogenicity of the c.584A>G (p.Y195C) and c.835A>G (p.N279D) variants remains uncertain.

Mutation analysis of the family members of the index patient with the p.Y195C variant revealed that this variant was also present in the patient's asymptomatic mother, but neither detected in the symptomatic father nor the affected sister (Supplementary Fig. 1, Additional file 1), suggesting that the p.Y195C variant is likely benign. The p.N279D variant, which has never been reported and is absent in the gnomAD v4.1.0, is predicted to be damaging by computation algorithms including Polyphen-II and CADD. However, according to the ACMG guideline [28], it is classified as variant of unknown significance. Further study is needed to determine its pathogenicity. The patient with the p.N279D variant presented with spastic paraparesis since the age of 18 years, but she had normal cognitive function with a score of 93 on the CASI exam and a normal brain MRI without neuroradiological signs indicative of AD at age 63 years (Supplementary Fig. 2, Additional file 1). In addition, none of her siblings are symptomatic may also hint that N279D could be a benign variant.

Clinical evaluation of patients with pathogenic *PSEN1*

The two families harboring the pathogenic *PSEN1* variants (p.F386S and p.P284S) underwent further genetic analysis and clinical evaluation. The proband Q397, carrying the *PSEN1* c.1157T > C (p.F386S) variant, had a strong family history of spastic paraparesis. The proband R963, with the c.850C>T (p.P284S) variant, appeared to be sporadic. Eight patients, including the two probands and six family members, were found to carry the pathogenic *PSEN1* variants. The pedigrees and Sanger sequencing traces for these patients are presented in Fig. 1. Clinical data for all the eight patients are summarized in Table 1. The mean age of symptom onset was 40.1 ± 4.8 years. Six patients (75%) initially presented with spastic paraparesis, and seven (88%) developed dementia. Additionally, one patient presented with limb weakness, and two experienced psychiatric symptoms. Although cerebellar involvement has been reported to be associated in patients with *PSEN1*-related spastic paraparesis [29–31], this feature was not found in our cohort.

In the family of proband Q397 (Family A in Table 1; Fig. 1B), six of the seven affected family members underwent genetic testing (patient II-4 does not have DNA sample available for genetic testing), and all the six family members carried the *PSEN1* variant, c.1157T>C (p.F386S). Five patients including the proband Q397 initially presented with spastic paraparesis, one exhibited cognitive decline, and another manifested with personality changes in the beginning. Four of the five initially presenting with spastic paraparesis later developed dementia. Regardless of their initial symptom, the age of onset was similar (41.3 ± 3.7 years, range 37–49 years). MRI exams were performed in three patients at symptom onset and their results varied drastically.

Table 1 Clinical characteristics of spastic paraparesis patients identified with a pathogenic *PSEN1* variant in this cohort

Pedigree			**Q397**					**R963**
Patient	**III-3**	**III-7**	**III-9 (Index)**	**III-11**	**IV-3**	**IV-8**	**IV-9**	**Index**
***PSEN1* variant**	**c.1157T>C (p.F386S)**							**c.850C>T (p.P284S)**
Initial symptom	Cognitive decline	Spastic paraparesis	Spastic paraparesis	Spastic paraparesis	Personality change	Spastic paraparesis	Spastic paraparesis	Spastic paraparesis
Sex	Male	Male	Male	Male	Male	Male	Female	male
Age of disease onset	49	40	40	42	41	40	37	32
Dementia	+	+	+	+	+	+	-	+
Spastic paraparesis	+	+	+	+	+	+	+	+
Cerebellar signs	-	-	-	-	-	-	-	-
Limb weakness	-	-	-	-	+	-	-	-
Psychiatric symptoms	-	-	-	-	+	-	-	+

Note. + = presence, - = absent

Generalized brain atrophy was present in patient IV-3 at age 41 (Fig. 2A), but there was no significant brain atrophy in patients IV-8 and IV-9 at age 42 and 38 respectively (Fig. 2B and C). Proband Q397 initially presented with spastic paraparesis at age 43, and later developed cognitive decline at 46 with MMSE score of 7 at age 47. He passed away at age 48 because of pneumonia. Patient IV-3 exhibited spastic paraparesis and psychiatric symptoms, including mania and visual hallucinations at age 41. He suffered from profound cognitive decline leading to total dependency. Patient IV-8 initially presented with spastic paraparesis at age 40. He was a computer

