Neuromuscular Disorders 32 (2022) 527–532

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Distal spinal muscular atrophy featured by predominant calf muscle involvement in VRK1 associated disease – Case series and review

Koen Demaegd[a,*], Eva H. Brilstra[b], Jessica E. Hoogendijk[a], Charlotte I. de Bie[b], Mirjam S. de Pagter[b], Wim van Hecke[c], Angelika Mühlebner[c], Michael A. van Es[a], Margherita Milone[d], Wouter van Rheenen[a]

[a] Department of Neurology, UMC Brain Center, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Department of Genetics, Center for Molecular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands
[c] Department of Pathology, University Medical Center Utrecht, Utrecht, the Netherlands
[d] Department of Neurology, Mayo Clinic, Minnesota, USA

ARTICLE INFO

Article history:
Received 8 December 2021
Revised 13 April 2022
Accepted 25 April 2022

Keywords:
Distal weakness calf weakness distal spinal muscular atrophy vaccinia-related kinase 1 (VRK1) gene

ABSTRACT

We describe the shared clinical, biochemical, radiological and myopathological characteristics of four patients with distal spinal muscular atrophy (dSMA) caused by vaccinia-related kinase 1 (VRK1) variants and provide a review of the literature on phenotype-genotype correlations in VRK1-related disease. The clinical phenotype was characterized by adult-onset dSMA with predominant calf muscle involvement and mildly elevated serum creatinine kinase (CK) levels. Muscle imaging showed predominant atrophy and fatty replacement of calf muscles. We identified the novel compound heterozygous variants c.607C>T (p.Arg203Trp) and c.858G>*T* (p.Met286Ile) in two siblings with adult-onset dSMA. Additionally, two unrelated patients both carried the known c.583T>*G* (p.Leu195Val) VRK1 variant, with either c.197C>G (p.Ala66Gly) or c.701A>*G* (p.Asn234Ser) as a second variant. We conclude that compound heterozygous VRK1 variants cause distal spinal muscular atrophy with predominant posterior leg muscle involvement.

Introduction

Patients presenting with adult-onset pure motor distal weakness often pose a diagnostic challenge in the neuromuscular clinic. The differential diagnosis includes two main categories, distal myopathies and distal spinal muscular atrophy (dSMA), also called distal hereditary motor neuropathies (dHMN), which themselves are extremely heterogeneous. In the absence of sensory involvement, clinical and electrophysiological distinction between these neuromuscular disorders can be challenging, as involvement of very distal muscles can occur at onset of neurogenic as well as myopathic disorders, and needle electromyography can detect large motor unit potentials in chronic myopathies. Sometimes specific clinical features or the combination of clinical and pathological features can provide clues to target genetic testing [1]. For example, calf muscle weakness occurs in distal myopathies caused by, e.g., ANO5 and DYSF variants [2]. The combination of foot dorsiflexors weakness and rimmed vacuoles in the setting of spared quadriceps is found in GNE hereditary inclusion body myopathy [3]. Distal weakness can also be part of a broad phenotypic spectrum, such as multisystem proteinopathy (MSP) caused by variants in VCP, hnRNPA1, hnRNPA2B1, SQSTM1, MATR3, TIA1 [1,4]. In these cases, understanding the full phenotypic spectrum is important for providing diagnosis and adequate genetic counselling, especially when different family members show different phenotypes.

Here, we describe the clinical and laboratory features of four patients of European ancestries with adult-onset dSMA caused by compound heterozygous VRK1 variants, underscoring the predominant involvement of posterior compartment leg muscles. We also provide an overview of the phenotypic spectrum of VRK1-related disease, which includes dSMA/dHMN, motor neuron disease and neurodevelopmental disorders.

We obtained the approval of the UMCU ethics committee and written informed consent by the patients described here.

