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A novel homozygous *KY* variant causing a complex neurological disorder

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Abstract

Mutations in the gene *kyphoscoliosis peptidase* (*KY*) are known to cause myofibrillar myopathy-7 and hereditary spastic paraplegia. We investigated the genetic cause of a complex neurological phenotype in a consanguineous Pakistani family with four affected members, manifesting lower limb spasticity and weakness, toe walking, *pes equinovarus*, and a speech disorder. Genome-wide linkage analysis with microsatellite markers delineated chromosome 3q22.2-q24 harboring the disease gene. Whole exome sequencing was performed for two subjects, identifying a homozygous 14-bp frameshift deletion NM_178554.6:c.842_855del;p.(Val281GlyfsTer18) in *KY*.

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The authors declare that they have no conflict of interest.

The variant segregated with the phenotype and was absent from public databases and 100 ethnically matched controls. We confirm a novel homozygous *KY* variant causing a complex neurological phenotype in this family. A review of previously reported *KY* variants suggests that variants in this gene can cause a spectrum of neurological phenotypes.

Keywords

Hereditary spastic paraplegia; kyphoscoliosis peptidase; KY; *pesequinovarus*; speech disorder

Introduction

Homozygous loss of function variants in the gene *kyphoscoliosis peptidase* (*KY*) have primarily been implicated as a cause of rare neuromuscular phenotypes such as myofibrillar myopathy (MFM). The MFMs are a heterogeneous group of hereditary muscle diseases characterized by ectopic protein aggregates and a distinct pattern of myofibrillar disorganization (Fichna *et al.*, 2018). Two reported variants, NM_178554.6:c.405C>A;p.(Tyr135Ter) and NM_178554.6:c.1071delG;p.(Thr358LeufsTer3) cause MFM7, characterized by *pes cavus*, muscular weakness and reduced reflexes in two Arab-Israeli brothers (Straussberg *et al.*, 2016), and a Turkish girl (Hedberg-Oldfors *et al.*, 2016), respectively. Another study reported a frameshift variant, NM_178554.6:c.51_52insTATCGACATGTGCTGTATCTATCGACAT; p.(Val18TyrfsTer56) causing hereditary spastic paraplegia (HSP) in twelve Arab-Bedouin individuals (Yogev *et al.*, 2017). More recently, an Iranian patient with lower limb deformity and motor disorders was found to have a nonsense NM_178554.6:c.415C>T;p.(Arg139Ter) variant in *KY* (Ebrahimzadeh-Vesal *et al.*, 2018).

The autosomal recessive *ky* mouse mutant exhibits a neuromuscular and skeletal phenotype with primary degenerative myopathy preceding chronic thoraco-lumbar kyphoscoliosis (Blanco *et al.*, 2001). *KY* expression has been detected in several tissues including the brain (Fagerberg *et al.*, 2014), and it encodes a protease which interacts with several muscle proteins such as filamin C (FLNC) and myosin-binding protein C (MYBPC1), suggesting that KY is an central part of the protein networks underlying the molecular mechanism of many limb-girdle muscular dystrophies (Beatham *et al.*, 2004).

Clinical Report

We performed genome-wide linkage analysis and whole exome sequencing to find the underlying cause of a complex neurological disorder in four of six affected individuals of a family (Figure 1A, 2 family members were deceased and not available to study). This consanguineous family with multiple affected family members was selected for a potential gene discovery or novel gene-phenotype association. The study was conducted after approval by the institutional review board of School of Biological Sciences, University of the Punjab, Lahore, Pakistan and written informed consent of all participants. Assistance with clinical phenotyping was provided by authors KRK, GA and the Baylor-Hopkins Center for Mendelian Genomics.

All four subjects shared the same phenotype of *pes equinovarus* which they acquired at six years of age (Figure 1B, Supplementary Table 1), a tiptoe gait and an unspecified voice disorder characterized by hoarseness manifesting at the age of 12 years. Progressive muscular weakness developed in all affected individuals. Clinical examination of III:7 and IV:2 revealed the absence of fasciculation, asymmetrical lower limb spasticity (Modified Ashworth Scale 2), intact deep tendon reflexes, and equivocal plantar responses. There was no cognitive dysfunction, bladder disturbance, sensory impairment, or Parkinsonism in affected family members. In the proband III:7, the peroneal motor studies showed a reduced compound muscle action potential on the right and absent F-wave responses bilaterally. The sensory studies were normal and needle electromyography (EMG) showed chronic neurogenic changes in all muscles tested (Supplementary Tables 2–4). Complete blood examination and MRI of the brain for III:7 and IV:2 revealed no abnormalities. Further investigation with creatine kinase levels, muscle MRI and muscle biopsies could not be carried out due to reluctance of the patients to donate tissue samples.

