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Skeletal muscle involvement in biallelic *SORD* mutations: case report and review of the literature

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Biallelic mutations in the sorbitol dehydrogenase (*SORD*) gene have been identified as a genetic cause of autosomal recessive axonal Charcot-Marie-Tooth disease 2 (CMT2) and distal hereditary motor neuropathy (dHMN).
We herein review the main phenotypes associated with *SORD* mutations and report the case of a 16-year-old man who was referred to our outpatient clinic for a slowly worsening gait disorder with wasting and weakness of distal lower limbs musculature. Since creatine phosphokinase (CPK) values were persistently raised (1.5fold increased) and a Next-Generation Sequencing CMT-associated panel failed in identifying pathogenic variants, a muscle biopsy was performed with evidence of alterations suggestive of a protein surplus distal myopathy. Finally, Whole-Exome Sequencing (WES) identified two pathogenic *SORD* variants in the heterozygous state: c.458C > A (p.Ala153Asp) and c.757delG (p.Ala253Glnfs*27).
This is an isolated report of compound heterozygosity for two *SORD* mutations associated with clinical and histological signs of skeletal muscle involvement, expanding the phenotypic expression of *SORD* mutations.

Key words: Sorbitol Dehydrogenase, *SORD*, myopathy, dHMN

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Introduction

Biallelic mutations in the sorbitol dehydrogenase (*SORD*) gene have been identified as a genetic cause of autosomal recessive axonal Charcot-Marie-Tooth disease 2 (CMT2) and distal hereditary motor neuropathy (dHMN) [1]. The most frequent pathogenetic variant is c.753delG (p.Ala253Glnfs*27) in homozygous or compound heterozygous state, which is responsible for about 10% of cases of undiagnosed CMT2 and dHMN [1]. The *SORD* gene encodes sorbitol dehydrogenase, an enzyme that catalyzes the reversible nicotinamide adenine dinucleotide-dependent oxidation of sorbitol into fructose [2]. The decrease of sorbitol dehydrogenase resulting from mutations in the *SORD* gene leads to a rise in serum sorbitol levels and sorbitol accumulation [1]. Notably, the absence of sorbitol dehydrogenase and increased intracellular sorbitol levels have been detected in patient-derived fibroblasts [1]. Cortese and colleagues also demonstrated the occurrence of synaptic degeneration and motor impairment in *Drosophila melanogaster* models of *SORD* mutations [1].
A case of juvenile amyotrophic lateral sclerosis associated with homozygous c.757delG mutation in *SORD* has recently been described [3], supporting the involvement of *SORD* in motor neuron disorders. Some patients with *SORD*-related neuropathy also exhibit positive

signs of dermographism [4] and a small nerve fibre involvement has also been hypothesized [5]. No association between *SORD* variants and muscle involvement has been described so far.
We herein report the case of a man with biallelic *SORD* mutations, distal lower limb weakness, and histological signs supporting muscle impairment.

Case report

In 2013, a 16-year-old man was referred to the neurological outpatient CMT clinic of the University of Genoa for distal weakness and gait impairment, starting at the age of 11. No other family member had clinical and neurophysiological muscular signs and the parents had normal serum creatine phosphokinase (CPK) values (the pedigree of the patient is shown in Fig. 1).
Neurological examination revealed bilateral symmetric muscle wasting and weakness of the tibialis anterior and gastrocnemius muscles (Medical Research Council [MRC] score 4/5) and extensor hallucis longus weakness (MRC 4/5). Sensitivity and coordination were normal. The patient had reduced deep tendon reflexes, bilateral pes cavus, and mild steppage gait. He did not have tremors, hearing impairment, or cataracts, but had scoliosis for which he had undergone rehabilitative therapy since the age of 10.
Nerve conduction studies revealed low-amplitude compound muscle action potentials in the nerves of lower limbs, while sensory nerve conductions were normal (Tab. I). Needle electromyography (EMG) showed normal insertion activity but frequent spontaneous activity (positive potentials and fibrillation discharges) in the anterior tibialis and medial gastrocnemius muscles bilaterally. Recruitment activity at maximum voluntary effort was not assessable due to pain avoidance, while the pattern of submaximal effort recruitment was regular. The morphology of motor unit potentials was irregular with an increased number of turns and increased amplitude and duration in both the anterior tibialis and medial gastrocnemius muscles. No fasciculation potentials were recorded. Overall, the neurophysiological evaluation was consistent with active and chronic neurogenic changes involving distal lower limb muscles.