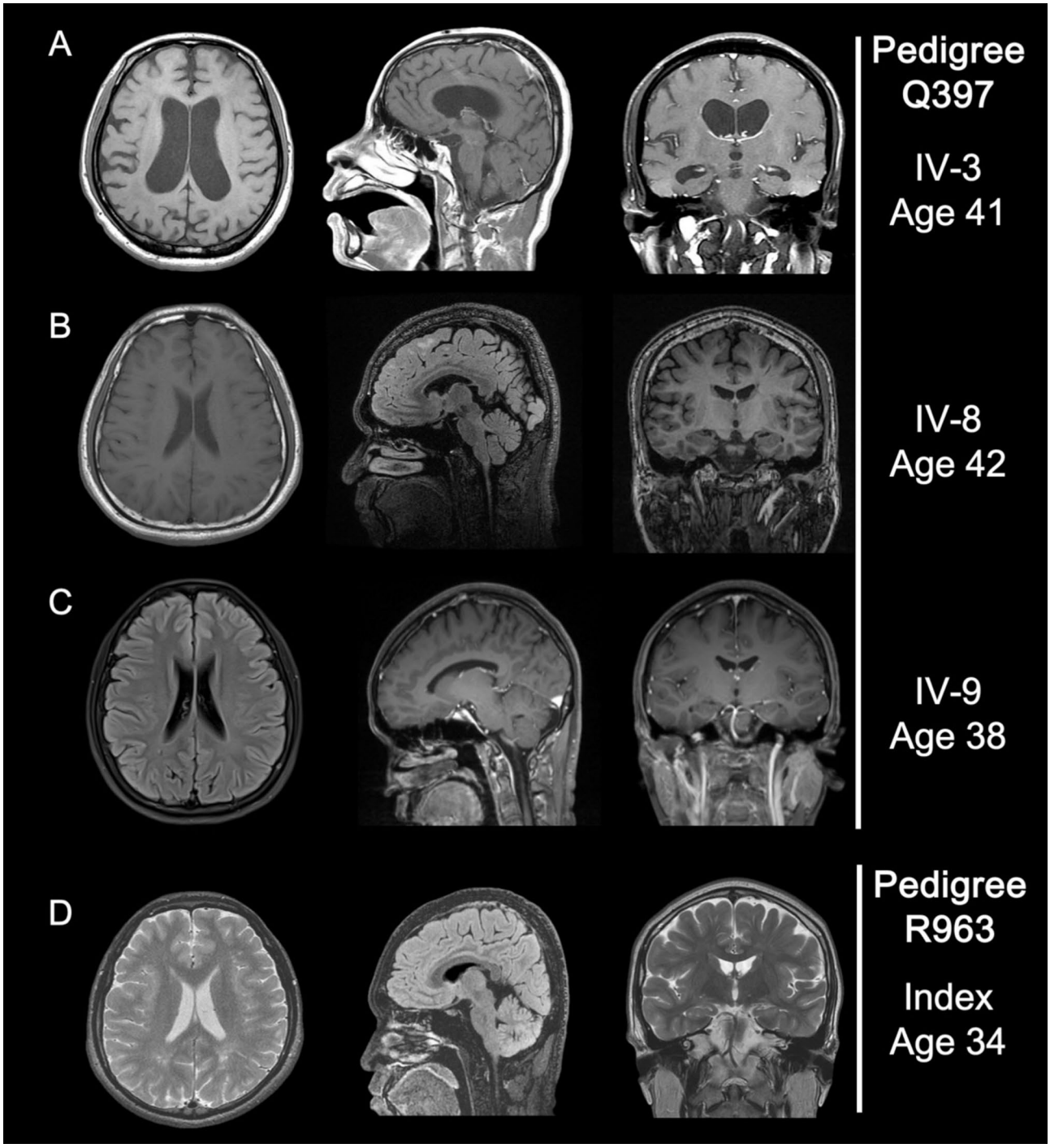

Fig. 2 Brain MRI images of patients with *PSEN1*-related spastic paraparesis. **(A-C)** The three patients carrying a heterozygous *PSEN1* p.F386S variant from Pedigree Q397. Patient IV-3 showed generalized brain atrophy (**A**) whereas the other two patients showed no remarkable atrophic change (**B** and **C**). **(D)** The patient R963 carries a heterozygous *PSEN1* p.P284S variant. The MRI images showed no remarkable brain atrophy

programmer at the time of diagnosis and later developed cognitive decline at 43 with a score of 26 on the MMSE and a score of 84 on the CASI. Susceptibility weighted images at age 42 showed multiple cerebral microbleeds (Supplementary Fig. 3, Additional file 1), which is a common MRI feature of patients with *PSEN1* related AD [32]. Patient IV-9, a teacher presented with spastic paraparesis at age 37, showed no cognitive decline and refused neuropsychological testing.

