

Novel *PSEN1* and *PSEN2* Mutations Identified in Sporadic Early-onset Alzheimer Disease and Posterior Cortical Atrophy

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Background/Purpose: Sporadic early-onset Alzheimer disease (sEOAD) and its visual variant, posterior cortical atrophy (PCA), have a disease onset at less than 65 years of age with no familial aggregation. The etiology and genetic basis of these diseases remain poorly understood. Our study aimed to identify additional mutations or variants associated with sEOAD and PCA and to further examine their genetic and phenotypic spectrums.

Methods: We performed whole-exome sequencing and analyzed the clinical and neuroimaging features of mutation carriers with 29 patients having sEOAD and 25 having PCA.

Results: Nine rare damaging variants were identified in 4 patients with sEOAD and 3 with PCA. A novel mutation (p.A136V) in *PSEN1* was identified in a patient with sEOAD and a likely pathogenic variant (p.M239T) was identified for *PSEN2* in a patient with PCA. In addition, 7 rare damaging variants were detected in other genes related to neurodegenerative diseases. The patient carrying the *PSEN1* p.A136V mutation presented with typical clinical and imaging features of sEOAD, and the PCA patient with the *PSEN2* p.M239T mutation presented with visuospatial impairment as the initial symptom.

Conclusion: Our study expands the *PSEN1* mutation spectrum of sEOAD and highlights the importance of screening *PSEN1* and/or *PSEN2* mutations in PCA patients.

Key Words: sporadic, early-onset, Alzheimer disease, posterior cortical atrophy, mutation

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Sporadic early-onset Alzheimer disease (sEOAD) is a subtype of Alzheimer disease (AD) with patients developing symptoms before the age of 65 years and less apparent or no familial aggregation.¹ Besides the typical sEOAD, there are clinical variants of sEOAD, including logopenic variant primary progressive aphasia, posterior cortical atrophy (PCA), and behavioral/dysexecutive AD.² PCA is one of the most common variants of sEOAD, which is characterized by visuospatial or visuo-perceptual impairments and predominant involvement in occipitoparietal regions.³

Although genetic factors have been associated with sEOAD, their roles in disease development and progression remain unclear.⁴ It is well known that the $\epsilon 4$ allele of the *apolipoprotein E* (*APOE*) gene is a major risk factor for sEOAD.⁵ However, an increasing number of pathogenic variants in the 3 genes—*APP*,⁶ *PSEN1*⁷ and *PSEN2*⁸—causative for familial AD have also been identified in sEOAD.⁹ Moreover, rare variants in other genes associated with neurodegenerative diseases, such as *PARK2*, *FUS*, and *MAPT*, have also been associated with sEOAD.¹⁰ Genetic studies on PCA are relatively few and there are only 4 pathogenic mutations (*PSEN1* G223R, *PSEN2* M239I, *MAPT* V363I, and *GRN* R110X) that have been reported.¹¹

To identify additional mutations or variants associated with sEOAD and PCA and further examine their genetic and phenotypic spectra, we performed whole-exome sequencing (WES) and analyzed the clinical and neuroimaging features of the mutation carriers in 54 patients with sEOAD or PCA.

METHODS

Participants

From October 2014 to December 2019, a total of 54 patients (29 sEOAD; 25 PCA) and 87 cognitively normal controls (NC) were recruited from the Department of Neurology of Xuanwu Hospital and Xijiekou Community Medical Health Service Center, Beijing. Family history was investigated up to 3 sequential generations, and cases with a positive history were excluded.

All patients completed detailed clinical interviews, physical examinations, neuropsychological assessments, and imaging studies within 1 month of recruitment. Patients with sEOAD met the diagnosis criteria established by the International Working Group (IWG-1),¹² and those with PCA fulfilled the consensus classification of PCA.¹³ NC participants were recruited from the general elderly community population based on the education-adjusted cutoff values for the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), in addition to a 0 score for the Clinical Dementia Rating sum of boxes.^{14–17} All participants were clinically screened for the

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exclusion of symptoms and signs of frontotemporal dementia (FTD), Parkinson disease (PD), and amyotrophic lateral sclerosis (ALS) (Fig. S1, Supplementary Digital Content 1, <http://links.lww.com/WAD/A322>, shows the flowchart of the study).