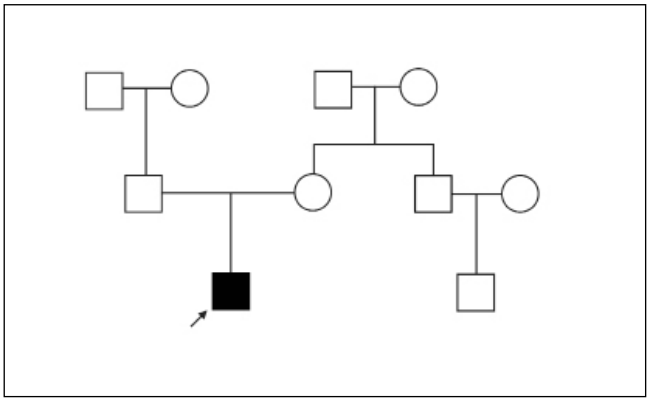

Figure 1. Pedigree of the family. Females are represented by circles and males by squares. The subjects with filled symbols have neuromuscular signs or symptoms while those with clear symbols are not affected. The proband is indicated by an arrow.

Table I. Motor and sensory nerve conduction studies.

Nerve	Onset (ms)	Amp	CV (m/s)
Ulnar motor left			
Wrist-Abductor digiti minimi	3.2	9.2 mV	
Below elbow-Wrist		9.1 mV	57.9
Above elbow-Below elbow		9.1 mV	50.0
Ulnar motor right			
Wrist-Abductor digiti minimi	1.97	11.3 mV	
Below elbow-Wrist		13 mV	47.4
Above elbow-Below elbow		12.9 mV	51.4
Median motor right			
Wrist-Abductor pollicis brevis	2.85	17.0 mV	
Elbow-Wrist		19.0 mV	58.3
Peroneus motor right			
Ankle-Extensor digitorum brevis	5.2	1.1 mV	
Fibular head-Ankle		1.1 mV	40.0
Popliteal region-Fibular head		1.0 mV	55.6
Peroneus motor left			
Ankle- Extensor digitorum brevis	5.5	1.3 mV	
Fibular head-Ankle		1.3 mV	39.1
Popliteal region-Fibular head		1.1 mV	43.5
Tibialis motor right			
Medial Malleolus-Abductor hallucis	4.75	5.5 mV	
Popliteal region-Medial malleolus		4.1 mV	44.2
Tibialis motor left			
Medial malleolus-Abductor hallucis	7.1	4.5 mV	
Popliteal region-Medial malleolus		4.5 mV	42.9
Suralis sensory right			
Middle lower leg-External malleolus	3.4	32.0 µV	48.5
Suralis sensory left			
Middle lower leg-External malleolus	3.2	48.8 µV	48.8
Ulnar sensory right			
Wrist-Digit V	2.2	37.5 µV	49.3
Median sensory right			
Wrist-Digit II	2.4	24.7 µV	57.4

Amp = amplitude; CV = conduction velocity.

Lumbosacral magnetic resonance imaging (MRI) was unremarkable. A Next-Generation Sequencing (NGS) panel comprising 57 genes associated with CMT, but not including the *SORD* gene, detected no pathogenic variants.
Since persistent mild hyperCKemia was noted (1.5 x Upper Limit of Normal [ULN]), we performed dried blood spot (DBS) screening for Pompe disease [6], lactic acid measurement, and search for Jordan's anomaly, all negative. A NGS panel containing 43 genes associated with distal and myofibrillar myopathies also yielded a negative result.

To evaluate the hypothesis of distal myopathy, we performed a gastrocnemius muscle biopsy with evidence of scattered angular fibres, and prevalence of severe myofibre degeneration and alterations suggestive of a protein surplus distal myopathy (Fig. 2). In particular, a wide variability of fibre size was evident with several small rounded atrophic fibres and a few large fibres. The endomysial connective tissue showed an increase with initial fibrosis of muscle tissue in some areas. With trichrome staining, several small and large fibres exhibited fuchsinophilic deposits in the sarcoplasm. Whorled and splitting fibres were also evident. Adenosine triphosphatase (ATPase) staining showed a poor distinction in fibre types, with a prevalence of type 2 fibres and a few large type 1 fibres with irregular areas of no activity. Immunohistochemical examination revealed a normal signal and distribution of the sarcolemmal proteins (dystrophin, sarcoglycans, merosin, caveolin, spectrin), negative staining for cytoplasmic p-tau deposits (SMI-31), and for autophagy markers (LC3). The inclusion bodies resulted positive at desmin and ab-crystallin staining (Fig. 2D) thus suggesting a myopathy with surplus protein.

