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Case Report

A Novel de Novo Missense Mutation in *KIF1A* Associated with Young-Onset Upper-Limb Amyotrophic Lateral Sclerosis

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Abstract: Objectives: To investigate the etiology of amyotrophic lateral sclerosis (ALS) in an adult female patient. Methods: We conducted trio genome sequencing on a 35-year-old woman with progressive weakness in her left upper limb, as well as on her parents. Prior to sequencing, we performed a comprehensive neurological work-up on the patient, including neurological exam, electrophysiology, biomarker assessment, and brain and spinal cord MRI. Results : The propositus experienced weakness and atrophy in her left hand 6 months before the evaluation. This was associated with brisk reflexes and Hoffman sign in the same arm. Electroneuromyography revealed lower motor neuron involvement in three body regions. Neurofilament light chains were elevated in her cerebrospinal fluid. Brain imaging showed asymmetrical T2 hyperintensity of the corticospinal tracts and T2 linear hypointensity of the precentral gyri. Genome trio sequencing identified a likely pathogenic de novo variant in the propositus's *KIF1A* gene (NM_001244008.2): c.574A>G, p.(Ile192Val). Discussion: Pathogenic variants in the *KIF1A* gene have been associated with a wide range of neurological manifestations called KIF1A-associated neurological diseases (KAND). The present report describe a likely pathogenic de novo variant in *KIF1A* associated with ALS, expanding the phenotypic spectrum of KAND and our understanding of the pathophysiology of ALS.

Keywords: Amyotrophic Lateral Sclerosis; Genome sequencing; *KIF1A*; de novo mutation

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by the degeneration of upper and lower motor neurons leading to death a median three years after onset. However, a considerable variability in the rate of progression of disease can be observed [1], ranging from slow to acute and dramatic forms. With the growing number of causal genes found to be associated with the disease, which is approaching 40, and the easier access to sequencing technologies, a pathogenic mutation is now identified in 70% of familial ALS cases [2] and up to 10% of sporadic ones [3]. However, due to usual late onset of the disease, interpretation of rare gene variants can be challenging in ALS due to the absence of proven segregation of the suspected variant or by the potential death of the parents of the proband, precluding the discovery of de novo variants.

The kinesin family member 1A gene (*KIF1A*) encodes a protein that is responsible for the ATP-dependent anterograde axonal transport of synaptic vesicle precursors along the axonal and dendritic microtubules [4]. Initially, biallelic pathogenic mutations in *KIF1A* were linked to two phenotypes: a recessive form of HSP called spastic paraplegia-30 (SPG30), and the hereditary sensory and autonomic neuropathy type II. Further reports have shown that monoallelic variants in *KIF1A* are associated with a wide range of neurological manifestations, which are collectively referred to as *KIF1A*-associated neurological diseases (KAND). These neurological manifestations include pure or complex HSP, Rett-like syndrome, ataxia, epilepsy, PEHO syndrome, or optic atrophy [5].

In this report, we conducted a genome sequencing of a trio consisting of young-onset ALS patient and her parents. This analysis revealed a likely disease-causing new genetic variant in *KIF1A* that arose spontaneously in the patient. This finding broadens the range of phenotypes associated with KAND and supports the suggested link [6,7] between *KIF1A* and the pathophysiology of ALS.

2. Case Description

The proband was a 35-year-old woman; the eldest of two sisters. Her parents did not present any neurological disorder (Figure 1A). She had no significant medical history. She reported a 6-month history of distal left upper limb weakness preceded by cramps, without any sensory disturbance nor pain. Clinical examination found weakness and atrophy of hand muscles (Medical Research Council 2-3/5 in distal and 4/5 in proximal left upper limb muscles). Rare fasciculations were observed on both shoulders and thighs. Deep tendon reflexes were brisk in the four limbs, with left Hoffman sign, indicating upper motor neuron involvement. Needle electromyography found chronic and active denervation in proximal and distal muscles of cervical, thoracic and lumbar regions, with normal sensory conduction. Elevated NfL was found in the CSF (1614 ng/L; normal value <750 ng/L). Spinal cord MRI was unremarkable. Brain MRI was evocative of motor neuron disease, displaying asymmetrical T2 hyperintensity of corticospinal tracts and T2 linear hypointensity of precentral gyri, more pronounced in the right hemisphere (Figure 2). Diagnosis of ALS was made according to El Escorial (definite) and Gold Coast criteria. Riluzole was initiated and the patient enrolled in a clinical trial. After 18 months of follow-up, disease progression was rather slow: left arm weakness aggravated but only minor proximal right upper limb weakness developed, without impairment in walking, respiratory or bulbar symptoms.