Ethical Assurances

The clinical study protocols and informed consent forms were approved by the Ethics Committees of Xuanwu Hospital of Capital Medical University, China. Written informed consent was obtained from each patient or their guardian.

WES, Raw Data Analysis, and Variant Annotation

For WES, whole blood-derived DNA from all the recruited participants was captured to generate a sequencing library using the Agilent SureSelect Human All Exon V6 Kit (Agilent Technologies, Santa Clara, CA) according to the manufacturer's protocol. The prepared libraries were sequenced on the HiSeq-2000 platform (Illumina, San Diego, CA). The sequenced reads were aligned to the human genome (GRCh37/hg19). Reads were then aligned to the targeted regions and collected for SNP calling and subsequent analysis using the Burrows-Wheeler Aligner (BWA) software. The low-quality variations were filtered out.

Variants were annotated using the Realigner Target Creator in Genome Analysis Toolkit (GATK) and the ANNOVAR¹⁸ program, and filtered and selected according to the flowchart shown in Figure 1A. Briefly, open databases including ExAC_EAS, 1000 genomes_EAS, gnomAD genomes_EAS, and gnomAD exomes_EAS, and our in-house exome-sequencing database were used as the sources of reference variant

frequencies. SIFT, PolyPhen-2, and Combined Annotation-Dependent Depletion (CADD) pathogenicity prediction algorithms were utilized to estimate the effects of variants on protein function. Phylogenetic conservation was estimated using genomic evolutionary rate profiling (GERP++). All analyses were performed on the Seqmax (www.seqmax.com, accessed March 2020) and the Pubvar platform (www.pubvar.com, accessed March 2020). Rare coding variants (minor allele frequency < 0.01) predicted to be damaging (rare damaging variants) were selected for further analyses. Finally, variants were classified as pathogenic, likely pathogenic, or variant with uncertain significance according to the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) criteria.¹⁹

Selection of Dementia-associated Genes for Analyses

The genes reported to be associated with “dementia” were searched up to March 2020 in the Human Gene Mutation Database (HGMD, www.hgmd.cf.ac.uk/ac/search.php), Online Mendelian Inheritance in Man (OMIM, www.omim.org/), Clinvar (www.ncbi.nlm.nih.gov/clinvar), and GeneCards (www.genecards.org). All shortlisted dementia-associated genes were further verified by UniProt (www.uniprot.org/, accessed March 2020), a web resource that curated the comprehensive, high-quality annotated information of genes, and their corresponding protein functions. The selected genes were further confirmed by MalaCards (www.malacards.org/, accessed March 2020), an integrated database of public literature on human diseases and