Genome-wide linkage analysis was conducted on samples of all participants (Supplementary Methods) in order to detect the chromosomal interval harboring the disease gene. The data revealed a 6.674 Mb chromosomal region located on 3q22.2–3q24, at which only the affected individuals were homozygous for the marker alleles, while others were heterozygous (Figure 1A), supporting linkage of the disease to this region. Significant LOD scores of 3.37 were obtained for the tightly linked markers (Supplementary Table 5). Whole exome sequencing was completed for individuals III:8 and IV:2 at the Baylor-Johns Hopkins Center for Mendelian Genomics using Agilent SureSelect HumanAllExonV5Clinical_S06588914 for library preparation, on a HiSeq2500 platform with an average depth of coverage of 44X (Supplementary Methods). Exonic or splice site homozygous variants were considered candidates if they were located in the mapped linkage region on chromosome 3.

Whole exome sequencing data analyses revealed two gene variants in the filtered data located within the linkage interval; a deletion in *KY*, and a synonymous variant in *MRPS22*. Both of these variants segregated with the phenotype. The loss of function variant detected in *KY* was absent from all public databases, including gnomAD (Karczewski *et al.*, 2019), ExAC (Karczewski *et al.*, 2017), 1000 Genomes (Auton *et al.*, 2015), HGMD (Stenson *et al.*, 2003), and 100 ethnically matched chromosomes. The variant, NM_178554.6:c.842_855del;p.(Val281GlyfsTer18) (LOVD variant ID #0000597848), was located in exon 9 of the *KY* gene. The *MRPS22* variant (c.9C>T) was rare (<0.1%) in public databases, but was found to be present in 1% of ethnically matched Pakistani controls (3 of 300 chromosomes) and was therefore not considered further.

Discussion

Our study has expanded both the phenotypic and genotypic spectrum due to *KY* variants. Interestingly, all *KY* variants described to date are predicted to either severely truncate the encoded protein or invoke nonsense mediated decay of the mRNA (Table 1). The *KY* variants may manifest with a spectrum of neurological phenotypes including myopathic, neurogenic or spastic paraplegia presentations.

The phenotype in the presented family included a mixture of upper and lower motor neuron signs. Given the evidence of upper motor neuron involvement on examination in the lower limbs (lower limb spasticity), the disorder could be considered a form of complicated HSP, consistent with a previous report (Yogev *et al.*, 2017). However, the affected individuals in this family could not be reliably categorized as HSP due to the markedly asymmetrical nature of the lower limb spasticity. Furthermore, the lower limb reflexes were not exaggerated, although this may have been due to a coexisting lower motor neuronopathy or myopathy. The lower motor neuron signs were supported by the electrodiagnostic studies and may be consistent with a motor neuropathy or anterior horn cell disorder. However, we cannot exclude that the EMG/nerve conduction study findings were due to a motor radiculopathy. Additionally, chronic or end-stage myopathies may produce large amplitude, long duration motor unit action potentials, and such potentials have been reported in other cases of *KY* mutations that were clearly myopathic (Malfatti *et al.*, 2016; Straussberg *et al.*, 2016).

In the patients presented in this study, we attributed the ankle deformity to lower motor neuron dysfunction and lower limb spasticity. Toe walking may also be due to muscle contractures because of myopathic changes and muscle fibrosis in the gastrocnemius and soleus muscles. However, we found chronic neurogenic (rather than myopathic) changes in the left gastrocnemius in the proband, arguing against a myopathic process, although with the caveats mentioned above. Unfortunately, the patients declined further testing with creatine kinase testing, muscle MR imaging, and particularly invasive testing with a muscle biopsy, which would have allowed further elucidation of muscle pathology and the nature of the weakness.

In conclusion, the 14-bp deletion in *KY* we describe results in a complex neurological disorder with affected individuals having some or all the following features: spasticity, lower motor neuron signs, *equinovarus* foot deformity, toe walking and a speech disorder. Taken together with past research, our work confirms that *KY* variants may manifest with myopathic, neuropathic or HSP presentations (Table 1). Clinicians should consider genetic testing with gene panels that include *KY* for a broad range of neurological phenotypes. So far, *KY* variants have only been reported in a handful of cases. Identifying additional patients will further expand our knowledge of the phenotypes associated with variants of *KY*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Patients with a homozygous *KY* frameshift variant are presented
- We report mixed upper and lower motor neuron features in the same individual
- Additional features include toe walking, *pes equinovarus* and a speech disorder
- *KY*-associated disorders manifest in a broad phenotype spectrum

