

Atypical motor manifestations of PSEN 1 c.1292C>A (p.Ala431Glu) variant (Jalisco founder effect). An analysis of three cases

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KEY TAKEAWAY: The PSEN1 c.1292C>A Jalisco founder variant may present with clinically prominent motor manifestations beyond cognitive decline, including parkinsonism, pyramidal signs, spastic gait, and an ALS-like phenotype.

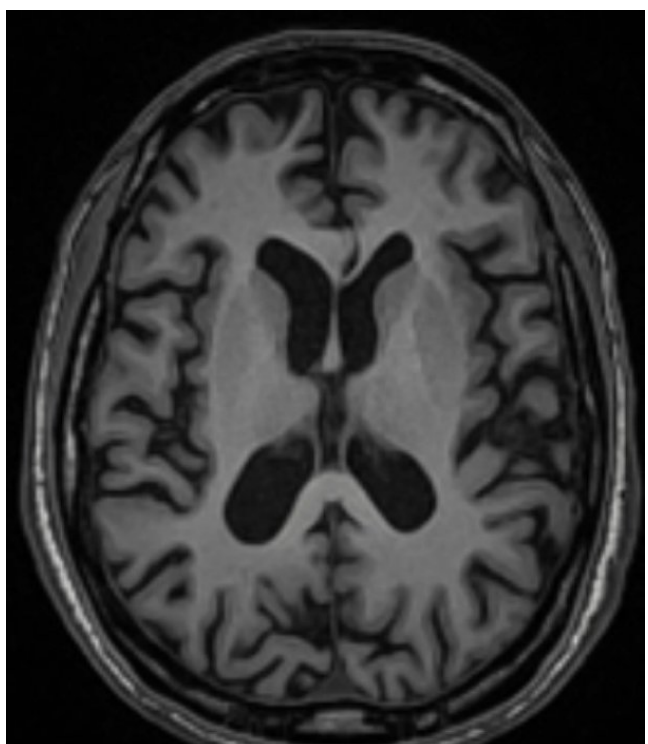
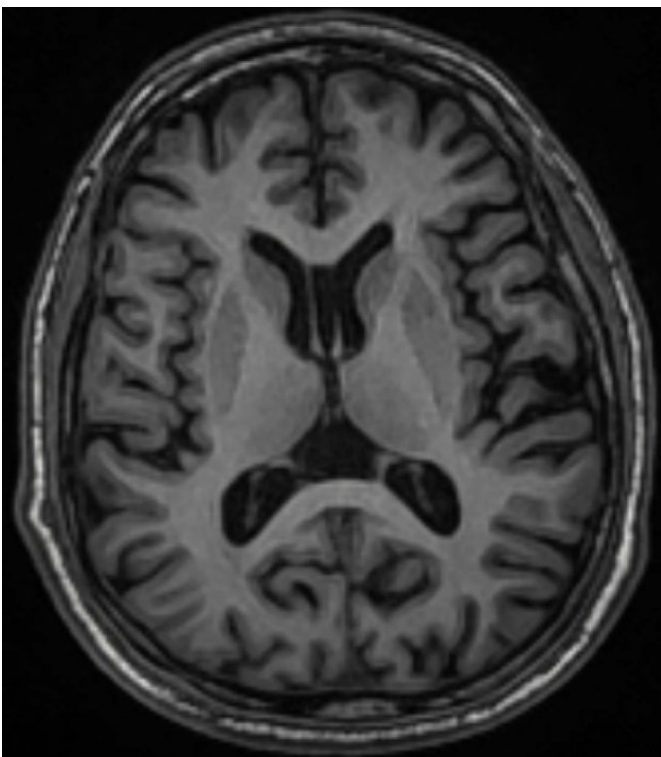
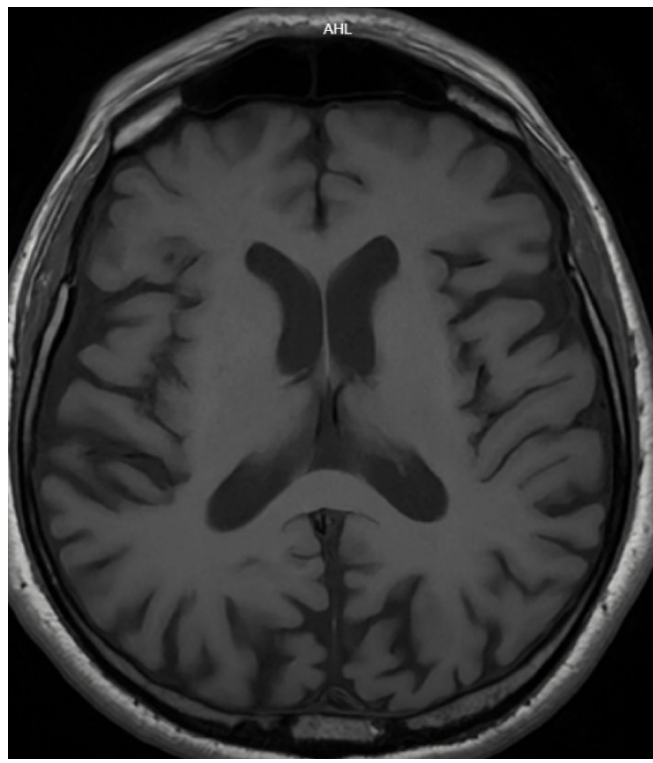
INTRODUCTION

