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Homozygosity for the A431E mutation in *PSEN1* presenting with a relatively aggressive phenotype

John Parker[1,2], **Tahseen Mozaffar**[2], **Ashlynn Messmore**[3], **Joshua L. Deignan**[4], **Virginia E Kimonis**[3], **John M. Ringman**[1,*]

[1]Department of Neurology, Keck School of Medicine at USC

[2]Department of Neurology, University of California, Irvine

[3]Department of Pediatrics, Division of Genetic and Genomic Medicine, University of California, Irvine

[4]UCLA Molecular Diagnostics Laboratories, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA

Abstract

Objective: We report a 35 year-old male with childhood learning disability and early onset dementia who is homozygous for the A431E variant in the PSEN1 gene. Presenilin1 mutations are associated with autosomal dominant Alzheimer's dementia with young and somewhat stereotyped onset. Such variants may cause Alzheimer's dementia through aberrant processing of amyloid precursor protein through effects on γ-secretase activity. γ-secretase is involved in the cleavage of many proteins critical to normal function, including brain development. Therefore, manifestations in persons without normal Presenilin1 function is of interest.

Methods: Clinical evaluation including family history, examination, brain MRI, and genetic analysis.

Results: Our patient had mild developmental delay, chronic nighttime behavioral disturbance, and onset of progressive cognitive deficits at age 33. Clinical evaluation demonstrated spastic

*Correspondence: Dr. John M. Ringman, M.D., M.S., Helene and Lou Galen Endowed Professor of Clinical Neurology, Department of Neurology, Keck School of Medicine of USC, Center for the Health Professionals, 1540 Alcazar Street, Suite 209F, Los Angeles, CA 90033, (323) 442-0321 Phone, John.ringman@med.usc.edu.

AUTHOR CONTRIBUTIONS:

JP: Assessed and described the index patient, drafted and edited the manuscript.

TM: Identified the index patient and provided intellectual input into the drafting of the manuscript.

AM: Assessed the genetic history of the index patient, drafted this portion of the manuscript and provided further input into the final draft of the manuscript.

JD: Performed the molecular analysis involved in the paper, drafted this portion of the manuscript, and provided further input into the final draft of the manuscript.

VK: Assessed the genetic history of the index patient, drafted this portion of the manuscript and provided further input into the final draft of the manuscript.

JR: Identified the significance of this patient and provided oversight into the drafting of the manuscript and intellectual input into the final draft.

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paraparesis and pseudobulbar affect. Brain MRI revealed cerebral atrophy disproportionate to age. Chronic microhemorrhages within bilateral occipital, temporal, and right frontal lobes were seen. Sanger sequencing confirmed homozygosity for the A431E variant in PSEN1, which is a known pathogenic variant causing autosomal dominant Alzheimer's dementia.

Conclusions: Our report demonstrates that homozygosity for pathogenic Presenilin1 variants is compatible with life, though may cause a more aggressive phenotype with younger age of onset and possibly REM behavior disorder.

Keywords

PSEN1; homozygote; Alzheimer's disease; spastic paraparesis; A431E; autosomal dominant; REM behavior disorder

Introduction

While variants in the genes coding for Presenilin-1 (*PSEN1)*, Presenilin-2 (*PSEN2)*, and amyloid precursor protein (*APP)* are known to cause early onset Alzheimer disease (AD) which are inherited in an autosomal dominant fashion, the effects of homozygosity for these variants has not been well-documented. Variants in *PSEN1* affect the endopeptidase activity of the γ-secretase complex and are thought to predispose to AD through their effects on APP cleavage[1]. Such variants cause an altered preponderance of the γ-secretase cleavage products of APP such as Aβ37, Aβ38, Aβ39[2], Aβ40, Aβ42, and Aβ43[3]. Transgenic animal models suggest that some *PSEN1* variants may be embryonic lethal when homozygous[3] though others show more aggressive development of AD pathology[4]. As γ-secretase cleaves many proteins[5], some of which play roles in neural development, it is possible that aberrant γ-secretase function leads to abnormal brain development.

Kosik et al[6] identified 6 individuals homozygous for the c.839A>C (p.Glu280Ala, E280A) substitution in *PSEN1* from an extended kindred in Colombia[7]. Of the 6, 2 met criteria for dementia at 5 and 13 years prior to the mean age of dementia diagnosis associated with this variant. One homozygous child had mild intellectual disability. As age of symptom onset and dementia diagnosis is frequently consistent within families and within autosomal dominant Alzheimer's disease (ADAD) variants[8], this provides evidence for a more aggressive phenotype associated with homozygosity. The developmental delay seen in one of 6 such persons suggests an effect of homozygosity on neural development, though this single case is far from conclusive. The characterization of other persons homozygous for variants in *PSEN1* is therefore of interest.