* Corresponding author at: Postal: G.03.129, Mailbox 85500, 3508 GA Utrecht, the Netherlands.
E-mail address: k.c.demaegd@umcutrecht.nl (K. Demaegd).

https://doi.org/10.1016/j.nmd.2022.04.007

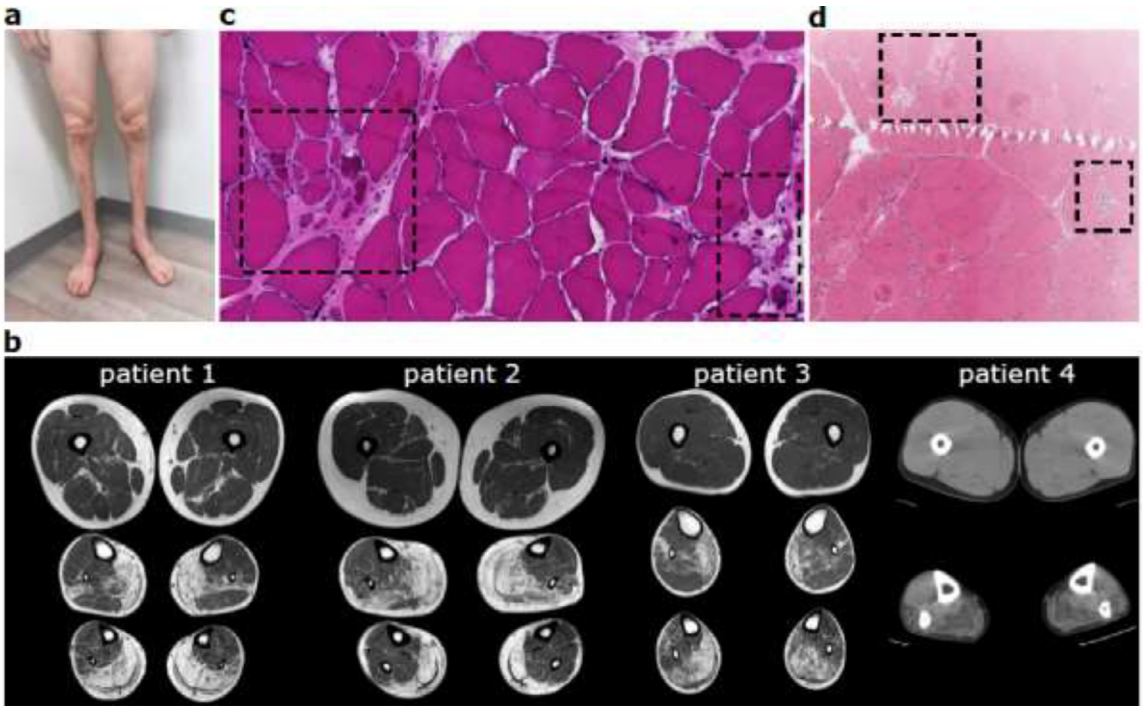

Fig. 1. Clinical, imaging and pathology characteristics of patients. a) severe symmetric distal atrophy of the legs in patient 4 at age 43 years. b) T1-weighted MRI in patient 1–3 and CT in patient 4 (at age 37 years) shows symmetric atrophy and fatty replacement in the posterior compartment of the lower legs with apparent sparing of the anterior compartment and upper legs. c) HE-staining of the muscle biopsy of left tibialis anterior muscle in patient 1 shows groups of atrophic fibers (dashed boxes) that on ATPase stained sections were of either histochemical type (not shown), suggestive of denervation atrophy. d) HE-staining of the muscle biopsy of left gastrocnemius muscle in patient 4 showing muscle fibre necrosis (dashed box).

Case series report

Patient 1, a 59-old man, suffered from muscle cramps from age 30 years. One year prior to presentation at our clinic, he noticed difficulties walking on toes and rising from kneeling position, and more recently tendency to drop heavy objects and nightly hypoventilation. Clinical examination showed symmetric calf muscle atrophy and weakness, as suggested by his inability to walk on toes, while walking on heels was impaired but possible. He had symmetric weakness (MRC grade 4) of ankle dorsiflexors but normal strength of extensor digitorum brevis muscles. Sensory testing was unremarkable as well as reflexes except for absent ankle reflexes. Supine forced vital capacity was 3.2 L (70% of predicted value for age, sex and height) and mid-day capillary pCO_2 5.2 kPa (39 mmHg). Serum creatinine kinase (CK) activity was 172 – 345 U/L (normal value < 170 U/L). Nerve conduction studies showed normal motor and sensory responses with normal conduction velocities. Needle electromyography (EMG) showed fibrillation potentials and sharp positive waves, and giant or large motor unit action potentials (MUAPs) with poor recruitment in gastrocnemius and tibialis anterior muscles. Small, polyphasic potentials with poor recruitment were found in a biceps brachii muscle and a flexor carpi radialis muscle. Subsequent T1 weighted MRI images showed symmetric fatty replacement and atrophy of medial gastrocnemius and soleus muscles with relatively spared tibialis anterior muscles (Fig. 1, panel B). A biopsy of the left tibialis anterior muscle showed an increase in fibre size variation with small groups of atrophic fibres of either histochemical type suggesting denervation atrophy (Fig. 1, panel C). ATPase and cytochrome c oxidase (COX) staining did not show fibre-type grouping. Additional enzyme histochemistry, immunohistochemistry, and electron-microscopy showed no further abnormalities. Next Generation Sequencing (NGS) revealed two variants in the VRK1 gene: c.607C>T (p.Arg203Trp) and c.858G>*T* (p.Met286Ile). His-unaffected mother was found to carry the p.Met286Ile variant only, suggesting the patient's compound heterozygous state, which was confirmed by the affected brother's genotype (Table 1).

