

**CASE REPORT**

PSEN1 p.Met233Val in a Complex Neurodegenerative Movement and Neuropsychiatric Disorder

Silke Appel-Cresswell,^{1,2} Ilaria Guella,^{3,4} Anna Lehman,⁴ Dean Foti,² Matthew J. Farrer^{1,3,4}¹Pacific Parkinson's Research Centre and Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada²Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada³Centre for Applied Neurogenetics, University of British Columbia, Vancouver, BC, Canada⁴Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada**ABSTRACT**

Mutations in presenilin 1 (*PSEN1*) are the most common cause of autosomal dominant Alzheimer's disease. Here, we report a Canadian-Vietnamese family carrying a *PSEN1* p.Met233Val mutation with an exceptionally early and severe presentation that includes a wide range of atypical symptoms, including prominent ataxia, Parkinsonism, spasticity, dystonia, action tremor, myoclonus, bulbar symptoms, seizures, hallucinations and behavioral changes. Whole-exome sequencing (WES) was performed on the affected proband after many assessments over several years proved diagnostically inconclusive. The results were analyzed using the AnnEx "Annotated Exomes" browser (<http://annex.can.ubc.ca>), a web-based platform that facilitates WES variant annotation and interpretation. High-throughput sequencing can be especially informative for complex neurological disorders, and WES warrants consideration as a first-line clinical test. Data analyses facilitated by web-based bioinformatics tools have great potential for novel insight, although confirmatory, diagnostically accredited Sanger sequencing is recommended prior to reporting.

Key Words Neurodegeneration; exome; bioinformatics; Alzheimer; mutation.

Mutations in presenilin 1 (*PSEN1*) are the most common cause of autosomal dominant Alzheimer's disease (AD), with over 215 different mutations reported so far (<http://www.molgen.vib-ua.be/ADMutations>).¹ *PSEN1* heterozygotes have varied clinical presentations, although a correlation between the mutation site and the phenotype is noted.² Here, we present a Canadian-Vietnamese family in which affected subjects have a *PSEN1* p.Met233Val mutation. The proband has an unusually low age of onset and atypical neurological features.

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The affected proband (III-2) (Figure 1) had a history of substance abuse (alcohol, ecstasy, crack cocaine and marijuana, but

not intravenous drugs) from age 16 to 22. At age 22, she developed gradually progressive memory and global cognitive problems, and her Montréal cognitive assessment (MoCA) at age 26 was 15/30. At age 27, a neurological exam revealed gait and appendicular ataxia, dystonia, slow speech and a shuffling gait. She had auditory hallucinations and exhibited verbally aggressive behaviors. At age 29, she developed generalized tonic-clonic and myoclonic seizures and urinary incontinence. Examination demonstrated bradykinesia, rigidity, spasticity and action tremor. By age 30, she had severe dysphagia and was immobile, incontinent and mute. She had frequent myoclonic jerks and pronounced rigidity, and she was unable to follow commands.

Cerebrospinal fluid collected at age 27 was normal for cells and protein, oligoclonal bands were negative, and both the 14-3-3

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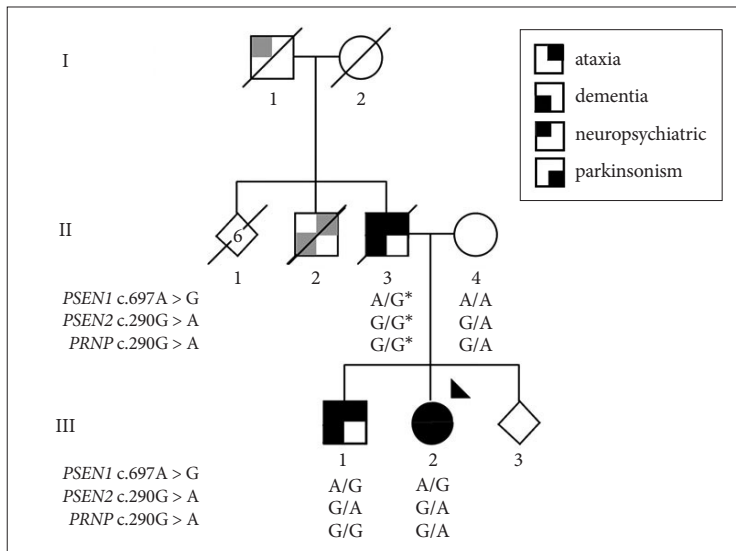


