# A case of frontal variant Alzheimer's disease due to the c.C236T variant of PSEN1

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**Background** Presenilin-1 (PSEN1) is the most frequently mutated gene in familial Alzheimer's disease (AD). We describe a case of autosomal dominant AD associated with a rare pathogenic mutation of PSEN1 with only a few cases described in the literature (1).

**Case report** A 75-years old female was referred to our Memory Clinic for progressive cognitive decline began 5 years before. She complained of episodic memory deficits and depression that have been treated with venlafaxine (150 mg/day). Neuropsychological examination revealed a mild cognitive decline (MMSE 25/30) with deficits in working memory, executive functions and delayed prose recall. She had a positive family history with brother, father and paternal grandmother diagnosed with early onset (< 65 y/o) dementia. Her brother was diagnosed with Pick's disease. Patient underwent brain **MRI** that revealed only mild asymmetrical hippocampal atrophy (**Fig. 1**). Brain **PET** with FDG showed preeminent frontal hypometabolism involving the anterior cingulate cortex, the right temporal lobe and the inferior parietal lobes (**Fig. 2**). **CSF biomarkers** were indicative of AD (**Fig. 3**) and **PET amyloid** scan was positive (**Fig. 4**). Therapy with rivastigmine patch was started. During one-year follow-up the patient presented sudden episodes of brief repetitive arms movements compatible with the diagnosis of focal seizures. **EEG** showed epileptic activity on right temporal regions. Therapy with levetiracetam (1000 mg/day) was added with benefit.

Genetic analysis for genes associated with early onset dementia was performed, and mutational analysis disclosed the **heterozygous c.236C>A transition in PSEN1 exon 4 which substituted a alanine with a valine at codon 236 (p.Ala79Val)**.

**Conclusions** The PSEN1 c.236C>T mutation is considered pathogenic and leads to an increase in Aβ42 level and Aβ42/Aβ40 ratios in cell cultures (2). This variant is associated with a later onset compared to the other PSEN1 variants (1). Frontal hypometabolism in a patient with dysexecutive syndrome and biomarkers indicative of AD (CSF, amyloid PET) as well as the presence of concomitant epilepsy might suggest performing genetic analysis of PSEN1 gene, regardless the age of onset

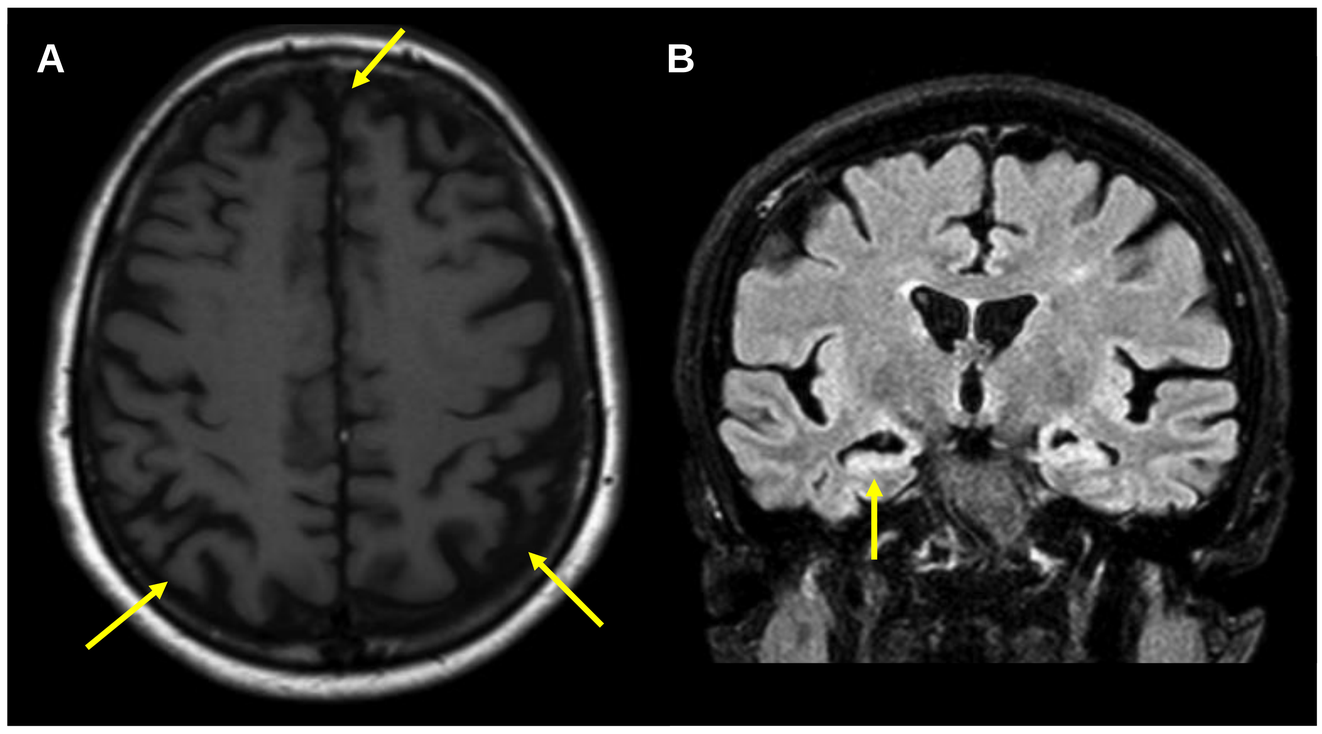


***Fig. 1.*** *Axial T1 (A) MRI scan shows mild frontal and parietal atrophy, in the FLAIR T2 (B) scan see the mild hippocampal atrophy.*