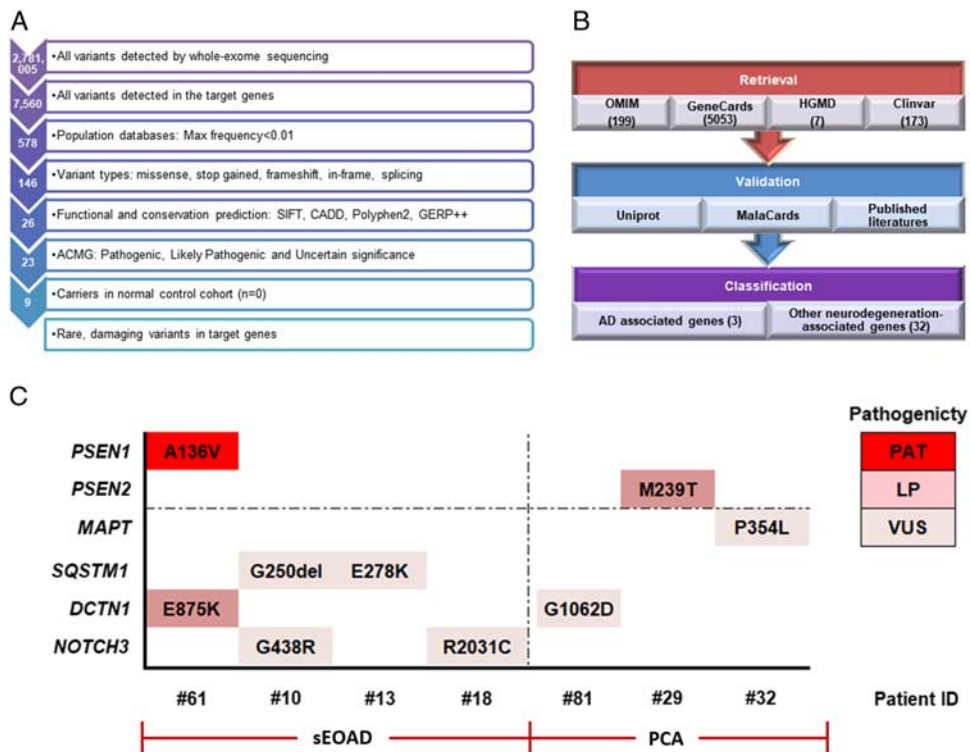


FIGURE 1. Rare, deleterious coding variants identified in sEOAD or PCA patients. A, Schematic presentation of the number of variants among selected genes resulting at each step of screening. B, Flow diagram of dementia-associated gene selection and classification using different online databases. C, Presentation of rare, deleterious protein-altering variants of selected genes in recruited sEOAD or PCA patients with different gray scales representing different pathogenicity according to American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP). AD indicates Alzheimer disease; LP, likely pathogenic; PAT, pathogenic; PCA, posterior cortical atrophy; sEOAD, sporadic early-onset Alzheimer disease; VUS, variant of uncertain significance. [full color online](#)

disorders. Finally, all the resulting genes were classified into 2 categories: causative genes for AD and other neurodegenerative diseases, such as PD, ALS, and FTD. The final gene list included 35 genes for analyses (Table S1, Supplemental Digital Content 2, <http://links.lww.com/WAD/A323>).

Genotyping of APOE Alleles

The *APOE* genotyping was performed using Sanger sequencing for rs7412 and rs429358 on the ABI 3730XL DNA Sequencer (Applied Biosystems, Thermo Fisher Scientific), and sequencing results were analyzed using Chromas Lite v2.01 (Technelysium Pty Ltd, Tewantin, QLD, Australia).

Statistical Analyses

Normal distribution was evaluated using the Shapiro-Wilk test. All data were compared between groups according to the normality of their distributions. Analyses of variance or *t* tests were used for normally distributed data, and the Kruskal-Wallis test was used for skewed data to compare differences between groups. All statistical analyses were performed using IBM SPSS Statistics, v22.0.0.0 (2013; SPSS Inc., Chicago, IL) and GraphPad Prism, v6.0 (2009; GraphPad Software Inc., La Jolla, CA). *P*-values <0.05 were considered statistically significant.

RESULTS

Demographic and Clinical Features of the Patients

The demographic data and scores for neuropsychological assessments of all patients and NC patients are summarized in Table 1. For all the patients, the average age of patients was 58.48 ± 4.94 years and their age at onset (AAO) was 55.39 ± 4.83 years. There was no significant difference between the sEOAD and PCA groups in terms of sex, AAO, years of education, disease duration, MMSE, and MoCA scores.

Sequencing Data of the Participants

We performed WES on samples from all recruited individuals. The overall sequencing data size was 14.8 GB in the cases and 14.7 GB in controls. The mean sequencing depth was $129.6 \times$ in cases and $122.1 \times$ in controls. The mean coverage of reads with a sequencing depth of $\geq 20 \times$ was 95.29% in cases and 94.86% in controls. A total of 578 rare coding variants were identified in cases and 587 in controls,

including 26 rare damaging variants in cases and 18 in controls (see Table S2, Supplementary Digital Content 3, <http://links.lww.com/WAD/A324>, which demonstrates sequencing statistics for the samples in this study).

Rare Damaging Variants Identified in Genes Associated With Early-onset Alzheimer disease (EOAD), PCA, and Other Neurodegenerative Diseases

Genes Selected for Analyses

Because of the relatively small sample size of our study, the power of association analyses for all the WES-targeted genes was low. We then investigated the genes proven to be causative for or associated with neurodegenerative diseases. By searching the open databases, we initially identified 199 genes in OMIM, 5053 in GeneCards, 7 in HGMD, and 173 in Clinvar databases. After excluding overlapping records, verifying genetic and functional relevance based on Uniprot and PubMed databases, 35 genes, including 3 known AD-associated genes (*APP*, *PSEN1*, and *PSEN2*), and 32 others associated with other neurodegenerative or cerebral vascular diseases (eg, PD, ALS, FTD, CADASIL), were selected for the genetic analysis (shown in Fig. 1B, Table S1, Supplemental Digital Content 2, <http://links.lww.com/WAD/A323>, which showed the selected gene for analyses).