Twenty-four-hour ambulatory (Holter) electrocardiography was normal except for a slight conduction delay with regular recovery in the right branch, while echocardiography showed only mild mitral and tricuspid insufficiency. The patient did not experience chest pain, dyspnea, or palpitations.

Whole Exome Sequencing was performed on the proband and his parents and two pathogenic [1] *SORD* variants in the heterozygous state were identified: c.458C > A (p.Ala153Asp) and c.757delG (p.Ala253Glnfs*27). Sanger sequencing was performed to confirm both variants and evaluate segregation among the patient's parents. We thus confirmed that these variants were in trans. Both variants are reported in the international registry of already described mutations (ClinVar) and are present in the database of human polymorphisms (GnomAD) with an extremely reduced frequency. Unfortunately, sor-

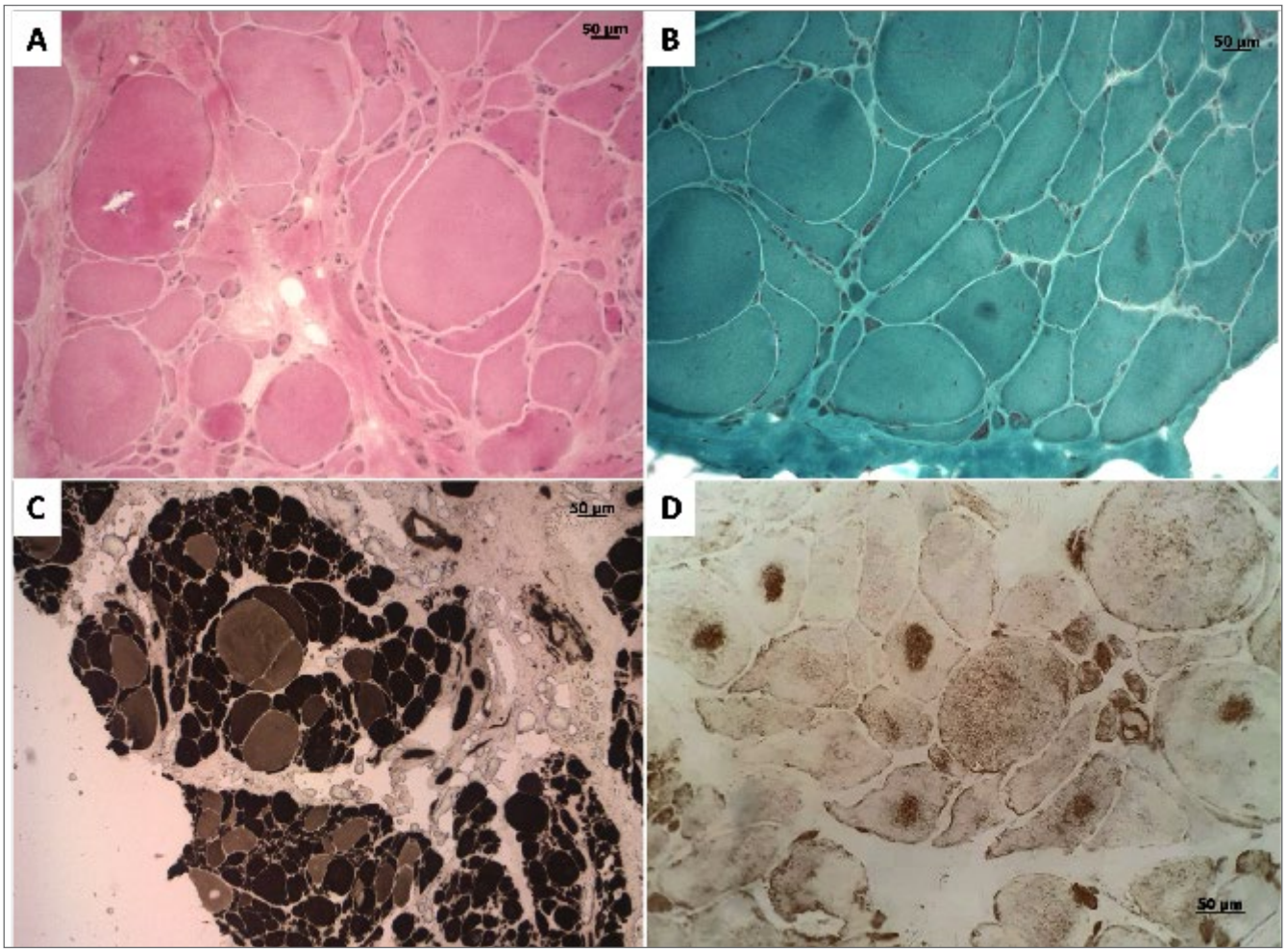

Figure 2. Right lateral gastrocnemius muscle biopsy. (A) Hematoxylin and eosin staining (HE) magnification 20x; (B) Modified Gomori trichrome staining (TG) magnification 20x; (C) ATPase at 9.4 staining (ATP) magnification 10x; (D) Immunohistochemistry for desmin magnification 20x. HE and TG display marked variability in the fibre diameter with a few large, rounded fibres and numerous small atrophic fibres with a disrupted dense sarcoplasm. The large fibres have a splitting, whorled appearance, and contain numerous internal nuclei. Some larger fibres also present irregular vacuolization. There are also a few degenerating fibres invaded by macrophages. The endomysial connective tissue is increased with initial fibrosis. At TG, some fibres, especially small atrophic fibres, contain cytoplasm dense bodies and "rods-like" fuchsinophil deposits. **ATPase demonstrates a diffuse predominance of type 2 fibres, grouped atrophy of type 2 fibres and hypertrophic type 1 fibres.** The inclusion bodies centrally located in the larger fibres are positive at desmin staining thus suggesting a myopathy with surplus protein.

bitol serum measurement was not performed.

Discussion and review of the literature

We describe a patient carrying two pathogenic variants in *SORD*, who presents persistent mild hyperCKemia and histologic signs supporting a muscular impairment, which has never been described in association with *SORD*-related disorders [1,3-5].