Patient 2 is the brother of patient 1, who was found to carry the same VRK1 variants and was subsequently seen at our out-patient clinic. At the age of 57 years, he had no neuromuscular symptoms. Clinical examination showed no muscle atrophy and normal muscle strength by manual testing, but inability to stand and walk on toes, with decreased ankle reflexes. Sensory testing was unremarkable. Forced vital capacity was 3.4 L (78% of predicted value for age, sex and height). Serum CK was 557 U/L (normal value <170 U/L). Needle EMG showed poor recruitment in the medial gastrocnemius muscle without abnormal spontaneous muscle activity, and nerve conduction studies were normal. Muscle MRI revealed symmetrical atrophy and fatty replacement of the soleus and medial gastrocnemius, a pattern similar to that observed in his brother (Fig. 1, panel B).

Patient 3 noticed gait difficulties and a mild bilateral drop foot since the age of 20 years, without evident progression. Examination at the age of 36 years showed mild pes cavus and hammer toes, symmetrical lower leg atrophy with preserved extensor digitorum brevis muscles, symmetric MRC grade 4 weakness of anterior and posterior lower leg muscles by manual testing, and reduced ankle reflexes. There was a bilateral drop foot while walking, and he was unable to stand or walk on toes or heels. His forced vital capacity was 5.5 L (86% of predicted for age, sex and height). Serum CK was 266 U/L (normal value <170 U/L). Nerve conduction studies showed normal motor and sensory responses with normal conduction velocities. Needle electromyography showed abnormal spontaneous muscle fibre activity (sharp positive waves and few fibrillation potentials) in the gastrocnemius muscles and large polyphasic MUAPs with poor recruitment in upper and lower leg muscles. Muscle

Table 1
VRK1 mutations in present case series.

Mutation	Patient	Confirmed compound heterozygous with second variant	Published phenotypes	gnomAD v2.1 AF	SIFT/Polyphen-2/Mutation taster prediction
p.Arg203Trp	1 and 2	Yes	No	0.00004	Deleterious/Prob/DC
p.Met286Ile	1 and 2	Yes	No	0.001	Tolerated/Poss/DC
p.Leu195Val	3 and 4	Yes*	Juvenile MND + microcephaly	0.00001	Deleterious/Prob/DC
p.Asn234Ser	3	Unknown**	No	0.00004	Deleterious/Benign/DC
p.Ala66Gly	4	Yes	No	0	Tolerated/Prob/DC

Abbreviations: AF = allele-frequency, DC = Disease causing, MND = motor neuron disease, PCH = Pontocerebellar hypoplasia, Poss = Possibly damaging, Prob = Probably damaging, * Compound heterozygous state only confirmed in patient 4. ** No co-occurence with p.Leu195Val observed in gnomAD.

MRI showed atrophy and slightly asymmetrical fatty changes in lower leg muscles, predominantly involving the posterior compartment (Fig. 1, panel B). No muscle biopsy was performed. Next Generation Sequencing revealed a known pathogenic variant c.583T>*G* (p.Leu195Val) in the VRK1 gene as well as a second variant, c.701A>*G* (p.Asn234Ser). There were no family members for DNA testing to confirm a compound heterozygous configuration of these variants. Of note, no co-occurence of the p.Asn234Ser and p.Leu195Val variant was observed in gnomAD (Table 1).

