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Letter to the Editor: New Observation

Exploring Clinico-Genetic Heterogeneity with Two Novel Mutations in KIF1A Gene

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Since its first description in 2011, the clinical spectrum of Kinesin Factor 1 A (KIF1A) neurological disorders (KAND) has expanded from pediatric-onset hereditary spastic paraplegia (HSP) to include early-onset neuropathy, intellectual disability, cerebellar ataxia, progressive encephalopathy and optic atrophy.[1,2] This complex phenotype is reflective of its widespread expression in the nervous system and its critical role in axonal transport. The type and location of the KIF1A gene mutation (motor vs non-motor domain) determine the varying inheritance patterns, heterogeneous clinical course and unique combination of presenting symptoms.[3,4] We aim to expand the genotypic spectrum of KAND by describing two novel missense mutations in the motor and non-motor domains of the KIF1A gene. In addition, we discuss the clinical heterogeneity determined by the location of the mutation and finally postulate KAND to be a prudent addition to the ever-expanding etiologies of idiopathic late-onset cerebellar ataxia (ILOCA).

Case 1

A 66-year-old Canadian man presented with an imbalance while walking for five years. He reported struggling with learning difficulties since childhood without any delay in motor and language development and couldn't complete his education beyond high school. Neurological examination indicated cognitive impairment (MoCA assessment: 21/30, with points lost in recall and visuospatial domains), scanning dysarthria, upper limb and severe gait ataxia and subtle saccadic dysmetria in the upgaze, consistent with cerebellar dysfunction. Tone and power were normal with generalized areflexia. Vibration sensation in the lower limbs was decreased bilaterally. MRI of the brain and spine demonstrated mild atrophy of cerebellar hemispheres. Testing for Spinocerebellar Ataxia and HSP panels was negative. Whole-exome sequencing revealed a heterozygous variant c.2332*C* >T in the KIF1A gene (p.Pro778Ser) (NM_001244008.2 ClinVar), which was confirmed by Sanger sequencing. The identified variant, previously unreported in the 1000 genomes and gnomAD databases, was a missense, non-tolerated variant absent in controls, predicted to be damaging by both Sorting Intolerant From Tolerant (SIFT) and Polymorphism Phenotyping v2 (PolyPhen2). Based on American College of Medical Genetics and Genomics (ACMG) criteria,[6] the variant was classified as likely pathogenic:[5]

Supporting pathogenic criteria: Low rate of benign missense variants and pathogenic missense variants common (PP2); multiple lines of computational evidence suggest a deleterious effect on the gene/gene product (PP3); missense variants are a known cause for this specific disease, and the phenotype matches with the disorder caused by pathogenic variants in the KIF1A gene (PP4)

Moderate pathogenic criteria: Mutational hot spot or well-studied functional domain without benign variation (PM1), absence from controls in Exome Sequencing Project, 1000 Genomes Project or Exome Aggregation Consortium (PM2)

Strong pathogenic criteria: Same amino acid change as an established pathogenic variant (PS1); prevalence in affected statistically increased over controls (PS4).

Case 2

A 25-year-old man, diagnosed with spastic diplegic cerebral palsy since childhood, presented with recent-onset visual impairment. Physical examination revealed bilateral optic atrophy, strabismus, mild down-gaze restriction, bilateral lower extremity spasticity and hyperreflexia. Coordination assessment, detailed cognitive and ancillary neurological examination were not possible. MRI demonstrated generalized cerebral, cerebellar and callosal atrophy. Whole-exome sequencing revealed a heterozygous variant c.742*G* > A (p.Asp248Asn) in the KIF1A gene, which was confirmed by Sanger sequencing. His parents tested negative for this mutation, confirming the mutation as de novo. It was predicted to be damaging by SIFT and PolyPhen2 and has been reported in the 1000 genomes and gnomAD databases. The variant was classified as likely pathogenic:[5] as per ACMG criteria (PP2, PP3, PP4, PM2 and PS4).

The KIF1A gene is composed of several key domains: the N-terminal motor domain, a stalk region including coiled domains and the C-terminal tail domain. The motor domain is highly conserved and uses Adenosine Triphosphate to control the movement along microtubules, while the tail region is highly

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diverse. The stalk region facilitates dimerization and interactions with cargoes. The cargo transported by a KIF is determined by the tail domain.[6] They move from the negatively charged to positively charged ends of the uniformly oriented microtubules in axons (anterograde transport), transporting synaptic vesicle precursors, synaptic vesicles, dense core vesicles and active zone precursors from the soma to the axonal terminus.[3] The kinesin motor domain uses amino acid residues of 3–362.[6,7] Our second patient's mutation in KIF1A at polypeptide position 248 is predicted to be in the motor domain. De novo missense variants in the motor domain have been reported in association with neurodegeneration, spasticity, cerebellar atrophy and visual impairment (NESCAV) syndrome, consistent with the second patient's phenotype.[2] The amino acid residue in our first case is known to code for the low complexity complex in the non-motor domain responsible for interaction with the transport substances and regulation of dimerization.[1,2,3,4] Interestingly, SPG30, also caused by KIF1A mutations in the motor domain, is reported to typically exhibit a more pure HSP phenotype[6] with onset as late as the second or third decade of life in the autosomal recessive form.[7] However, a more complicated SPG30 phenotype including mild intellectual disability, epilepsy and optic atrophy, similar to our second patient, has been reported with autosomal dominant inheritance, demonstrating significant clinico-genetic overlap.[8]

While the clinical course of our second patient was characterized by early-onset global development delay and severe disability with associated optic atrophy, our first patient was functionally independent despite childhood learning difficulties, up until presenting with ataxia in the fifth decade. The difference in the onset and evolution of symptoms is related to the location of the variant in the KIF1A gene. Mutations affecting the motor and non-motor domains influence motility of heterodimeric motors and the autoinhibitory mechanisms regulating microtubule binding, respectively.[4,8] The monoallelic variants were predominant in the motor domain, with early-onset spastic ataxia being most common, typically caused by loss-of-function and missense variants in the kinesin motor domain, and presenting with a more severe and syndromic phenotype than biallelic cases.[2] However, the monoallelic variant identified in our first case was missense and heterozygous in the non-motor domain translating into intermediate deficits in axonal transport and a less severe clinical phenotype unlike the second patient.[6]

ILOCA has remained a diagnostic challenge characterized by progressive cerebellar ataxia beginning after the age of 40 without a positive family history. Next Generation Sequencing contributed to identifying the novel KIF1A variant in our first patient with an essentially ILOCA phenotype. The slow clinical progression was another interesting point in the first patient with this KIF1A mutation. The location of the mutation in the non-motor domain, coupled with its heterozygosity, may be the underlying reason behind the otherwise benign course in this patient.

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