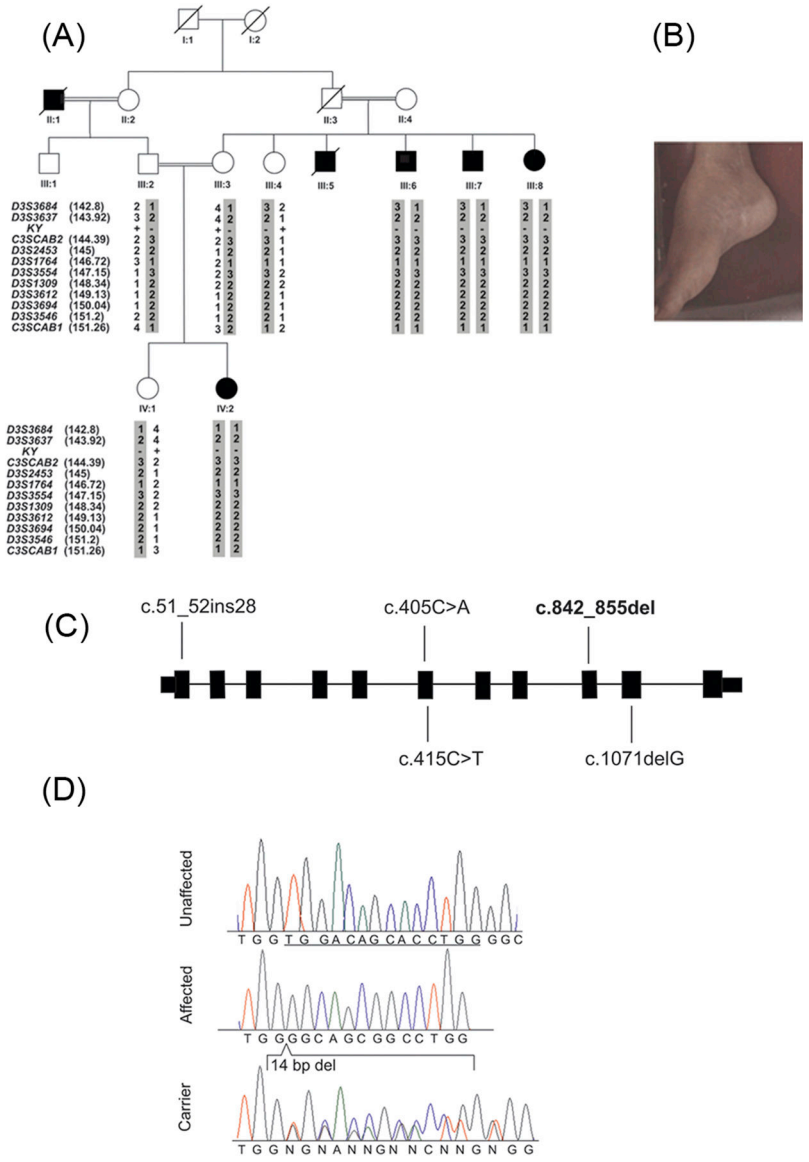

Figure. 1.

Pedigree, Phenotype, Gene *KY*,and sequencing analysis of *KY*

(A) Family tree of DYAF08. Affected individuals are represented by filled symbols; deceased individuals are marked by a diagonal line; double lines denote the presence of inbreeding loops in the pedigree. The haplotype with marker alleles on chromosome 3q22.4–24 linked to the disorder is shaded in gray. The genotype status for *KY* variant is shown ("+", wild-type allele; "-" deletion allele). *C3SCAB1* and *C3SCAB2* are microsatellite repeats which were genotyped using custom designed primers.

(B) Right *pesequinovarus* of patient III:7.

(C)Schematic representation of*KY*, with the previously reported pathogenic variants. The variant identified in this work is indicated in bold. exons; ■ introns;. —

(D) Partial sequence electropherograms of *KY* from an unaffected individual homozygous for wild type sequence, an affected individual homozygous for the variant and an unaffected

heterozygous carrier of the variant, respectively. The 14-bp deletion is underlined in the wild type sequence and is also indicated by the curly brackets below the DNA trace sequence of the affected individual.

Table 1.

Clinical findings in families with homozygous *KY* variants

Clinical analysis	Comparison of phenotypes associated with *KY* variants				
	Present study	**Hedberg-Oldfors *et al.***	**Straussberg *et al.***	**Yoge*vet al.***	**Ebrahimzadeh-Vesal*et al.***
Variants	NM_178554.6:c.842_855del; p.(Val281GlyfsTer18)	NM_178554.6:c.1071delG; p.(Thr358LeufsTer3)	NM_178554.6:c.405C>A; p.(Tyr135Ter)	NM_178554.6:c.51_52insTATCGACATGTGCTGTATCTATCGACAT; p.(Val18TyrfsTer56)	NM_178554.6:c.415C>T; p.(Arg139Ter)
Age at onset (y)	6	3	Birth	Infancy	3
Pes cavus	+	+	+	+	+
Kyphosis/Scoliosis	-	-	+	+	+
Progression	+	NA	+	+	NA
Spasticity of lower limbs	+	NA	NA	+	NA
Nerve conduction studies	Reduced compound muscle potentials of peroneal nerves, absent F waves	Normal	Normal	Normal	NA
EMG findings	Neurogenic changes	Neurogenic changes	Myopathic changes	NA	NA
Phenotype description summary	Complex neurological disorder	Early-onset neuromuscular disorder	Novel congenital myopathy with core targetoid defects	Hereditary spastic paraplegia	Myofibrillar myopathy

+, present; -, absent; NA, not available