Patient 4 noticed difficulties walking on toes on the left side since age of 23 years on, followed by the right lower leg weakness a year later. His calves gradually became thinner. Furthermore, he experienced weakness in his left hand. On examination at age 25, there was asymmetrical pronounced atrophy and weakness of the calves [MRC grade 2 (left) and 4 (right)] and of the ankle dorsiflexors MRC 4. No weakness was detected in the hand muscles. Sensory testing was unremarkable and ankle tendon reflexes were absent. Walking on heels was difficult but possible, but he was unable to walk or stand on toes. Forced vital capacity was 93% of the predicted value for age, sex and height. Serum CK was slightly elevated (275 – 584 U/L; normal value <170 U/L). Motor and sensory nerve conduction studies were normal. Electromyography showed diffuse high amplitude long duration MUAPs with reduced recruitment, especially in anterior and posterior lower leg muscles, where fibrillation potentials were also present. CT Imaging showed atrophy and asymmetrical fatty replacement of the gastrocnemius and soleus muscles. A biopsy taken from a gastrocnemius muscle showed increased endomysial tissue, abundant internalized nuclei, muscle fibre necrosis and regeneration, hypertrophic and atrophic muscle fibres, and pseudo-type grouping in ATP-ase staining due to fibre splitting, (Fig. 1, panel C) suggesting a myopathic process. NADH dehydrogenase stained sections showed target formations suggestive of a coexistence neurogenic process. A repeated biopsy from the asymptomatic lateral vastus muscle showed only a mild increase in fibre size variation, increased number of fibres with internalized nuclei, and some dispersed atrophic fibres, predominance of type 2 fibres without evidence of type grouping in the ATP-ase staining. Follow up examination at age 43 showed symmetrical MRC grade 0 and 3 weakness of posterior and anterior lower leg muscles, respectively, as well as severe calf muscle atrophy (Fig. 1, panel A) and slight atrophy of the first interosseus and abductor digiti minimi muscles. Next Generation Sequencing identified a double variant in the VRK1 gene: the known c.583T>*G* (p.Leu195Val) variant, in combination with a novel c.197C>G (p.Ala66Gly) variant. Subsequent genetic testing of both parents confirmed the compound heterozygous configuration where one variant was inherited from each parent (Table 1).

Review of literature

Including our four patients, 30 patients with VRK1 variants have been described to date (Table 2). All patients harbour two variants in VRK1 either in homozygous, compound heterozygous or suggested compound heterozygous state, as not all reports provide evidence for the compound heterozygous configuration. This is compatible with the reported autosomal recessive mode of inheritance, or (apparently) sporadic disease. There is a broad range of complex neurological phenotypes associated with VRK1 variants, including neurodevelopmental disorders, juvenile motor neuron disease, and dSMA (Fig. 2). The most severe phenotype is a neurodevelopmental disease, which includes microcephaly and pontocerebellar hypoplasia leading to motor developmental delay. This is accompanied by severe muscle weakness, resembling predominantly distal spinal muscular atrophy, but electrophysiologically accompanied by sensory involvement. Most patients are wheelchair bound in early childhood and need a percutaneous gastrostomy tube placement. Patients with juvenile motor neuron disease (MND) due to VRK1 variants present in childhood or teenage with distal weakness and brisk reflexes. Across the full spectrum of VRK1-related diseases progression of muscle weakness varies, but it is faster in patients with earlier onset and in those with central nervous system involvement, such as microcephaly and intellectual disability. In total, nine patients with dSMA due to VRK1 variants have been described. Their age of disease onset varies between the first and fifth decade and predominantly involves distal leg muscles, later spreading to the proximal leg and hand muscles. Predominant calf atrophy has been described [5]. Overall, the rate of progression is faster in the early onset dSMA patients who became wheelchair bound in the second or third decade [6]. Respiratory muscles involvement requiring non-invasive ventilation can occur especially in young-onset patients [6], but it was also described in a patient with adult onset dSMA who was still ambulatory with a walking-aid [5] and was recently also started in our patient 1. There is no apparent genotype-phenotype correlation with respect to the clinical manifestation of disease severity.