Rare Damaging Variants in the Selected Genes

In total, we detected 7560 variants of all types in the 35 selected genes. After sequential screening and filtering as per the flowchart in Figure 1A, 9 rare damaging variants were identified in 7 patients, predicted to be deleterious by Polyphen-2 and SIFT programs. Among all the rare damaging variants, 1 was predicted as pathogenic, 2 as likely pathogenic, and 6 as variant with uncertain significance, according to the ACMG/AMP guidelines. Two were identified in the known AD genes (*PSEN1* and *PSEN2*), whereas the remaining 7 were identified in the genes related to other neurodegenerative/cerebral vascular disease (*MAPT*, *SQSTM1*, *DCTN1*, and *NOTHC3*). The 4 AD patients carried 6 variants, including 1 in *PSEN1* (A136V) and 5 in the other genes. Three patients diagnosed with PCA carried a variant in *PSEN2* (M239T), *MAPT* (P354L), and a different gene, respectively (Fig. 1C). In contrast, no predictive pathogenic variant was detected in the remaining 47 patients.

TABLE 1. Demographic Data and Neuropsychiatric Assessment of the 3 Groups

| | Case | | | Control | <i>P</i> |
|----------------------|------------------|------------------|------------------|------------------|----------|
| | sEOAD | PCA | Total | | |
| N | 30 | 24 | 54 | 87 | — |
| Age | 58.73 ± 4.47 | 58.17 ± 5.56 | 58.48 ± 4.94 | 60.61 ± 3.23 | 0.043† |
| Sex (male/female) | 13/17 | 9/15 | 22/32 | 30/57 | 0.685‡ |
| Years of education | 11.83 ± 3.58 | 9.71 ± 5.09 | 10.89 ± 4.40 | 11.24 ± 2.67 | 0.240† |
| Age at onset (y) | 55.93 ± 4.38 | 54.71 ± 5.35 | 55.39 ± 4.83 | — | 0.359* |
| Disease duration (y) | 2.77 ± 1.27 | 3.50 ± 1.44 | 3.09 ± 1.39 | — | 0.053* |
| MMSE | 16.52 ± 6.40 | 14.39 ± 5.48 | 15.58 ± 6.05 | — | 0.212* |
| MoCA | 11.62 ± 6.19 | 7.91 ± 4.41 | 9.98 ± 5.73 | — | 0.019* |

Data are presented as mean \pm SD.

*Comparisons are between the sEOAD and PCA cases using 2-sided unpaired *t* test.

†*P*-value for nonparametric statistics among the sEOAD, PCA, and control group.

‡*P*-value for χ^2 test among the sEOAD, PCA, and control group.

MMSE indicates Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PCA, posterior cortical atrophy; sEOAD, sporadic early-onset Alzheimer disease.

In this study, 2 novel variants were classified as pathogenic/likely pathogenic. In patient #61, the *PSEN1* A136V variant was categorized as pathogenic based on 1 pathogenic strong (PS), 2 pathogenic moderate (PM), and 2 pathogenic supporting (PP) pieces of evidence. The details were as follows. PS3: several reported studies showing a specific decreased protease activity with *APP*²⁰; PM1: well-studied functional domain without benign variation; PM2: absence in multiple ethnic populations in the Exome Sequencing Project, 1000 Genomes Project, ExAC or Genome AD; PP3: multiple computational evidence supporting a deleterious effect on the gene/gene product; and PP4: highly specific phenotypes in patients with AD with *PSEN1* mutations. Similarly, the *PSEN2* M239T variant in patient #29 was classified as likely pathogenic based on the evidence of 2 PM and 2 PP (PM2+PM5+PP3+PP5). Apart from the evidence described above, the novel missense variant occurred at the same position as another pathogenic missense change (M239I, M239V), as reported previously which supports the PM5 evidence.^{8,21} In addition, the pathogenicity predicted by in silico analyses supported the PP5 evidence (as shown in www.pubvar.com, accessed March 2020).