Figure 1. Pedigree of the family. The family's presentation is consistent with dominant inheritance of a neurodegenerative disease. Symbols provide a segmented view of the most consistent clinical features reported [parkinsonism and ataxia, (lower or upper left quadrants), dementia and neuropsychiatric disturbance (lower and upper right quadrants)]. However, data on different symptom components may be incomplete and/or by history (gray quadrants). The proband analyzed by whole-exome sequencing is indicated by an arrowhead. Genotypes for the *PSEN1*, *PSEN2* and *PRNP* mutations are reported. The (*) indicates inferred genotypes. *PSEN1*: presenilin 1, *PSEN2*: presenilin 2, *PRNP*: prion protein.

protein assay and the quaking-induced conversion assay (carried out when the patient was 31) to test for prion disease were negative. At the age of 28, an MRI revealed mild to moderate, generalized, predominantly supratentorial atrophy. Testing was normal for human immunodeficiency virus, syphilis, hepatitis B, hepatitis C, N-methyl-D-aspartate receptor antibodies and paraneoplastic antibodies, vitamin E and B₁₂, copper collected over 24 hours in urine, ceruloplasmin, Kayser-Fleischer rings, creatine kinase, liver function and renal function. Her pelvic ultrasound was normal. Genetic testing for spinocerebellar ataxia types 1, 2, 3, 6, and 7; Huntington's disease; Friedreich's ataxia; and dentato-rubral pallidolusian atrophy was negative. Electroencephalography (EEG) at age 28 revealed a very disorganized background and spike-wave activity. An EEG at age 31 showed moderate slowing, one short myoclonic seizure and several myocloni without EEG equivalent. There is no history of any neurological issues on the maternal side. Medical records for the proband's father (II-3) describe hallucinations that began at age 15, and by age 30, he was drug and alcohol dependent. At age 32, disorientation, slurred and incoherent speech, gait disturbance, paranoia and se-

vere aggression were noted. He was admitted to a long-term psychiatric institution. At age 36, severe ataxia, wandering, urinary and fecal incontinence, inappropriate laughing and auditory and possibly visual hallucinations were described. His Mini Mental Status Examination was 11/30. He lost his ability to walk, became mute and had generalized tonic-clonic seizures, and he died at age 40.

Anecdotally, the paternal grandfather (I-1) died at the age of 45. His death was attributed to alcohol abuse. A paternal uncle (II-2) is also described to have had memory and balance issues that were possibly related to alcohol abuse. The affected proband's older brother (III-1) developed a progressively unsteady gait and progressive cognitive problems at the age of 15. At age 32, his exam showed appendicular and gait ataxia with falls, spastic paraparesis, rigidity and mild dysarthria. He scored 16/30 on the MoCA. At age 34, he developed dysphagia, myoclonus, and behavioral changes, including verbal aggression, apathy and repetitive behaviors. He had episodes suggestive of absence seizures, and his EEG was markedly abnormal with fragments of spike-and-slow-wave discharges.

The affected proband underwent numerous laboratory and imaging studies and several single gene tests, which led to the identification of a prion protein (*PRNP*) mutation (NM_000311: c.290G > A, p.Ser97Asn) previously described in a subject presenting with sporadic AD.³ The unresolved clinical presentation and the finding of a *PRNP* variant were suggestive of a transmissible spongiform encephalopathy. Infection control precautions were implemented making further interventions and laboratory testing challenging. However, we determined the *PRNP* mutation was inherited from the unaffected mother and was not shared by the affected brother. The lack of disease segregation and absence of putative damage to protein structure [Combined Annotation Dependent Depletion (CADD) = 0.001]⁴ indicates that the mutation is unlikely pathogenic.