The PSEN1 c.1292C>A Jalisco founder variant is a recognized cause of autosomal dominant early-onset Alzheimer’s disease in Mexico. Although cognitive impairment is the predominant phenotype, atypical features such as seizures and motor manifestations have been increasingly reported, highlighting the need for broader clinical characterization

Aim: To describe and compare the atypical motor manifestations observed in three patients carrying the PSEN1 c.1292C>A Jalisco founder variant

METHODS

We retrospectively reviewed three Mexican patients with genetically confirmed PSEN1 c.1292C>A variant and atypical clinical manifestations evaluated at the National Institute of Neurology and Neurosurgery “Manuel Velasco Suárez” over the last five years. Clinical and paraclinical data were extracted from anonymized medical records

RESULTS			
Age	47	44	48
Age of onset	30	44	43
Initial symptoms	Attention and calculation difficulties	Asymmetric limb weakness and bulbar symptoms	Memory difficulties and right leg weakness
Parkinsonism	+	--	--
Pyramidal signs	+	+	+
Spastic gait	+	+	+
Fasciculations	--	+	--
Bulbar symptoms	--	+	--
Motor neuron disease-like	--	+	--
Dystonic posturing	+	--	--
Complex attention	Impaired attention	Globally preserved with mild deficits	Fluctuating sustained attention deficits
Executive function	Bradypsychia; functional impairment	Impaired cognitive flexibility and self-monitoring	Poor compensatory strategies
Learning and memory	Impaired verbal and logical information retrieval	Moderate to severe memory impairment with impaired retrieval	Impaired visual, logical and semantic information retrieval
Language	Hypophonia, spastic dysarthria, impaired repetition	Marked dysarthria; impaired complex verbal, oral and written comprehension	Not prominently affected
Perceptual-motor	Praxis impairment; probable left cortico-subcortical involvement	Motor neuron disease-like syndrome	Visuospatial and visuoconstructive impairment
Social cognition/behavior	Severe behavioral impairment; blunted affect; irritability/aggression	Blunted affect; depressive and anxiety symptoms	Not prominently affected
Functional impact	Basic and instrumental ADL impairment; maximum dependence	Moderate dependence in basic ADL; severe dependence in instrumental ADL	Moderate multidomain cognitive impairment
Neurophysiological studies	Not performed	EMG/NCS: active denervation and facilitated F-waves, consistent with ALS-like motor neuron disease	SSEPs/F-waves: bilateral proprioceptive and corticospinal tract dysfunction
MRI			

DISCUSSION

These three cases suggest that the PSEN1 c.1292C>A Jalisco founder variant may be associated with a broader motor phenotype than previously recognized. Recognition of motor features is clinically relevant because these presentations may mimic other neurodegenerative disorders

CONCLUSIONS

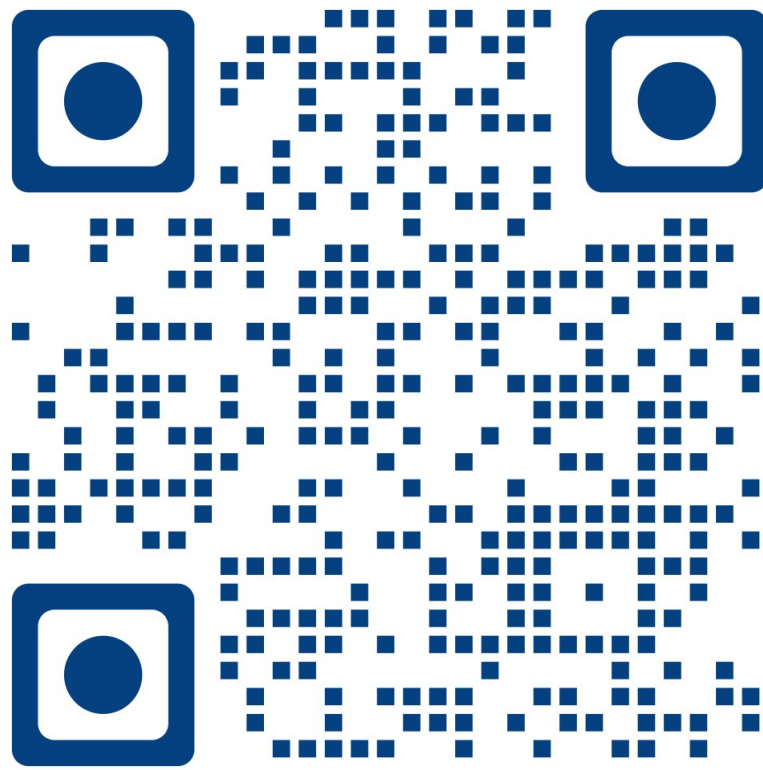
The PSEN1 c.1292C>A Jalisco founder variant may present with heterogenous and clinically prominent motor manifestations, including parkinsonism, pyramidal signs, spastic gait, and motor neuron disease-like features. Detailed neurological examination may improve phenotypic characterization, diagnostic suspicion, and genetic counseling in affected families

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