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CASE REPORT

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Upper motor neuron signs and early onset gait abnormalities in young children with bi-allelic *VWA1* variants

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Abstract

Bi-allelic loss-of-function variants in Von Willebrand factor type A (*VWA1*) were recently discovered to lead to an early onset motor neuropathy or neuromyopathy. What makes this discovery particularly notable is the high frequency of one of the *VWA1* (NM_022834.5) founder variants, c.62_71dup (p.Gly25ArgfsTer74), which nears 0.01% in European populations, and suggests that there may be a wide spectrum of disease features and severity. Here, we report two cases from nonconsanguineous families in North America that presented in early childhood with lower extremity weakness and prominent foot deformities, and were found to carry bi-allelic variants in *VWA1*. We draw focus to upper motor neuron signs and abnormal gait phenotypes as presenting symptoms in *VWA1*-related disorder and expand the clinical and molecular spectrum.

KEYWORDS
foot deformities, neuropathy, pyramidal signs, spasticity, Von Willebrand factor a domain containing 1

1 | INTRODUCTION

Bi-allelic loss-of-function variants in Von Willebrand factor type A (*VWA1*) were recently identified in patients with lower extremity weakness and congenital foot abnormalities including *pes cavus* or *equinovarus* (Deschauer et al., 2021; Pagnamenta et al., 2021). This discovery is particularly notable given the high frequency of one of the *VWA1* (NM_022834.5) founder mutations, c.62_71dup (p.Gly25ArgfsTer74), which nears 0.01% in certain European populations (Arribat, 2021). Although the age of onset is heterogeneous, the majority of the 32 reported cases (~80%) showed symptom onset in childhood (Deschauer et al., 2021; Pagnamenta et al., 2021). The differential diagnosis for childhood-onset neuromuscular diseases and hereditary neuropathies is broad and heterogeneous. For newly reported genes it is important to establish the full clinical spectrum, particularly if significant clinical heterogeneity and phenotypic pleiotropy exist. In order to expand the clinical spectrum of *VWA1*-related disorder, we report two additional cases from nonconsanguineous families in North America that presented in early childhood with lower extremity weakness and foot deformities. Specifically, we draw focus to upper motor neuron signs and abnormal gait phenotypes as presenting symptoms in *VWA1*-related disorder.

Dustin L. Gable and Alisa Mo contributed equally to this study.

2 | CLINICAL REPORT

2.1 | Case 1

A 6-months-old, ex-full-term female without prenatal or perinatal complications presented to the orthopedics clinic for evaluation of bilateral intoeing. This was followed by truncal and appendicular hypotonia and delayed onset of walking until 22 months. Evaluation in our neuromuscular clinic at 3 years revealed bilateral proximal lower extremity muscle weakness, distal lower extremity spasticity,

hyperreflexia, and a Babinski sign. Musculoskeletal examination showed Achilles tendon contractures and talipes equinovarus. Family history was notable for a great uncle with "clubfoot" (Table 1). Ancestry was mixed European (French Canadian, Irish, and Italian). Creatine kinase levels were within normal range (145 IU/L). Brain and spine MRI were normal. EMG at the age of 3 years showed normal sural and median sensory responses and normal median and tibial motor responses. The peroneal motor amplitude was low but this was thought to be related to extensor digitorum brevis atrophy due to her foot deformities. Needle EMG did not show neurogenic or myopathic changes in the lower limbs. A multigene panel for hereditary spastic paraplegia was unrevealing. Clinical exome sequencing identified a homozygous c.62_71dup (p.Gly25ArgfsTer74) variant (Table 1). At the current age of 9 years, the patient's spastic paraparesis has remained stable, and she is able to ambulate without support. She has required multiple orthopedic procedures including Achilles tendon lengthening as well as bracing and physical therapy. A repeat EMG was declined by the family.

2.2 | Case 2

A 2-years-old male with no significant prenatal or perinatal history initially presented to the orthopedics clinic for evaluation of abnormal gait and frequent falls. He started walking at 15 months of age. Clinical examination showed a positive Gowers' sign and prominent bilateral ankle supination during walking (Supporting Information Videos 1 and 2). He was subsequently referred to the Movement Disorders Program for possible lower extremity dystonia. Neurological examination did not reveal dystonia but was notable for proximal leg weakness and absent patellar and Achilles tendon reflexes bilaterally, in addition to Achilles tendon shortening, over-riding second toes and lumbar hyperlordosis (Figure 1a–d and Table 1). There were no pyramidal signs and sensation to light touch was intact. Gait examination showed a waddling gait, persistent bilateral ankle supination, and tonic extension of the great toes during walking. The lateral aspect of both feet showed significant callus formation as the result of his ankle posture during gait (Figure 1). Family history was negative for neurological or musculoskeletal conditions. Ancestry was mixed European (German, English, and Irish). Creatine kinase levels were within normal limits (124 IU/L). Brain and spine MRI were normal. EMG and nerve conduction studies were declined by the family. Clinical exome sequencing showed the recurrent *VWA1* founder mutation, c.62_71dup (p.Gly25ArgfsTer74) (maternally inherited), in trans with a novel paternally inherited missense variant, c.212T>C (p.Leu71Pro) (Table 1). The latter variant was initially classified as a variant of uncertain significance by American College of Medical Genetics and Genomics criteria (Richards et al., 2015). However, given the clinical context, low frequency of this variant in healthy controls (gnomAD version 3.1.2, allele frequency <0.0001, absent in homozygotes) and in silico analyses yielding a high CADD-PHRED (version 1.6) score of 27.6, we assume this variant to be disease-causing. In addition, the p.Leu71Pro variant resides at a conserved position within a conserved