Patient R963 carrying the *PSEN1* p.P284S mutation presented with apparently sporadic spastic paraparesis. His parents were asymptomatic in their sixties. Unfortunately, DNA samples from his parents were not available for genetic analysis. He initially manifested with spastic paraparesis at age 32. At that time, he had a master degree and worked as a software engineer. By age 34, he began to experience cognitive decline, accompanied with psychiatric symptoms including delusions and hallucinations. He had cognitive impairment at age 35 with a score of 77 on the CASI exam. Brain MRI images taken at age 34 showed generally intact brain parenchyma without significant atrophy in hippocampus (Fig. 2D). However, an amyloid PET scan at age 35 revealed amyloid deposition in bilateral lateral temporal, frontal, precuneus and parietal regions (Fig. 3, regional cortical tracer uptake score = 3 in all four regions). The PET exam has a brain amyloid plaque load (BAPL) score of 3 [22]. The clinical and neuroimaging studies of the patient R963 are consistent with the diagnosis of early stage of AD according to the NIA-AA criteria [33].

Discussion

Spastic paraparesis caused by a pathogenic *PSEN1* variant was first identified in a Finnish family who carried the deletion of *PSEN1* exon 9 [11]. Although several *PSEN1* variants have been associated with spastic paraparesis, cases presenting with pure spastic paraparesis at disease onset are rarely reported before. Figure 1A shows all *PSEN1* variants linked to spastic paraparesis phenotype, with most variants located within exons 8 to 11. Notably, patients initially manifested with pure spastic paraparesis have only been reported in the p.Y154N, p.R278S, p.R278K and p.T291P variants (Fig. 1A) [17–19, 34]. In our study, we identified two pathogenic *PSEN1* variants, p.F368S and p.P284S, in patients whose initial symptoms were spastic paraparesis. Interestingly, both variants are located within the hotspot regions (Fig. 1A) [19]. The two mutations had not been identified in a cohort of 77 Taiwanese autosomal dominant AD [35], the study of which mainly enrolled patients with pure AD phenotypes.

While early-onset dementia is a common feature of patients with *PSEN1* mutations, other neurological symptoms, such as spastic paraparesis, may precede cognitive decline by several years [11, 19, 34]. Most patients with spastic paraparesis due to *PSEN1* variants eventually developed cognitive impairment along their disease course [17–19, 34]. In our study, six patients initially presented with spastic paraparesis, and five of them developed dementia before the last follow-up (Table 1). This finding highlights the need to consider *PSEN1* mutations as a potential cause of spastic paraparesis, even in the absence of cognitive symptoms.

In this study, *PSEN1* mutations were identified in 2 of the 242 (0.8%) patients initially diagnosed with HSP. The prevalence is consistent with a recent study that identified one *PSEN1* variant among 60 probands with HSP (1.6%) [34]. The onset age of spastic paraparesis in patients carrying the *PSEN1* mutations is generally older than subjects with other common HSP subtypes. The onset ages are around 20 years for spastic paraplegia (SPG) 3 A and SPG5, and 28 years for SPG4 [36–38], whereas *PSEN1*-related spastic paraparesis typically develops symptoms after the age of 30 [34].

The exact pathological mechanism underlying *PSEN1*-related spastic paraparesis remains unclear. Conduction abnormalities in the corticospinal, transcallosal, and lemniscal tracts, along with diffuse white matter lesions, have been observed in the spastic paraparesis patients harboring the *PSEN1* p.A431E variant [39]. Post-mortem examinations of the original Finnish family with a deletion of *PSEN1* exon 9 and spastic paraparesis revealed numerus "cotton wool" plaques in the medial motor cortices, a feature less frequently found in typical AD pathology [29, 40] but frequently reported in *PSEN1* carriers presenting with spastic paraparesis [34, 41, 42]. However, brain tissues from affected individuals also showed hallmarks of AD pathology, including neurofibrillary tangles and high concentrations of amyloid-β [42, 43]. In addition, flortaucipir PET images demonstrated increased uptake at paracentral lobule compared to ADAD patients without spastic paraparesis [44]. These findings suggest that *PSEN1*-related spastic paraparesis shares certain features with typical AD with more prominent involvement in the motor cortex, but also owns distinct characteristics warranted further investigation.