Discussion

The four patients with VRK1-dSMA/dHMN described here show a strikingly similar phenotype, characterized by onset in their twenties, slow progression of distal weakness with conspicuous involvement of calf muscles, mildly elevated CK, neurogenic needle EMG findings without sensory involvement, and similar muscle radiological features. While the grouped atrophic muscle fibers of either histochemical type in the muscle biopsy of patient 1 suggested a neurogenic aetiology, the gastrocnemius biopsy in patient 4 showed mixed myopathic and neurogenic changes. This however is not surprising as gastrocnemius is particularly prone to develop myopathic changes as secondary phenomenon to a neurogenic process. This adds complexity in distinguishing neurogenic from myopathic diseases in patients with distal weakness [7], and highlights the limitation of calf muscle biopsies in patients with distal weakness. The MRI patterns were highly similar in our four patients showing marked atrophy

Table 2
Overview of cases in the literature.

Clinical syndrome	Variant 1	Variant 2	Onset	Primary symptoms	Accompanying features	Outcome	Refs
Microcephaly	c.1072C>T (p.Arg358*)	c.1072C>T (p.Arg358*)	Antenatal	Lissencephaly	Unknown	Aborted pregnancy	[9]
PCH	c.397C>T (p.Arg133Cys)	c.397C>T (p.Arg133Cys)	unknown	Intellectual disability	unknown	unknown	[10]
(d)SMA + PCH	c.1072C>T (p.Arg358*)	c.1072C>T (p.Arg358*)	antenatal	Developmental delay – distal SMA	progressive microcephaly, mild retardation, pontocerebellar hypoplasia, ataxia, motor and sensory neuropathy. Affected sibling and cousin without genetic diagnosis.	died at 11yo	[11]
(d)SMA + microcephaly	c.1072C>T (p.Arg358*)	c.1072C>T (p.Arg358*)	antenatal	Motor developmental delay - distal SMA	microcephaly with normal cognition, motor and sensory neuropathy, bulbar weakness, scoliosis.	wheelchair at 6yo	[12]
(d)SMA + microcephaly	c.266G>A (p.Arg89Gln)	c.706G>A (p.Val236Met)	antenatal	Motor developmental delay - distal SMA	microcephaly with normal cognition, bulbar weakness, motor and sensory neuropathy, hypotonia.	unknown	[12]
(d)SMA + microcephaly	c.266G>A (p.Arg89Gln)	c.706G>A (p.Val236Met)	infancy	Motor developmental delay - distal SMA	microcephaly with normal cognition, motor and sensory neuropathy, bulbar weakness, scoliosis.	wheelchair at 4yo	[12]
juvenile MND	c.1159 + 1 G>A (p.Arg387Hisfs*7)	c.1159 + 1 G>A (p.Arg387Hisfs*7)	infancy	Developmental delay	distal weakness, UMN involvement, scoliosis.	wheelchair at 13yo	[6]
juvenile MND + microcephaly	c.583T>G (p.Leu195Val)	c.403G>A (p.Gly135Arg)	childhood	Distal weakness	microcephaly, UMN and sensory involvement, scoliosis, respiratory insufficiency	respiratory failure at 14yo	[13]