TABLE 1 Clinical features of two children with biallelic *VWA1* (NM_022834.5) variants

Case	Initial specialty referral (age, chief complaint)	Initial diagnosis	Age at walking	Age at neurology referral	Neurological examination	Age at genetic diagnosis	*VWA1* variant (gnomAD allele frequency[a])
1	Orthopedics (6 months, bilateral intoeing)	Wide-based gait, metatarsus adductus, hypotonia	22 months	34 months	• Proximal lower extremity weakness (hip flexion and extension: 4/5[b]) • Distal lower extremity spasticity with hyperreflexia (patellar and ankle reflexes) and a positive Babinski sign • Achilles tendon contractures • Talipes equinovarus bilaterally	8 years	c.62_71dup (p.Gly25ArgfsTer74), homozygous (0.0003)
2	Orthopedics (15 months, abnormal gait)	Bilateral ankle supination	15 months	20 months	• Proximal lower extremity weakness (hip flexion and extension: 4/5[b]) • Diminished patellar and absent Achilles tendon reflexes • Gait impairment with persistent bilateral ankle supination and tonic toe extension during walking • Short Achilles tendons	2 years	c.62_71dup (p.Gly25ArgfsTer74) (0.0003) c.212T>C (p.Leu71Pro) (0.00005)

[a]gnomAD accessed February 12, 2022.
[b]Measure on Medical Research Counsel scale.