Case Report

Our patient completed high school at the age of 18 but reportedly required remedial classes earlier in his education. He achieved gainful employment in semi-skilled labor. At age 28 he was noted to have episodes of calling out in his sleep, apparently in association with nightmares. His first symptom of progressive disease manifested as alexia at age 33 followed soon thereafter with memory and gait impairment and falls due to lower extremity spasticity. The patient had an unremarkable medical history until the onset of symptoms.

Family History: The family history on both the parents' sides were strongly positive for dementia of onset around age 40 in an autosomal dominant inheritance pattern. The index patient's parents were first cousins with the paternal and maternal grandfathers being brothers. His father had onset of AD symptoms at age 38, dying at age 45. His mother died at age 54 from AD that started at around 50 years of age. An older sister was noted to have cognitive impairment from infancy but was lost to follow up. Our extensive review of the family history, focused on the presence of neurodegenerative disease, did not suggest an overall tendency towards intellectual impairment. A second-degree relative had the onset of memory problems at age 39 and died at the age of 47, with brain donation for neuropathological examination. During life, the relative was shown to be heterozygous for the A431E variant in *PSEN1.*

Clinical Findings: On examination at age 36, the patient was alert and oriented to name and location, but not to the year or month. Speech was fluent, though naming and repetition were impaired. Comprehension was intact with one step commands but impaired with multistep commands. MMSE score was 14/30. He had brisk reflexes, greater in the legs than in the arms. His tone was increased at his ankles and he was unable to fully dorsiflex his feet. His gait was slow, stiff and unsteady.

Diagnostic Assessment: MRI brain (Figure 1) revealed cerebral atrophy disproportionate for age with parietal lobe predominance. Multiple chronic microhemorrhages were seen within the bilateral occipital, temporal, and right frontal lobes on SWI. MPRAGE was acquired later and revealed substantial increased perivascular spaces in the centrum semiovale bilaterally. Sanger sequencing performed twice using independent primer pairs demonstrated homozygosity for the A431E variant in *PSEN1* (Figure 2).

Follow-up and Outcomes: Over the next 6 months, the spastic paraparesis progressed rapidly with increasing dependence on assistive devices, from intermittent cane use to alternating walker and wheelchair use. Labile moods responded to the combination of dextromethorphan/quinidine and citalopram. Memory further declined to include profound rapid forgetting. When seen at age 37 he had an MMSE score of 8/30, a Clinical Dementia Rating scale score of 3 (severe dementia) and requires full time assistance with activities of daily living. He is unable to walk independently and has bradykinesia with arm rigidity but no tremor or cogwheeling.

Discussion

(ADAD) is caused by the presence of essentially fully-penetrant variants in one of three genes; *PSEN1, PSEN2, and APP.* Persons with ADAD, particularly when due to *PSEN1* variants, can have features atypical for AD including myoclonus, pseudobulbar affect, and gait abnormalities due to spastic paraparesis[9]. The A431E substitution is a well-characterized pathogenic variant apparently arising as a founder effect in Jalisco State in Mexico[10, 11]. It is associated with early spastic paraparesis[12] in approximately 45% of cases and has an average age of symptom onset of 40 years and of dementia diagnosis at 42[10]. Neuropathological examination sometimes reveals atypical "cotton wool" amyloid plaques and Lewy Bodies. While cotton wool plaques and spastic paraparesis can be independent of

one another, they have been associated with numerous *PSEN1* variants that include deletions in exon 9, insertions into exon 6, codeletion I83/M84, and substitutions such as P264L, P284L, E280G, N405S, and P436Q[13] in addition to A431E. The neuropathologically examined relative was found to have frequent neuritic and cotton wool plaques and grade 3 amyloid angiopathy in widespread areas of cortex. Numerous Lewy Bodies and Lewy neurites in cortex as well as in the midbrain, pons, and medulla were also evident with anti-synuclein immunostaining (Ghetti et al, in preparation).