At age 31, high-throughput whole-exome sequencing (WES) was performed for the proband using the Ion Proton™ System according to the manufacturer's recommendations (Thermo Fisher Scientific, Carlsbad, CA, USA). Exonic regions were captured with the Ion AmpliSeq Exome Kit (57.7 Mb; Thermo Fisher Scientific). Sequence reads were aligned against the human reference genome (hg19). The results were

analyzed using the AnnEx “Annotated Exomes” browser (<http://annex.can.ubc.ca>), a contemporary web-based compendium of publicly available genetic resources to facilitate WES variant annotation. AnnEx includes expert-curated panels of genes linked to specific neurological disorders. Subsequent filtering was restricted to the patient’s predominant symptoms and genes linked to ‘dementia’ (59 genes), ‘Parkinsonism’ (36 genes) and ‘ataxia’ (148 genes). Analysis of the overlapping set of 229 genes revealed 11 variants, of which two heterozygous mutations are of particular clinical relevance: 1) *PSEN1* (NM_000021:c.697A > G, p.Met233Val), presumed structurally deleterious (CADD score = 25.7), not observed in control subjects [Exome annotation consortium (ExAC) allele frequency = 0] (<http://exac.broadinstitute.org/>) and referenced pathogenic in ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>), and 2) *PSEN2* (NM_012486:c.100G > A:p.Gly34Ser), which is modestly damaging to protein structure (CADD score = 18.6), rarely observed in control subjects (ExAC allele frequency = 0.0005) and without reference in ClinVar. The *PRNP* (NM_183079:c.290G > A, p.Ser97Asp) variant was observed and confirmed prior testing. All three mutations were validated by Sanger sequencing, but only *PSEN1* p.Met233Val was shown to segregate with disease (Figure 1).

DISCUSSION

This family has an exceptionally early and severe presentation that includes a wide range of atypical symptoms. The age of onset was in the second and third decade, whereas individuals with AD due to *PSEN1* mutations typically present between 40 and 50 years.⁵ Drug abuse may have been a contributor to and/or a consequence of the disease, but symptoms clearly progressed for years after the cessation of drug consumption. Of note, the affected brother never used recreational drugs, but behavioral and delusional presentations are documented in patients with *PSEN1* mutations.⁶ The father of the affected proband did not receive a diagnosis during his lifetime. No test results were diagnostically conclusive before the WES analysis of the proband despite numerous prior studies performed over many years.

PSEN1 p.Met233Val has been described in another family with an early-onset (third and fourth decade) and rapidly progressive disease with extrapyrami-

dal symptoms and seizures. Pathological examination showed amyloid plaques, neurofibrillary tangles and extensive Lewy body formation.⁷ *PSEN1* p.Met233Val also occurs at the same residue as three other substitutions: p.Met233Thr,⁸ p.Met233Leu,⁶ and p.Met233Ile,⁹ all of which are associated with early-onset, aggressive, familial AD with a similarly broad range of atypical symptoms, including executive dysfunction and behavioral changes, dysarthria, apraxia, dystonia, myoclonus, seizures and pyramidal signs (Babinski).^{8,10} Nevertheless, in such families, disease-modifying interventions targeting *PSEN1* and the amyloid pathway hold greatest promise. Within a family, patients may have variable onset and phenotypes even when an autosomal dominant, monogenic Mendelian pattern of inheritance is observed because penetrance/expressivity is influenced by other genetic, environmental and stochastic factors. Sanger sequencing and segregation analysis shows *PSEN1* p.Met233Val is necessary and sufficient for disease (etiologic) (Figure 1). It is unclear whether the rare coding variability observed in *PSEN2* p.Gly34Ser and *PRNP* p.Ser97Asp contributes to disease ontology. However, *PSEN1*, *PSEN2*, and *PRNP* proteins function in the same biological network and the proband had an especially early and rapid demise. Functional studies may provide more insight in this regard.

In complex neurological disorders, high-throughput sequencing can be especially informative. Indeed, WES should be considered as a first-line clinical test given the ease of genome-wide assessment, the high diagnostic yield, the accuracy of mutation detection, and the relatively low cost of DNA extraction from a mouthwash or blood sample. Web-based bioinformatics tools now simplify and accelerate data review relevant to symptoms. Genetic mutations have prognostic value and increasingly have treatment implications, and, with informed consent, may enable longitudinal re-analyses and discovery. This is especially important with disease development and when symptoms present insidiously. Nevertheless, prior to reporting, we recommend any WES findings are confirmed as pathogenic by diagnostically accredited Sanger sequencing.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgments

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