juvenile MND	c.710–14T>C	c.721C>T (p.Arg241Cys)	childhood	Distal weakness	UMN involvement	wheelchair at 15yo	[14]
juvenile MND	c.767C>T (p.Thr256Ile)	c.800A>G (p.Asp267Gly)	childhood	Intellectual disability	distal weakness, sensory and UMN involvement.	unknown	[15]
Juvenile MND	c.1072C>T (p.Arg358*)	c.683C>T (p.Thr228Met)	Childhood	Distal weakness	UMN involvement	Unknown	[16]
juvenile MND	c.265C>T (p.Arg89*)	c.769G>A (p.Gly257Ser)	teenage	Distal weakness	UMN involvement	walking aid at 25yo	[14]
juvenile MND	c.656G>T (p.Arg219Ile)	c.761G>T (p.Trp254Leu)	teenage	Distal weakness	UMN involvement	ambulatory at 47yo	[17]
juvenile MND	c.656G>T (p.Arg219Ile)	c.761G>T (p.Trp254Leu)	teenage	Distal weakness	UMN involvement	walking aid at 38yo	[17]
MND	c.961C>T (p.Arg321Cys)	c.356A>G (p.His119Arg)	adult	Distal weakness	Pes cavus, hammertoes, UMN involvement	unknown	[18]
dSMA	c.961C>T (p.Arg321Cys)	c.706G>A (p.Val236Met)	teenage	Distal weakness	Distal weakness, arm involvement	unknown	[19]
dSMA	c.706G>A (p.Val236Met)	c.706G>A (p.Val236Met)	adult	Distal weakness	Distal weakness	unknown	[19]
dSMA	c.1159 + 1 G>A (p.Arg387Hisfs*7)	c.1159 + 1 G>A (p.Arg387Hisfs*7)	childhood	Distal weakness	scoliosis, hyperlaxity, respiratory insufficiency	wheelchair at 18yo	[6]
dSMA	c.1159 + 1 G>A (p.Arg387Hisfs*7)	c.1159 + 1 G>A (p.Arg387Hisfs*7)	teenage	Distal weakness	scoliosis, hyperlaxity	wheelchair at 25yo	[6]
dSMA	c.1072C>T (p.Arg358*)	c.356A>G (p.His119Arg)	teenage	Distal weakness	respiratory weakness	walking aid at 35 yr	[13]
dSMA	c.1072C>T (p.Arg358*)	c.356A>G (p.His119Arg)	teenage	Distal weakness	none	walking aid at 40 yr	[13]
dSMA	c.1124 G >A (p.Trp375*)	c.1124 G >A (p.Trp375*)	teenage	Distal weakness	none	wheelchair at 42yo	[20]
dSMA	c.1124 G >A (p.Trp375*)	c.1124 G >A (p.Trp375*)	teenage	Distal weakness	Pes cavus, UMN involvement	ambulatory at 40yo	[20]
dSMA	c.1124G>A (p.Trp375X)	c.1124G>A (p.Trp375X)	teenage	Distal weakness	Pes cavus	unknown	[21]
dSMA	c.1160G>A (p.Arg387His)	c.1160G>A (p.Arg387His)	adult	Distal weakness	pes cavus, hammer toes, nocturnal respiratory difficulty	walking aid at 52yo	[5]
dSMA	c.1160G>A (p.Arg387His)	c.1160G>A (p.Arg387His)	adult	Distal weakness	none	ambulatory at 61yo	[5]
dSMA	c.583T>G (p.Leu195Val)	c.701A>G (p.Asn234Ser)	adult	Distal weakness	none	ambulatory at 37yo	current
dSMA	c.583T>G (p.Leu195Val)	c.197C>G (p.Ala66Gly)	adult	Distal weakness	none	walking aid at 48yo	current
dSMA	c.607C>T (p.Arg203Trp)	c.858G>T (p.Met286Ile)	adult	Distal weakness	Mild supine hypoventilation	ambulatory at 58yo	current
dSMA	c.607C>T (p.Arg203Trp)	c.858G>T (p.Met286Ile)	adult	Distal weakness	Mild supine hypoventilation	walking aid at 59yo	current