Our patient had a broadly similar phenotype though with symptoms consistent with REM behavior disorder (RBD) and the onset of progressive symptoms at age 33 and dementia diagnosis at age 35. He had significant progression in his cognitive and gait deficits over 6 months' time at age 36, suggesting a particularly aggressive form of the disease. MRI at age 37 revealed lobar microhemorrhages and enlarged perivascular spaces in the centrum semiovale, consistent with the presence of CAA(1) which is universally found in neuropathologically examined persons with the A431E PSEN1 mutation. He had been independently functional, gaining meaningful employment and supporting others. His full sister, on the other hand, was never able to live independently. Unfortunately, her genetic status and specifics regarding her development, course, and fate are unknown.

Though this is a single case of homozygosity for the A431E variant, our observations are consistent with those of Kosik et al[6] of persons homozygous for the E280A substitution. That is, homozygosity for *PSEN1* variants is compatible with life and can present with a phenotype similar to that of heterozygotes. The E280A cases' ages of onset were also suggestive of a more aggressive form of the disease though all reported patients' (including the current one) ages of onset were within the ranges previously described in association with heterozygosity for their respective variants. Both reports are consistent with, though far from conclusive for, intellectual deficits being associated with homozygosity.

Like other variants in *PSEN1*, the A431E substitution has been shown to be associated with an abnormal proportion of APP cleavage products of different lengths, suggesting a potential pathogenic disease mechanism[2]. The effects of *PSEN1* variants on γ-secretase cleavage are quantitative, rather than qualitative. As such, a more aggressive form of illness with a generally similar phenotype might be anticipated in homozygotes. Though our data and those of Kosik et al[6] are inconclusive regarding the presence of life-long intellectual impairment in persons homozygous for *PSEN1* variants, they raise the possibility of a *PSEN1* function in human development. Animal studies indicate a role of *PSEN1* in neuronal differentiation and migration[14–16] and a human case of AD with onset at age 29 in association with a *PSEN1* variant was found to have ectopic neurons in white matter[17]. In the only known description of homozygosity for an *APP* variant (A713T), there did not appear to be a more aggressive phenotype in 3 homozygotes relative to their heterozygous family members[18]. This raises the possibility that the more aggressive phenotype apparent in *PSEN1* homozygotes may be due to effects of these variants upstream from and independent of APP processing. However, the lack of a comprehensive premorbid intellectual history in our patient and the likelihood of homozygosity for a multitude of other loci in our patient and his sister due to the consanguinity of their parents leave this an open question.

Of interest is the patient's history of dream-enactment behavior. Though confirmation by polysomnography is lacking, the potential presence of RBD is consistent with the known propensity for persons with ADAD to develop Lewy Body pathology[19, 20] as was found in the brainstem of the index patient's second degree relative. Should development of Lewy Body pathology in the brainstem be an early event in ADAD, the "premorbid" presence of RBD might be expected but has not been reported previously to our knowledge.

In summary, this case confirms that homozygosity for some *PSEN1* variants are compatible with life but appear to lead to a more aggressive, though qualitatively similar phenotype. Despite the indirectness of the evidence presented herein, the possibility of a role for *PSEN1* in brain and intellectual development deserves further study, particularly in light its potential as a target in AD therapeutics.

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Highlights:

- Homozygous autosomal dominant mutations in Presenilin-1 are compatible with life.
- The homozygous state seems to confer a more severe phenotype, with earlier clinical onset and more rapid progression of neurodegeneration.
- The homozygous state for A431E in PSEN1 may present with earlier onset, but are otherwise phenotypically similar to the heterozygous state and include spastic paraparesis, cortical atrophy, cerebral microhemorrhages, and dementia.