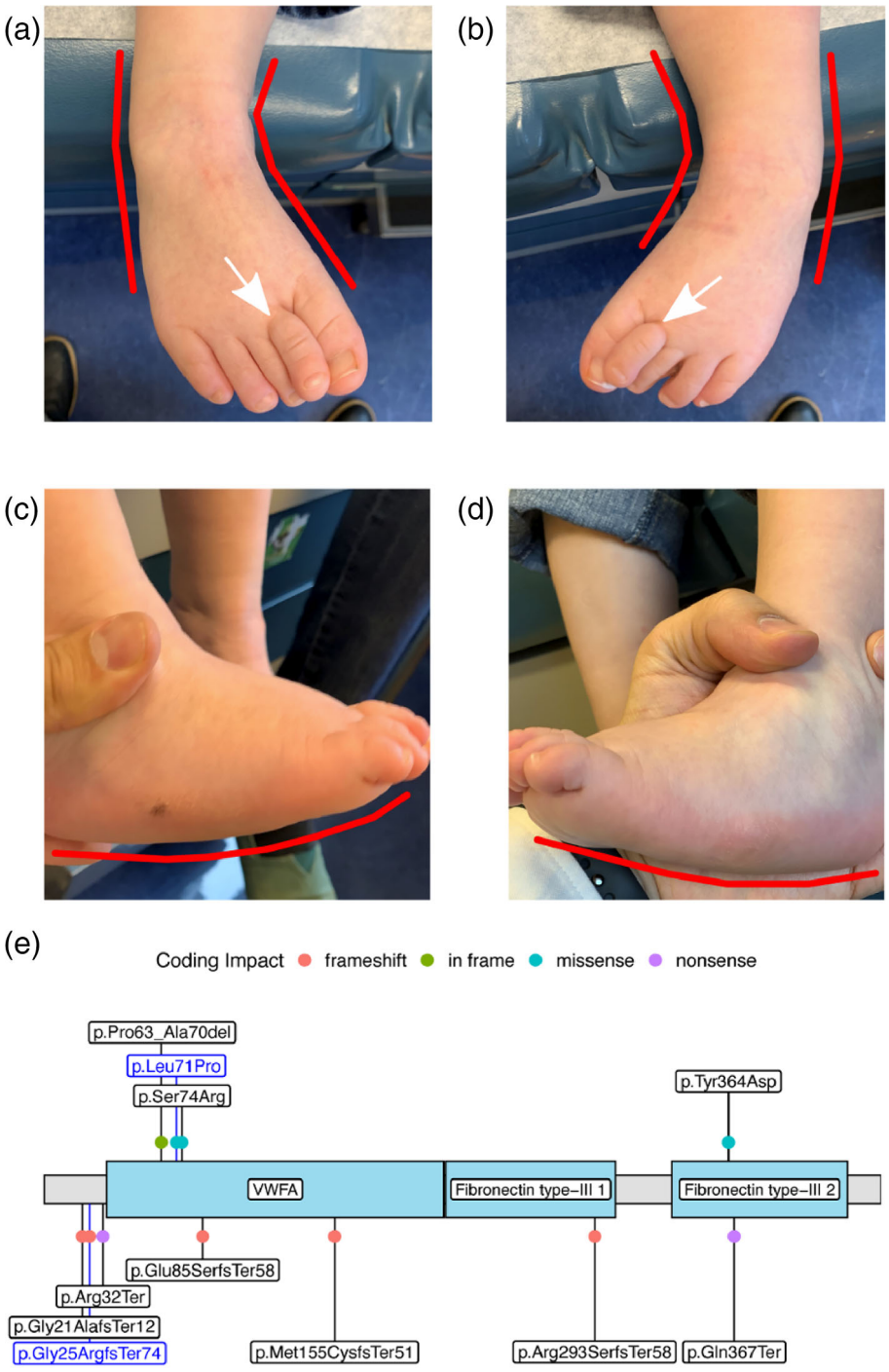

FIGURE 1 Bilateral foot supination in a 2-years-old male harboring biallelic *VWA1* variants showing prominent overlying second toe (white arrow) on the right (a) and left (b) foot causing substantial callus formation on the lateral aspect of each foot (c, d). Red lines delineate abnormal curvature. (e) Protein structure of Von Willebrand factor a domain-containing protein 1 (VWA1) isoform 1 at locus 1p36.33 (UnitProt ID: Q6PCB0) and the reported disease-causing variants. VWA1 contains three conserved domains: A VWFA domain from amino acids 34–213 and two fibronectin type III domains (amino acids 214–304 and 327–420, respectively). An N-terminal signaling protein is present from amino acids 1–18 (not shown here). All reported disease-associated variants are depicted. Variants predicted to undergo nonsense mediated decay are printed below the protein structure, while those potentially retaining residual protein function are depicted above. Coding impacts are shown as colored dots. Blue font indicates the variants identified in the two cases reported here). All variants were harmonized to the canonical Ensembl transcript ENST00000476993.2 [Color figure can be viewed at wileyonlinelibrary.com]

domain and clusters near other previously established disease-causing missense and small deletion alleles (Deschauer et al., 2021; Pagnamenta et al., 2021; Figure 1e).

3 | DISCUSSION

The two cases presented here expand the core phenotype of hereditary nonlength dependent motor neuropathy seen in the majority of patients with the newly reported *VWA1*-related disorder. The presence of distal spasticity and pyramidal signs in the first case suggests additional upper motor neuron involvement. Supportive of this, several patients in the cohorts reported by Pagnamenta et al. (2021) and Deschauer et al. (2021) displayed brisk patellar reflexes, a finding that is difficult to reconcile with a motor neuropathy or neuromyopathy. This distinction has implications for understanding the mechanism of disease in the central and peripheral nervous systems moving forward, as prior studies have been limited.

Genotype–phenotype correlations remain to be established. Only one of the 12 previously reported cases with the homozygous

p.Gly25ArgfsTer74 founder variant was noted to have possible upper motor neuron involvement, indicated by hyperreflexia in the lower extremities. Further, this case was in a 40-years-old patient and other medical comorbidities were unknown.

An additional limitation of our study and of research on *VWA1*-related disorder, in general, is the lack of longitudinal investigations. We were unable to obtain a repeat EMG and nerve conduction studies in our first patient, hence it remains uncertain if the absence of neuropathic changes persisted or if a peripheral neuropathy will develop eventually.

VWA1 encodes the extracellular matrix protein WARP (Von Willebrand factor A-domain-related protein), which is predominantly expressed in chondrocytes, peripheral nerves, and skeletal muscle (Allen et al., 2006; Fitzgerald, 2020). *Vwa1* knockout mice display impaired motor coordinator and delayed response to painful stimuli, supporting that loss of WARP function leads to peripheral nervous system impairment (Allen et al., 2009). Motor impairment is also found in *vwa1* knockdown zebrafish larvae, which along with impaired motor neuron outgrowth suggests an important developmental role of *VWA1* (Pagnamenta et al., 2021). How loss-of-function variants in *VWA1* lead to pyramidal dysfunction as suggested by our cases remains to be explored.

Our second case highlights that prominent early onset and progressive foot deformities with shortening of the Achilles tendons, proximal leg weakness and resultant abnormal gait can be presenting symptoms. Along these lines, it is notable that the path to diagnosis for both cases started in the orthopedic clinic, highlighting the importance of considering testing for *VWA1* variants in individuals with foot deformities of unclear etiology. We hope that our report will facilitate molecular testing in similar cases and raise awareness for the early manifestations of this evolving syndrome.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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