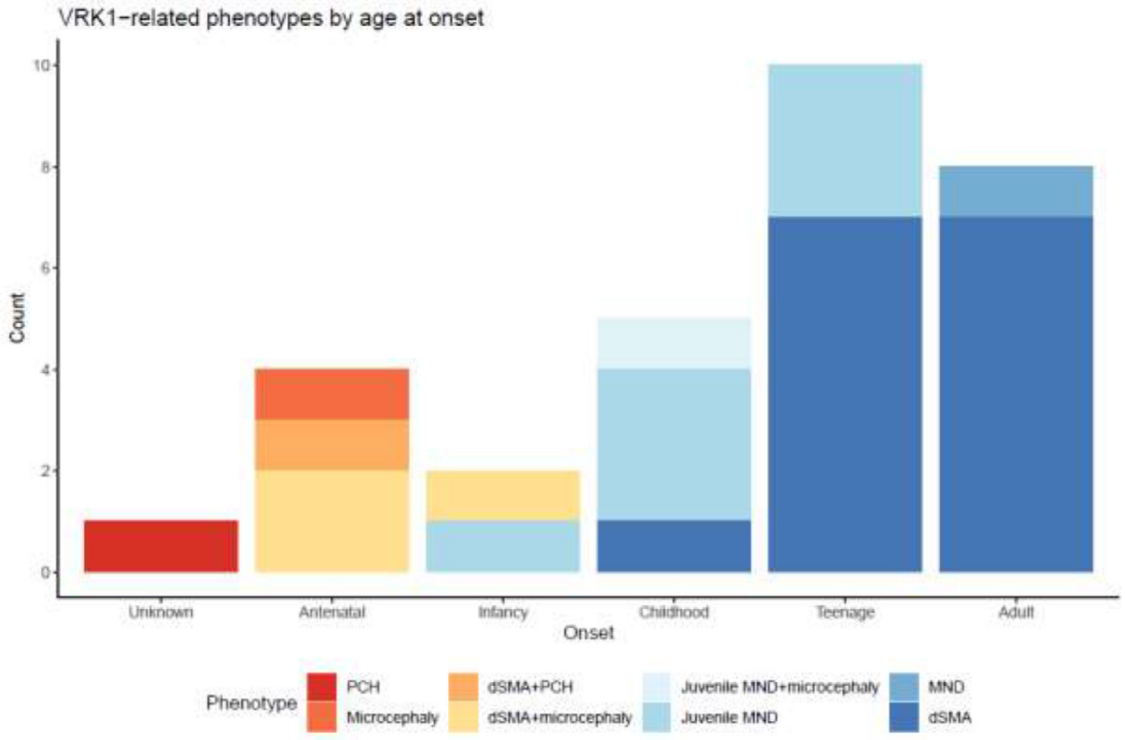

Fig. 2. VRK1-related phenotypes by age at onset Overview of the age of onset of all cases currently described in literature, as well as their phenotypes. PCH = pontocerebellar hypoplasia, dSMA = distal spinal muscular atrophy, MND motor neuron disease.

of the posterior lower leg compartment, similar to that observed in patients with distal myopathies caused by ANO5 and DYSF variants [8]. This pattern can help the interpretation of genetic findings or motivate targeted sequencing of VRK1 in these patients.

Of the five genetic variants we found in our patients with dSMA, four have been reported in ClinVar though with unclear phenotypic associations, except for c.197C>G (p.Ala66Gly). Algorithms developed to predict the pathogenic effect of variants on protein structure and function (SIFT, PolyPhen-2, Mutation Taster) all suggest the p.Arg203Trp variant disruptive, while the predictions for p.Met286Ile and p.Asn234Ser variants are contradictory. However, the segregation analysis concluding a compound heterozygous state for patients 1 and 2 suggests p.Met286Ile to be pathogenic as well. While for patient 3 we lack segregation analysis, in both patients 3 and 4 their respective variants p.Asn234Ser and p.Ala66Gly are likely compound heterozygous as well, as they are combined with the known pathogenic p.Leu195Val variant. While these observations provide support for the pathogenicity of the VRK1 variants, factors causing the vast phenotypic variability in this disorder remain elusive. This indeed is not readily explained by the location of variants, type of variant (e.g. missense or loss-of-function) or consanguinity leading to increased homozygosity at other sites.

Given the homogenous phenotype in our series of patients, we suggest including VRK1 gene analysis in the diagnostic work up of patients with predominant calf muscle weakness.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Declarations of interest

Margherita Milone reports Research funding from the Neurology Department and CCaTS-CBD Pilot Awards for Team Science, Mayo Clinic; a Muscular Dystrophy Association Care center grant (MDA 497263), and honorarium to serve as associate editor for Neurology Genetics.