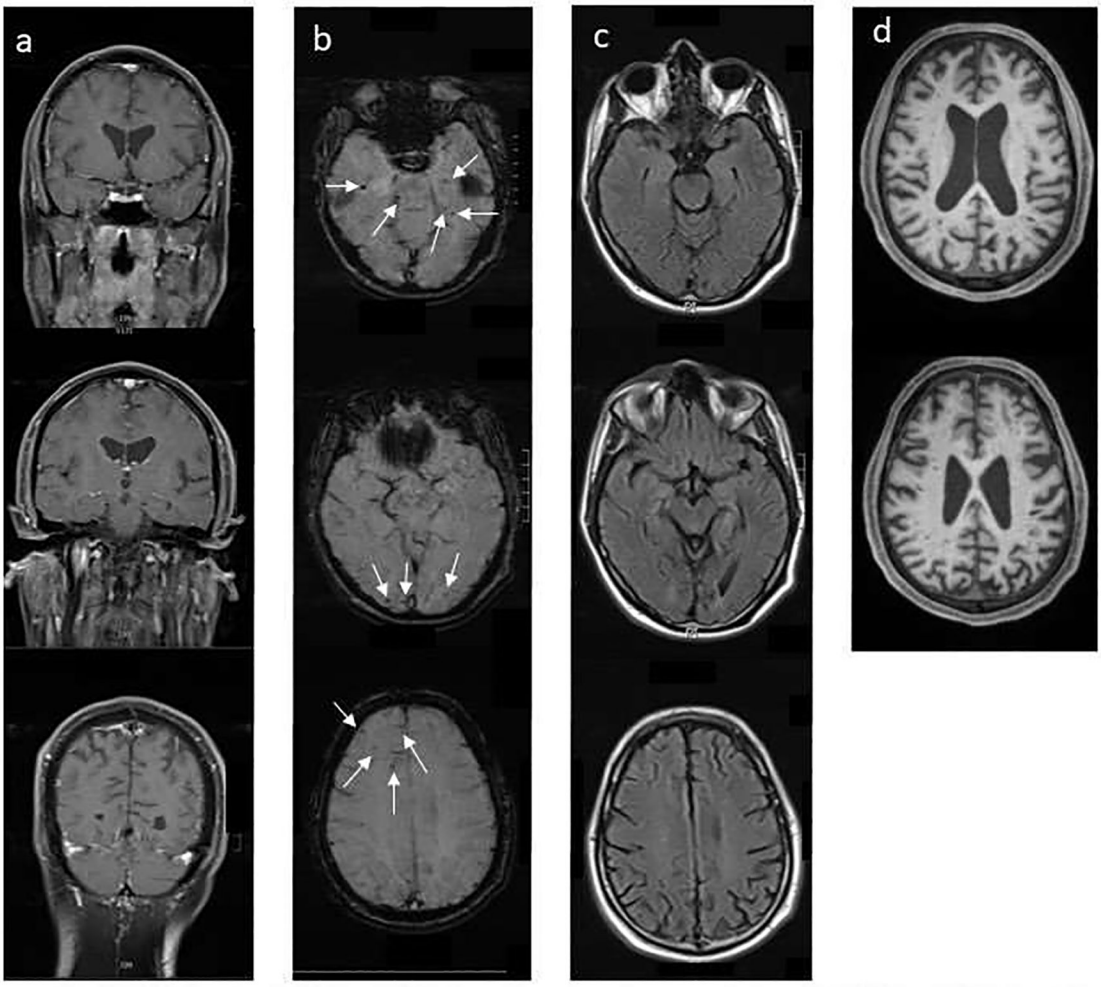

Fig. 1.

MRI brain. (a) T1 weighted post contrast coronal view. (b) SWI weighted axial view demonstrating micro-hemorrhages. (c) FLAIR sequence demonstrating pattern of atrophy. (d) MPRAGE sequence on 11 month follow up showing substantially increased perivascular spaces.

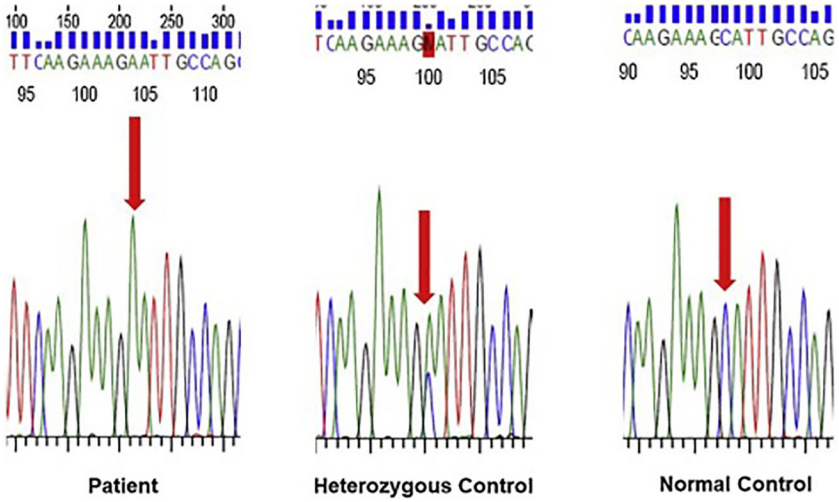

Fig. 2.

Sanger sequencing demonstrating homozygosity for the A431E variant in *PSEN1.*