Clinical and Imaging Features of Patients Carrying the Novel Damaging Variants

An overview of the genetic (including *APOE* genotypes), clinical, and imaging features is shown in Table 2. All these features meet the diagnostic criteria for AD or PCA. The specific characteristics of the 2 patients carrying the novel variants were detailed as follows.

Patient (#61) Carrying PSEN1 A136V Mutation

The patient began to complain of memory decline at the age of 50 years, manifesting as frequently forgetting words and repeating questions, in addition to apathy. At the age of 53 years, he started to get lost in new surroundings. At 54 years, he felt sadness as his mother passed away and, thereafter, developed progressive memory loss, language disturbance, impairment in daily living, and incompetence in his work. At that time, he was diagnosed with cognitive impairment and received treatment with memantine and Exelon (rivastigmine). Brain magnetic resonance imaging (MRI) suggested global brain atrophy, particularly pronounced in the bilateral hippocampi (Fig. 2). Positron emission tomography of fluorine-18 fluorodeoxyglucose (¹⁸F-FDG-PET) indicated significant hypometabolism in the bilateral parietal, temporal, and occipital lobes (Fig. 3). Cerebrospinal fluid analyses showed a significantly elevated amyloid beta (Aβ) 42/tau ratio (10.23; normal range: ≤2.75). On the basis of clinical, imaging, and cerebrospinal fluid findings, this patient met the diagnosis of definite sEOAD.

Patient (#29) Carrying PSEN2 M239T

The patient developed progressive visual disturbance and short-term memory deficit at 59 years of age. His initial symptoms were object agnosia, right-left confusion, and impaired episodic memory. Apart from these symptoms, the patient displayed impairment of daily activities such as poor personal hygiene behavior. Neuropsychological tests showed an MMSE score of 14/30 and an MoCA score of 7/30. In addition, severe simultanagnosia and prosopagnosia were observed. Brain MRI showed significant bilateral parietal and occipital cortex atrophy (Fig. 2), and brain ¹⁸F-FDG-PET suggested significant hypometabolism in the bilateral cortex of the parietal, temporal, and occipital lobes

TABLE 2. Demographics, Neuropsychological Assessment, and Clinical and Imaging Features of Novel Mutation Carriers

| ID | Diagnosis | Sex | AAO | DD | ApoE | FH | MMSE | MoCA | CDR | MRI | ¹⁸ F-FDG-PET | AV-45-PET | Gene Mutation |
|----|-----------|--------|-----|----|-------|----|------|------|-----|---|----------------------------|-----------|--------------------------------|
| 10 | sEOAD | Female | 47 | 2 | ε3/ε3 | No | 10 | 4 | 2 | Diffuse cerebral atrophy | BT, BP, BF↓ L > R | NA | SQSTM1: G250del; NOTCH3: G438R |
| 13 | sEOAD | Female | 51 | 2 | ε3/ε3 | No | 13 | 5 | 2 | NA | BT, BP↓, R > L RF↓, LF↓ | NA | SQSTM1: E278K |
| 18 | sEOAD | Female | 57 | 4 | ε3/ε3 | No | 6 | 4 | 2 | Bilateral hippocampi atrophy | BT, BP, BF↓ | NA | NOTCH3: R2031C |
| 61 | sEOAD | Male | 56 | 2 | ε2/ε4 | No | | | | Bilateral hippocampi atrophy | BT, BP, BO↓ | NA | PSEN1: A136V; DCTN1: E875K |
| 81 | PCA | Female | 56 | 4 | ε3/ε3 | No | 17 | 6 | 1 | Bilateral hippocampi atrophy | L,T, LP, LO↓ | Positive | DCTN1: G1062D |
| 29 | PCA | Male | 59 | 5 | ε3/ε4 | No | 14 | 7 | 1 | Bilateral hippocampi and temporal atrophy | BT, BP, BO↓ R > L↓ | Positive | PSEN2: M239T |
| 32 | PCA | Male | 51 | 5 | ε3/ε4 | No | 15 | 8 | 1 | Bilateral parietal and occipital atrophy | BT, BO↓ | Positive | MAPT: P354L |

↓ indicates mild; L, left; severe; AAO, age at onset; ApoE, apolipoprotein E; AV-45-PET, florbetapir F18 positron emission tomography; B, bilateral; CDR, Clinical Dementia Rating; DD, disease duration; F, frontal; ¹⁸F-FDG-PET, positron emission tomography of fluorine-18 fluorodeoxyglucose; FH, family history; L, left; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; N/A, not available; O, occipital; P, parietal; PCA, posterior cortical atrophy; R, right; sEOAD, sporadic early-onset Alzheimer disease; T, temporal.