References

[1] Milone M, Liewluck T. The unfolding spectrum of inherited distal myopathies. Muscle Nerve 2019;59:283–94. doi:10.1002/mus.26332.
[2] ten Dam L, van der Kooi AJ, Rövekamp F, Linssen WHJP, de Visser M. Comparing clinical data and muscle imaging of DYSF and ANO5 related muscular dystrophies. Neuromusc Disord 2014;24:1097–102. doi:10.1016/j.nmd.2014.07.004.
[3] Nishino I, Carrillo-Carrasco N, Argov Z. GNE myopathy: current update and future therapy. J Neurol Neurosurg Psychiatry 2015;86:385–92. doi:10.1136/jnnp-2013-307051.
[4] Korb MK, Kimonis VE, Mozaffar T. Multisystem proteinopathy: where myopathy and motor neuron disease converge. Muscle Nerve 2020:27097 mus. doi:10.1002/mus.27097.
[5] Greenbaum L, Barel O, Nikitin V, Hersalis-Eldar A, Kol N, Reznik-Wolf H, et al. Identification of a homozygous VRK1 mutation in two patients with adult-onset distal hereditary motor neuropathy. Muscle Nerve 2019:395–400. doi:10.1002/mus.26779.
[6] Sedghi M, Moslemi AR, Olive M, Etemadifar M, Ansari B, Nasiri J, et al. Motor neuron diseases caused by a novel VRK1 variant – a genotype/phenotype study. Ann Clin Transl Neurol 2019;6:2197–204. doi:10.1002/acn3.50912.
[7] Lewis-Smith DJ, Duff J, Pyle A, Griffin H, Polvikoski T, Birchall D, et al. Novel HSPB1 mutation causes both motor neuronopathy and distal myopathy. Neurology Genetics 2016;2. doi:10.1212/NXG.0000000000000110.
[8] Bugiardini E, Morrow JM, Shah S, Wood CL, Lynch DS, Pitmann AM, et al. The diagnostic value of MRI pattern recognition in distal myopathies. Front Neurol 2018;0:456. doi:10.3389/FNEUR.2018.00456.
[9] Reches A, Hiersch L, Simchoni S, Barel D, Greenberg R, ben Sira L, et al. Whole-exome sequencing in fetuses with central nervous system abnormalities. J Perinatol 2018;38:1301–8. doi:10.1038/s41372-018-0199-3.
[10] Najmabadi H, Hu H, Garshasbi M, Zemojtel T, Abedini SS, Chen W, et al. Deep sequencing reveals 50 novel genes for recessive cognitive disorders. Nature 2011;478:57–63. doi:10.1038/nature10423.
[11] Renbaum P, Kellerman E, Jaron R, Geiger D, Segel R, Lee M, et al. Spinal muscular atrophy with pontocerebellar hypoplasia is caused by a mutation in the VRK1 gene. Am J Hum Genet 2009;85:281–9. doi:10.1016/j.ajhg.2009.07.006.
[12] Gonzaga-Jauregui C, Lotze T, Jamal L, Penney S, Campbell IM, Pehlivan D, et al. Mutations in VRK1 associated with complex motor and sensory axonal neuropathy plus microcephaly. JAMA Neurol 2013;70:1491–8. doi:10.1001/jamaneurol.2013.4598.

[13] Stoll M, Teoh H, Lee J, Reddel S, Zhu Y, Buckley M, et al. Novel motor phenotypes in patients with VRK1 mutations without pontocerebellar hypoplasia. Neurology 2016;87:65–70. doi:10.1212/WNL.0000000000002813.
[14] Silva DP, Soeiro E, Sá M, Silveira F, Pinto S, Gromicho M, Sousa AB, et al. VRK1 variants in two Portuguese unrelated patients with childhood-onset motor neuron disease. Amyotroph Lateral Scler Frontotemp Degenerat 2020;21:291–5. doi:10.1080/21678421.2020.1746343.
[15] Yamaura G, Higashiyama Y, Kusama K, Kunii M, Tanaka K, Koyano S, et al. Novel VRK1 mutations in a patient with childhood-onset motor neuron disease. Internal Med 2019;58:2715–19. doi:10.2169/internalmedicine.2126-18.
[16] Organizing L, Davide C, Milan P, Genoa AS, Maria G, Verona F, et al. 6 th international charcot-marie-tooth and related neuropathy consortium (CMTR) meeting. J Peripheral Nervous Syst 2016;21:229–314. doi:10.1111/jns.12181.
[17] El-Bazzal L, Rihan K, Bernard-Marissal N, Castro C, Chouery-Khoury E, Desvignes JP, et al. Loss of Cajal bodies in motor neurons from patients with novel mutations in VRK1. Hum Mol Genet 2019;28:2378–94. doi:10.1093/hmg/ddz060.
[18] Nguyen TP, Biliciler S, Wiszniewski W, Sheikh K. Expanding phenotype of VRK1 mutations in motor neuron disease. J Clin Neuromuscul Dis 2015;17:69–71. doi:10.1097/CND.0000000000000096.
[19] Sung A, Moretti P, Shaibani A. Adult-onset spinal muscular atrophy due to mutations in the VRK1 gene. Neurol Genet 2021;7:e599. doi:10.1212/nxg.0000000000000599.
[20] Li N, Wang L, Sun X, Lu Z, Suo X, Li J, et al. A novel mutation in VRK1 associated with distal spinal muscular atrophy. J Hum Genet 2019;64:215–19. doi:10.1038/s10038-018-0553-5.
[21] Feng S-Y, Li L-Y, Feng S-M, Zou Z-Y. A novel VRK1 mutation associated with recessive distal hereditary motor neuropathy. Ann Clin Transl Neurol 2019;6:401–5. doi:10.1002/acn3.701.