In addition to spastic paraparesis, *PSEN1* mutations are linked to several neurological phenotypes atypical for AD, such as epilepsy, ataxia, parkinsonism, and visual dysfunctions [8–10, 12, 15]. Previous studies suggest that specific regions of the mutant presenilin-1 protein, known as "hotspots", are associated with different phenotypes. For example, about a dozen of *PSEN1* variants have been associated with epilepsy, many of them were found in the first two transmembrane domains (TM) of the presenilin-1 protein (TM1 and TM2) [45], while spastic paraparesis-related variants are frequently located between TM6 and TM7, as illustrated in Fig. 1A. In contrast, variants associated with the parkinsonism

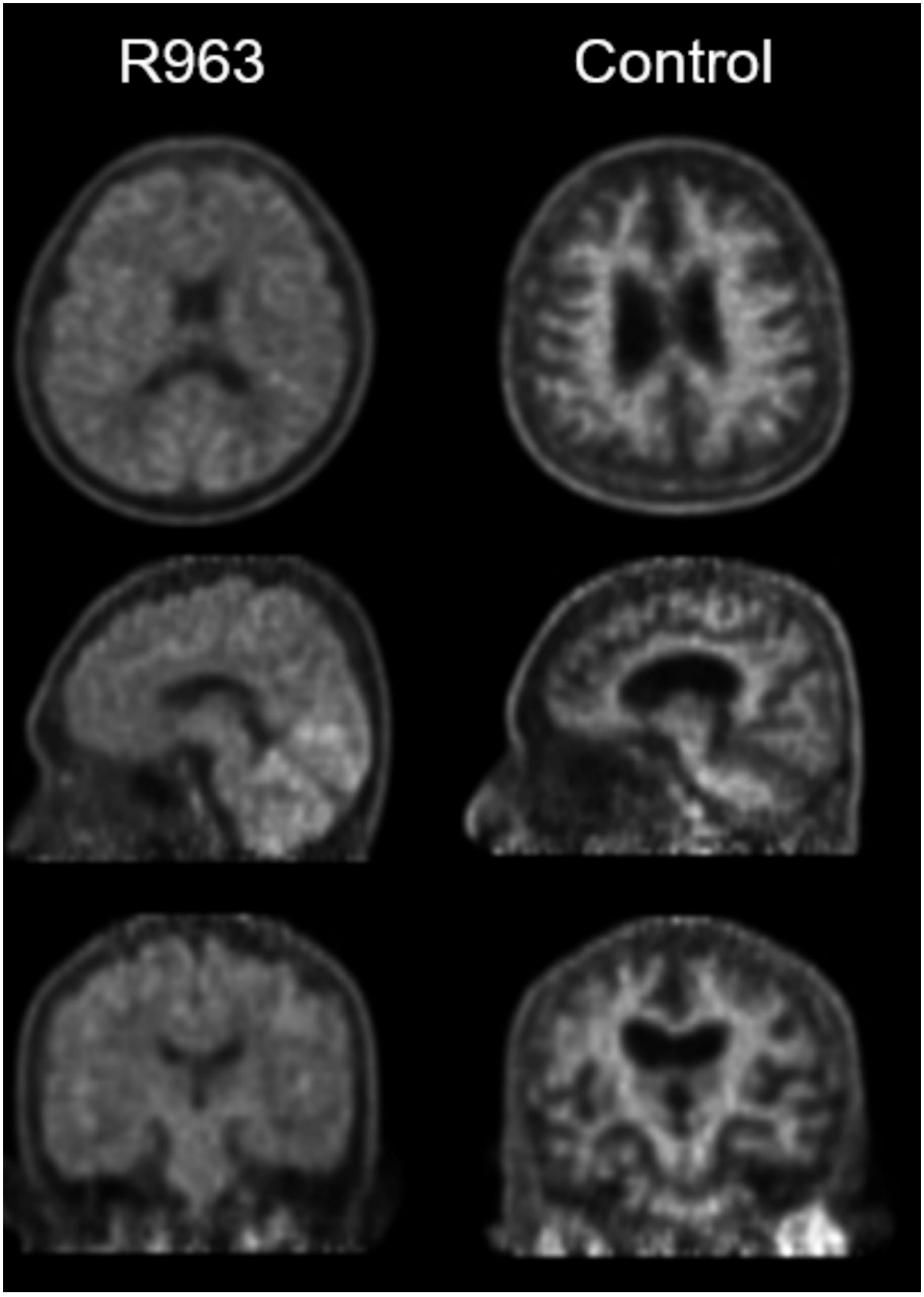

Fig. 3 Amyloid positron emission tomography images taken from patient R963 at age 35 years. The images revealed significant amyloid load (hyper-intensity in the cortex regions over subcortical white matter regions suggests higher amyloid load) in bilateral lateral temporal, frontal, precuneus and parietal regions and has a brain amyloid plaque load (BAPL) score of 3. For comparison, images from a healthy 64 years old control with a BAPL score of 1 were placed on the right

phenotype appear to be distributed throughout the entire presenilin-1 protein [45]. Understanding the distribution of these variants may provide insights into their pathogenic mechanisms. For example, the two spastic paraparesis-related *PSEN1* variants identified in this study are situated near the two aspartic acids (Asp275 and Asp385) in the catalytic center of γ-secretase complex, suggesting a potential link between the spastic paraparesis phenotype and γ-secretase activity [46]. Further research is needed to understand the molecular mechanism of *PSEN1*-related spastic paraparesis.

Recent advancements in AD treatment, particularly the approval of monoclonal antibody medications targeting amyloid β. Three drugs have been approved by the US FDA since 2021, namely Aducanumab, Lecanemab and Donanemab [47–49]. Although Aducanumab has been withdrawal from the market, Lecanemab is currently available in certain regions including the US, UK, Canada, Europe and Japan; and Donanemab is available in the US and UK. These novel medications offer potential therapeutic options for patients with *PSEN1*-related spastic paraparesis in certain regions. Early genetic diagnosis of *PSEN1* mutations is crucial, as it can significantly impact treatment strategies and genetic counseling. Recognizing *PSEN1* mutations as a possible cause of spastic paraparesis is essential for timely and accurate diagnosis and intervention.