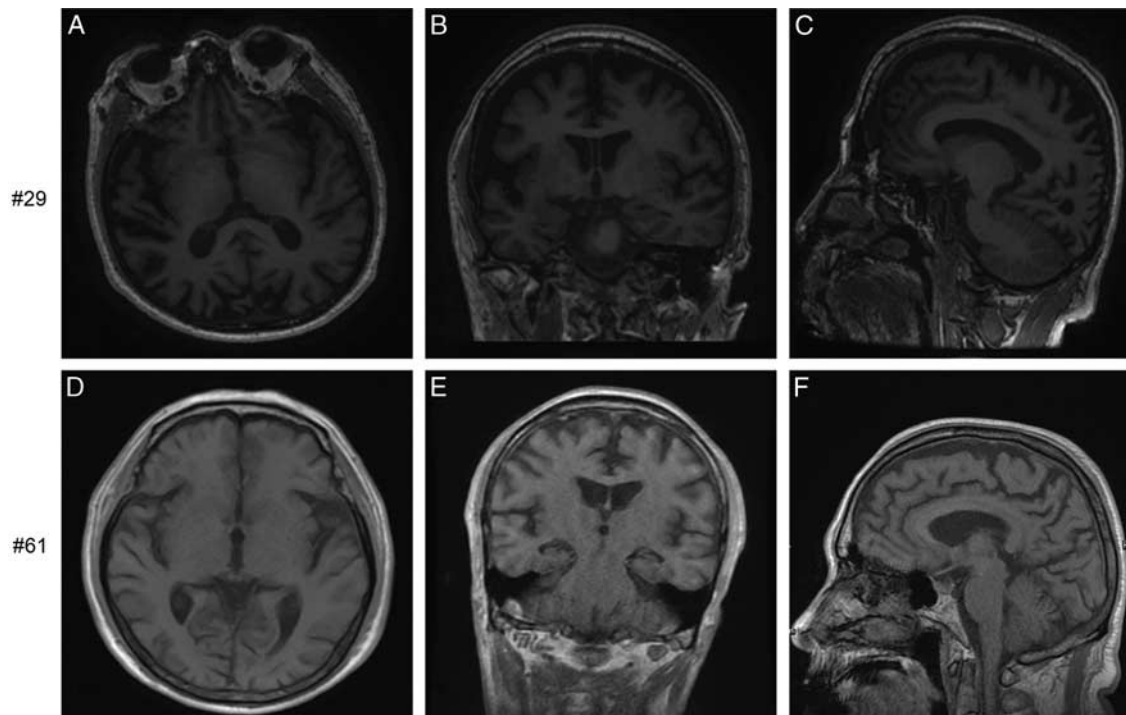


FIGURE 2. Brain magnetic resonance imaging in case #29 and case #61. A–C, Brain magnetic resonance imaging of case #29 showed bilateral hippocampal, temporal, and occipital lobe atrophy. D–F, Brain magnetic resonance imaging of case #61 showed bilateral hippocampi, temporal, and occipital lobe atrophy and mild cerebral atrophy.

(Fig. 3). Florbetapir F18 positron emission tomography (AV-45-PET) displayed extensive A β deposition. Given the symptoms of visual disturbance and memory loss, and findings of neuropsychological tests, MRI, and FDG-PET, this patient can be diagnosed with PCA.