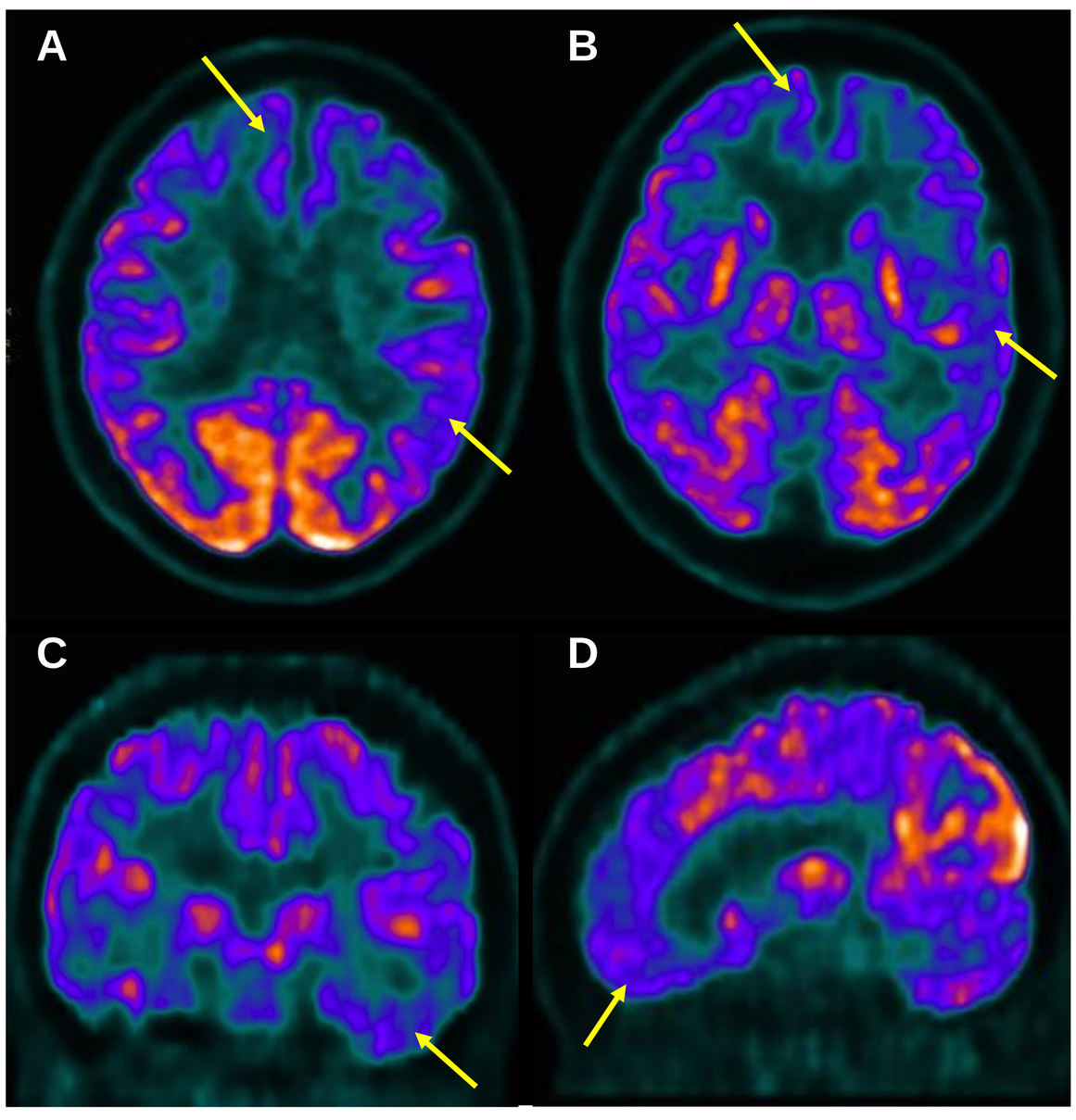


***Fig. 2.*** *$^{18}$FDG - PET axial (A, B) coronal (C) and sagittal (D) scans show bilateral frontal, anterior cingulate and parieto - temporal hypometabolism.*

| Aβ42 | TAU P | TAU tot |
|---|---|---|
| 414 ng/L | 65 ng/L | 437 ng/L |

***Fig. 3.*** *CSF biomarkers.*

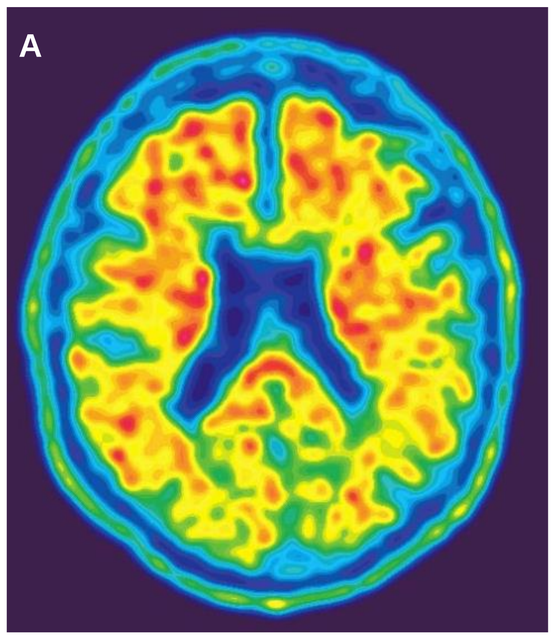


***Fig. 4.*** *PET with Flutemetamol tested positive.*

1 Lanoiselée HM et al. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. *PLoS Med*. 2017;14(3):e1002270.
2 Kumar-Singh S et al. Mean age-of-onset of familial alzheimer disease caused by presenilin mutations correlates with both increased Abeta42 and decreased Abeta40. *Hum Mutat*. 2006;27(7):686–695.