Trio genome sequencing revealed a novel heterozygous de novo missense variant in *KIF1A* in the proband (transcript ID ref: NM_001244008.2: c.574A>G, p.(Ile192Val); Figure 1B). This variant is not in public databases (e.g. gnomAD v4) and is located in the kinesin motor domain, which is known to be prone to mutations. In silico tools, such as PolyPhen2, ClinPred and Mistic predicted that the amino acid change (p.Ile192Val) is damaging. Isoleucine 192 is highly conserved across all eukaryotes, including plants (Figure 1C). According to the American College of Medical Genetics (ACMG) criteria [8], the *KIF1A* variant was classified as probably pathogenic (class 4). None of the other variants identified in this analysis exhibited sufficient evidence to support their involvement in the disease.

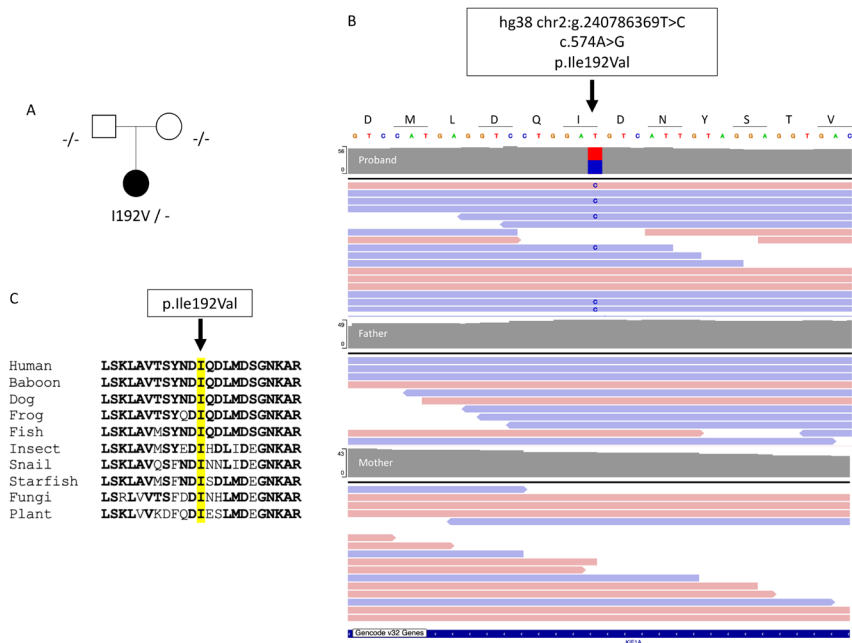


Figure 1. Identification of *KIF1A* mutation. (A) Pedigree of the affected family. (B) Visualization of whole-genome sequencing alignments using Integrative Genome Viewer software for the proband and her parents. The sequence of the *KIF1A* gene is displayed in reverse. The de novo heterozygous c.574A>G mutation in the *KIF1A* gene is indicated by an arrow. (C) Amino acid sequence comparison of the *KIF1A* motor domain and orthologous proteins from various species. Identical amino acids to the human *KIF1A* sequence are shown in bold. The missense mutation is indicated by an arrow on top of the mutated amino acid Isoleucine (I) 192 highlighted in yellow.