DISCUSSION

In this case study, we screened mutations in 54 Chinese patients with sEOAD or PCA by WES and identified 2 novel

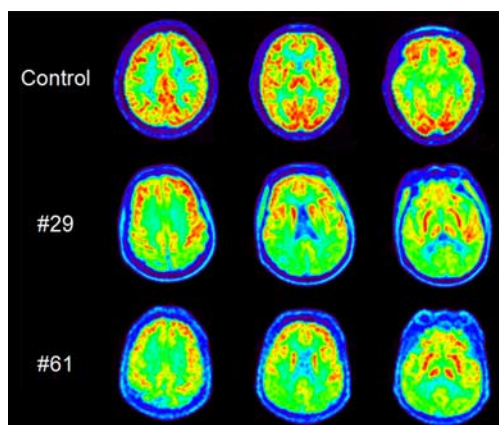


FIGURE 3. Brain positron emission tomography of fluorine-18 fluorodeoxyglucose in case #29 and case #61. Positron emission tomography of fluorine-18 fluorodeoxyglucose of the brain demonstrated significant hypometabolism bilaterally in the parietal lobe, temporal lobe, and occipital lobe in these 2 cases. full color online

mutations in *PSEN1* and *PSEN2*, respectively. We also detected 7 rare variants in 4 genes (*MAPT*, *SQSTM1*, *DCTN1*, and *NOTCH3*) associated with other neurodegenerative disorders and cerebral vascular disease. These findings may expand the genetic spectrum of EOAD and PCA.

Of all 3 causative genes for familial AD, *PSEN1* is most frequently mutated. To date, 314 rare variants have been reported, and these variants are pathogenic to both familial and sporadic AD (www.alzforum.org/mutations/app, accessed in March 2020).^{22,23} We identified a novel deleterious variant, A136V, in *PSEN1*, which was classified as pathogenic according to the ACMG/AMP guidelines. This novel mutation is located on exon 5 of the *PSEN1* gene, where another known mutation (*PSEN1* A136G) has been found in 7 affected and unaffected members in a large Chinese AD pedigree including 130 members.²⁴ Moreover, previous studies have demonstrated that *PSEN1* mutations usually result in EOAD (AAO: 30 to 50 y old), and those residing within amino acids 1 to 200 are usually related to sporadic cases.^{4,24} Furthermore, the patient carrying *PSEN1* A136V manifested an onset at 50 years and developed typical symptoms of AD, which were similar to previously reported sEOAD cases carrying *PSEN1* mutations.^{4,25} Therefore, although we did not conduct functional testing for this mutation, the available genetic and phenotypic evidence in patient #61 fulfilled the diagnostic criteria for a pathogenic variant. Collectively, the identification of *PSEN1* A136V further expands the mutational spectrum of sEOAD.

There had only been 1 mutation (M239I) and 1 variant with uncertain significance (S130L) reported in *PSEN2* among PCA patients. In our study, we detected a novel likely pathogenic variant (*PSEN2* M239T) carried by the PCA patient (#29). The variant was located in exon 7 of *PSEN2*, where other mutations (M239I and M239V) have been reported in sEOAD cases.^{8,26}

Patients with mutations at this position showed significant phenotypic diversity, possibly presenting as cognitively normal, late-onset AD, typical sEOAD or PCA.^{8,26–30} These evidences support a likely pathogenic role of this variant in PCA, which warrants further verification. At present, we are conducting in vitro functional tests to confirm its pathogenicity.

In view of the overlapping genetics of AD with multiple other neurodegenerative diseases, detecting variants beyond dementia-associated genes is appreciated.^{31,32} In contrast to the targeted capturing and sequencing in most previous studies, the WES strategy used in our study enables an extensive screening of mutations in genes other than *PSEN1* and *PSEN2*. In our study, 7 rare mutations with unknown significance were detected in genes other than *APP*, *PSEN1*, and *PSEN2*, distributed in *MAPT*, *SQSTM1*, *DCTN1*, and *NOTCH3*, respectively. These mutations provide a clue to further genetic and functional studies.

In summary, our study identified a novel pathogenic mutation in *PSEN1* (A136V) in a patient with sEOAD and a novel likely pathogenic variant in *PSEN2* (M239T) in a PCA case. These findings not only expand the genetic spectrum of sEOAD, but also suggest a genetic overlap between sEOAD and PCA, and further highlight the importance of genetic testing in both conditions. However, the interaction between the *APOE* risk alleles and the mutation/variant we detected was not analyzed because of the limited sample size. In addition, functional studies are needed to validate our genetic findings.

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