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LETTER TO THE EDITOR

Could some mutations of the *KIF5A* gene be responsible for a dominant CMT2 phenotype? (Case report)

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Introduction

The kinesin family member 5A (*KIF5A*) gene encodes the kinesin heavy chain subunits of tetrameric kinesin-1 protein, a motor protein playing an essential role in the intracellular transport of different cargos in nerve cells, such as mitochondria, neurofilaments and mRNA. It is expressed exclusively in neurons and is located in central and peripheral nervous system [1]. Mutations in *KIF5A* motor domain show a wide phenotypic spectrum from hereditary spastic paraplegia (HSP) (SPG10: AD, MIM #604187) to axonal Charcot–Marie–Tooth peripheral neuropathy type 2 (CMT2). Nevertheless, at this stage, even though the *KIF5A* gene has been reported several times as associated with the CMT2 phenotype [2–4], it has not yet been mentioned as the causative of the CMT2 phenotype in several reference classifications such as on the OMIM website. Furthermore, mutations in the stalk domain are rather associated with amyotrophic lateral sclerosis (ALS) (ALS25: susceptibility/incomplete penetrance, AD, MIM #617921) [5]. In this article, we report the case of a patient with a mutation of this gene which has only been described once in the literature with a rather different phenotype. This patient also presents with unusual symptoms in the context of HSP and CMT2.

Case report

We report the observation of a Belgian patient, born in 1987, presenting a gait disorder, a progressive loss of strength, a psychomotor retardation with cognitive (memory, attentional, dysexecutive) and behavioral (agitation, mood swings) impairments as well as episodes of anal incontinence since childhood. The clinical examination first revealed a dysmorphic syndrome (ogival palate, hypotelorism, eversion of the lower lip) with *pes cavus* and severe scoliosis. Then, it highlighted a proximal amyotrophy of the upper limbs and lateral compartments of the leg responsible of a discrete bilateral stepping. Deep tendon reflexes were absent except for weak bilateral brachioradialis, right patellar and Achilles ankle reflexes. Pyramidal signs were limited to bilateral Babinski's sign, and there was no cerebellar syndrome or sensory loss. The family history was free unremarkable of any neurological affections. In 2005, at the age of 17, he was hospitalized in the neurology department for an etiological assessment. Electrodiagnosis (EDX) showed a sensorimotor polyneuropathy, mainly axonal, with a very chronic pattern (no interference during full muscle contraction, increased recruitment frequency during weak muscle contraction with motor unit potentials of notably increased amplitude and duration). Given the proximal amyotrophy of the upper limbs and the possibility of myopathy, possibly mitochondrial, a muscle biopsy of the left deltoid muscle was performed which revealed no abnormalities. Genetic analyses excluded Friedreich's disease or a mutation in the PMP22 and MPZ genes. Cardiac assessment, chest CT Scan, cerebral and spine magnetic resonance imaging, skin biopsy as well as the dosage of creatine kinase (65 UI/l) and very long chain fatty acid assay were within normal range. A diagnosis of CMT2 was mentioned but could not be confirmed based on the genetic analyses available at the time. In 2008, a new EDX confirmed the existence of a severe sensorimotor axonal polyneuropathy of the four limbs but predominant in the lower limbs. In particular, the amplitude of sensory responses was markedly reduced in clinically non-deficient areas. The very chronic pattern of electromyography and the electro-clinical discordance were consistent with a hereditary neuropathy. Ten years later, in 2018, a control EDX revealed a progression of the axonal

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Table 1 Electrodiagnostic and electromyographic data from our proband in 2008 and 2018

Nerve conduction study												
Motor nerves	Amplitude (mV)		LN	DL (ms)		LN	CV (m/s)		LN	F-M latency (ms)		LN
	2008	2018		2008	2018		2008	2018		2008	2018	
Right median												
Wrist—APB	10.7	8	> 4.4	5.2	5.9	< 4.5				25.8	27	< 26.0
Above Elbow							45.3	46.9	> 50.0			
Left median												
Wrist—APB	8.9	7.2	> 4.4	5.2	5.2	< 4.5				26.2	26.2	< 26.0
Above Elbow							45.8		> 50.0			
Right ulnar												
Wrist– ADM	6.4	5.2	> 6.8	3.3	3.7	< 3.5				33	29.6	< 27.0
Above Elbow							46	46.1	> 49.0			
Left ulnar												
Wrist—ADM	6.8	5.7	> 6.8	3.2	3.8	< 3.5					28.5	< 27.0
Above Elbow								49.6	> 49.0			
Right fibular												
Ankle—EDB	NR	NR	> 2.3									
Fibula—TA	3.9	2	> 4.5	3.9	3.3	< 5.0						
PF- Fibula							38.1	39.1	> 40.0			
Left fibular												
Ankle—EDB	NR	NR	> 2.3									
Fibula—TA	3.3	4.5	> 4.5	5.1	3.1	< 5.0						
PF- Fibula								39.8	> 40.0			
Right tibial												
Ankle—AHB	NR	NR	> 6.2									
Left tibial												
Ankle—AHB	NR	NR	> 6.2									