This study had some limitations. Firstly, the number of cases was limited due to the scarcity of HSP and *PSEN1* variants in the population. Secondly, DNA samples were not available for some family members, making it difficult for assessing the pathogenicity and penetrance of the *PSEN1* variant discovered in this study. Future studies will require larger cohorts for further analysis.

Conclusions

Our study confirms that spastic paraparesis can be the first and only clinical presentation of patients carrying *PSEN1* mutations. Although *PSEN1* variants represent a rare cause of spastic paraparesis, they should be considered in the differential diagnosis, particularly in patients with a later age of onset. Given the potential availability of disease-modifying anti-amyloid therapies, genetic testing for *PSEN1* mutations may be warranted in selected cases of clinically suspected HSP.

Abbreviations

AD	Alzheimer's disease
BAPL	Brain amyloid plaque load
CASI	Cognitive Abilities Screening Instrument
HSP	Hereditary spastic parapaplegia
MMSE	Mini mental status examination
MRI	Magnetic resonance imaging
PET	Positron emission tomography
TM	Transmembrane domains

Supplementary Information

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Supplementary Material 1

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Author contributions

K-Y Jih designed the study, collected data, drafted and edited the manuscript. H-R Hsu collected data and edited the manuscript. J-L Fuh collected data and edited the manuscript. T-H Lee collected data and analyzed data. Y-H Lin collected data and edited the manuscript. S-Y Fang edited the manuscript. Y-C Liao designed the study, collected data, drafted and edited the manuscript. Y-C Lee designed the study, collected data, drafted and edited the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB No. 2017-02-008A) and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants prior to their participation in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Neurology, Taipei Veterans General Hospital, #201, Sec.2, Shih-Pai Road, Beitou District, Taipei 112201, Taiwan
[2]Department of Neurology, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan
[3]Department of Physiology, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan
[4]Department of Pediatrics, Taipei Veterans General Hospital, Taipei 112, Taiwan
[5]Department of Nuclear Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[6]Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan
[7]Center for Intelligent Drug Systems and Smart Bio-devices (IDS2B), National Yang Ming Chiao Tung University, Hsinchu, Taiwan

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