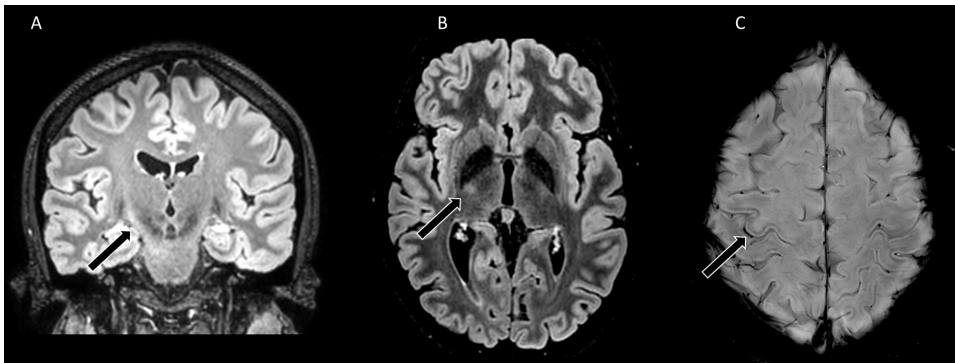


Figure 2. Brain MRI of a 35-year-old woman with ALS harboring a de novo probably pathogenic c.574A>G *KIF1A* mutation. Coronal (A) and axial (B) FLAIR sequences revealed asymmetrical hypersignal of the corticospinal tracts (black arrow indicating the right corticospinal tract). Axial SWI sequence (C) displayed linear hyposignal of the right precentral gyrus (black arrow). Abbreviations: FLAIR: Fluid-attenuated inversion recovery, SWI: Susceptibility weighted imaging.

3. Discussion

KIF1A has recently been identified as a candidate gene associated with ALS in two separate cohorts from Norway [6] and China [7]. In the Norwegian cohort, rare damaging variants of *KIF1A* were found in 3/279 ALS patients [6], while in the Chinese cohort, 10/941 ALS patients had these variants [7]. However, these variants were considered to have unknown significance according to the ACMG criteria, and therefore they were deemed unsuitable for definitive genetic counseling for these patients. The present study presents the evidence of a probably pathogenic variant, classified as ACMG class 4, in *KIF1A* that is associated with ALS. The proband exhibited classical spinal upper-

limb onset ALS associated with typical electrophysiological and MRI features. The only unusual aspects were the young age at onset and the relatively slow progression of the disease. The level of NfL in the CSF, which are known to be correlated with prognosis [9], were found to be 3 times lower than the mean levels observed in ALS patients [10].

KIF1A can be added to the list of ALS-causing genes that affect cytoskeletal dynamics, joining *ALS2*, *DCTN1* and *KIF5A* [11]. Drawing a connection between *KIF1A* and another member of the kinesin family, *KIF5A*, is an intriguing prospect. Expression of ALS-associated *KIF5A* mutant leads to the formation of cytoplasmic aggregates, inclusions of mitochondria, and synaptic vesicles that are toxic to motor neurons through a gain-of-function mechanism [12–14]. While the connection between *KIF1A* mutations and the characteristic extranuclear aggregates of TDP-43 in ALS is not yet understood, other kinesins, such as *DCTN1*, have been reported to disrupt the dynamics of stress granules and promote the formation of TDP-43 cytoplasmic aggregation in cultured cells [15].

The catalytic core of *KIF1A* (C351) is the crucial domain for highly processive movement [16] and confers *KIF1A* with the ability to move more than five times as processively as dimeric conventional kinesin [17]. Interestingly, isoleucine 192 is located in the alpha-5-helix of this catalytic core. Numerous mutations have been identified in the motor domain of *KIF1A* as a cause of KAND, with both loss-of-function and gain-of-function effects on axonal transport [18]. The elucidation of the mechanisms underlying neurodegeneration and the association with ALS pathological markers, including TDP-43 aggregates, can be further advanced through the future development of models such as motor neurons derived from patient induced pluripotent stem cells or *Drosophila*. This approach has already been successfully employed in the case of *KIF5A* [12,13].

As clinical trials in the nano-rare disease KAND are currently underway with antisense oligonucleotides targeting *KIF1A* [19], the present report emphasizes the importance of systematic trio sequencing in sporadic ALS. In the event of de novo mutations, this sequencing approach can upgrade the level of pathogenicity of suspected variants from unknown significance to probably pathogenic.

4. Methods

The patient and her parents provided informed written consent for genome sequencing and publication of findings. Peripheral venous blood was collected from the family trio. Whole-genome sequencing was performed following the recommendations of 2025 French genomic medicine initiative. Genomic DNA extracted from whole blood was sequenced according to standard procedures for a PCR-Free genome on a NovaSeq6000 instrument (Illumina). Sequencing data were aligned to the GRCh38p13 full assembly using Burrows-Wheeler Aligner version 0.7+. The sequencing achieved an average target depth of approximately 42x, with over 98% of the genome covered at a depth greater than 20x. Variants were called by several algorithms, including GATK4+, Bcftools1.10+, Manta1.6+, and CNVnator0.4+, and annotated using the variant effect predictor. Detected variants were prioritized using in-house procedures. Commercially available ELISA kits were used for the measurement of neurofilament light chain (NfL) concentration in cerebrospinal fluid (CSF; Uman Diagnostics). MRI was performed on a clinical 3.0-T Philips Ingenia system (Philips Healthcare).

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