Sensory nerves	Amplitude (μV)		LN	DL (ms)		CV (m/s)		LN
	2008	2018		2008	2018	2008	2018	
Right radial	4.3	1.5	> 25.0	2.5	2.4	48	45.5	> 50.0
Left radial	4.5		> 25.0	2.5		48		> 50.0
Right median	7.1	0.4	> 25.0	2.8	3.2	45.5	24.7	> 50.0
Left median	6.8	3.2	> 25.0	2.8	2.9	42.4	28	> 50.0
Right ulnar	3.9	0.7	> 10.0	2.8	2.3	43.8	43.7	> 50.0
Left ulnar	1.5	NR	> 10.0	3.3	NR	32.4	NR	> 50.0
Right sural	NR	NR	> 15.0	NR	NR	NR	NR	> 40.0
Left sural	NR	NR	> 15.0	NR	NR	NR	NR	> 40.0

Needle EMG								
Muscles	Fibrillation/PSW		Interference Pattern		MUP Amplitude/Duration		Interpretation	
	2008	2018	2008	2018	2008	2018	2008	2018
Right interosseous		0/10		Normal		Normal		Normal
Right anterior tibialis	0/10	0/10	Reduced	Reduced	↑/↑	↑↑/↑	Chronic neurogenic +	Chronic neurogenic + +
Right vastus lateralis	0/10		Normal		Normal		Normal	

DL distal latency; *CV* conduction velocity; *PF* popliteal fossea; *APB abductor pollicis brevis* muscle; *ADM abductor digiti minimi* muscle; *EDB extensor digitorum brevis* muscle; *AHB abductor hallucis brevis* muscle; *TA tibialis anterior* muscle; *NR* no response; *PSW* positive sharp wave; *MUP* motor unit potential; *LN* limits of normality established in our laboratory

Table 2 Comparison of clinical features in both patients with *KIF5A* c.694G > A (p.Asp232Asn) variant

Characteristics	Our proband	Patient from Liu et al. [4]
Sex	Male	Male
Age on the onset	6	40
Age at diagnosis	17	50
Predominant phenotype	CMT2	CMT2
Inaugural symptoms	Gait impairment and falls Clumsiness Attentional difficulties	Cramps and pain in the lower limbs
Weakness in UL	Moderate	Mean
Weakness in LL	Mean	Mean
Sensitivity to touch in UL	Normal	Moderately abnormal
Sensitivity to touch in LL	Normal	Moderately abnormal
Vibration sensitivity in UL	Normal	Moderately abnormal
Vibration sensitivity in LL	Normal	Severely abnormal
Pyramidal signs	Babinski's sign	Spasticity, hyperreflexia, spastic gait
Urinary symptoms	Moderate urinary emergencies	Moderate urinary emergencies
Additional symptoms and signs	Cognitive disorders Behavioral disorders Dysmorphic syndrome: ogival palate, hypotelorism, lower lip eversion* Severe scoliosis	–
Walking aid	Orthopedic shoes	Foot drop brace (left and right)

UL upper limb; *LL* lower limb

*The patient didn't allow us to use anonymized pictures of his dysmorphic features

loss (Table 1). In 2019, new genetic analyses (panel of 106 genes involved in hereditary neuropathies) revealed the presence of the heterozygous *KIF5A* c.694G > A (p.Asp232Asn) variant. According to standard international criteria to define pathogenic nature of a variant [6], note that this mutation: (1) was not present in the database of the normal population; (2) has already been described once in the literature in a patient with a CMT2 phenotype with numerous pyramidal signs [4]; (3) alters a highly conserved amino acid through the evolution of species; (4) was considered by 4/5 prediction software to be damaging mutation (MutationTaster: disease causing; polyPhen2: probably damaging; PROVEAN: damaging; SIFT: deleterious; BLOSUM62: 1). Therefore, these elements support the pathogenicity of this mutation. Due to dysmorphic features, cognitive/behavioural impairments and multisystem involvement, we performed a comparative genomic hybridization (CGH) array of the patient which excluded a chromosomal rearrangement.

Discussion

KIF5A c.694G > A (p.Asp232Asn) variant was described only once in the literature in a patient presenting a CMT2 added to numerous pyramidal signs (spasticity, hyperreflexia, hypertonia, spastic gait) and without any cognitive disorder [4]. We compared clinical features between both patients in Table 2. This finding confirms that the same mutation in the *KIF5A* gene can result in a variable phenotypic spectrum, ranging from CMT2 to HSP [7]. Our patient presented a CMT2 phenotype with signs not typical of a "classic" CMT2 [8]: sphincter, cognitive, behavioral and dysmorphic features. He had no pyramidal signs (spasticity, hyperreflexia, clonus) except for a bilateral Babinski's sign. Sphincter disorders are generally found in most HSPs including SPG10 but seem less presented in the main CMT2 phenotype. Cognitive impairments are rarer but are also described, mainly in complex HSP. In the context of *KIF5A* mutations, we identified a single patient with CMT2 phenotype and cognitive impairments [4]. Dysmorphic abnormalities, *pes cavus*, feet deformities and scoliosis are common [7]. However, most of the dysmorphic anomalies of our patient (ogival palate, hypotelorism, lower lip eversion) were not found in *KIF5A* patients in literature. Our proband is also the only one with psychomotor retardation.

In conclusion, the case of this patient with CMT2 phenotype associated with cognitive/behavioural impairments and dysmorphic features suggests to potentially extend the genotype–phenotype spectrum of KIF5A-related diseases.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13760-023-02248-4.

Data availability All relevant data are within the paper and its Supporting Information files.

Declarations

Competing interests We declare that no competing interests exist.

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