O'Donnell et al. recently identified fat accumulation and atrophy in the calf and less prominently in the thigh musculature of patients with *SORD* neuropathy using muscle MRI [7], but there are no descriptions of muscle histology in patients with *SORD* mutations since they are usually associated with neuropathy.

Motor neuron involvement associated with homozygous c.757delG mutation in *SORD* has recently been described [3] but our patient presented no signs indicative of upper motor neuron involvement, and even though EMG showed signs of denervation, no fasciculation potentials were observed. Moreover, the slow progression does not suggest motor neuron disease.

Mutations in other genes, such as *HSPB1* (heat shock protein B1) and *HSPB8* (heat shock protein 22), have been found to be responsible for combined muscle and nerve involvement with clinical pictures ranging from dHMN to distal myopathy/myofibrillar myopathy often with protein aggregates and inclusions [8,9]. Mutations in *BAG3* (Bcl-2-associated athanogene 3), which encodes for a multidomain cochaperone protein that forms a stable complex with HspB8 participating in the degradation of misfolded proteins, have recently been associated not only with myofibrillar myopathies but also with a late-onset axonal CMT phenotype [10]. *DNAJB2* has also recently been linked to both dHMN and rimmed vacuolar myopathy [11]. It should however be considered that dHMN can even determine a neurogenic myopathic picture, so the differential diagnosis with distal myopathies should always be considered. In the present case, neurophysiology did not help in distinguishing between axonal motor neuropathy and myopathy. The simultaneous presence of motor neuropathy cannot be ruled out. Interestingly, evidence of subclinical muscle involvement has recently been described in a few patients with *SORD* neuropathy [12], with a mild to moderate increase in serum CK levels, and more rarely with myogenic electrophysiological alterations or muscle edema on lower-limb MRI.

The histopathological picture of our case suggested a surplus or storage protein myopathy. This group is characterized by an excess of proteins present in a granular or filamentous form, such as desmin-related myopathies, actinopathy, and hyaline body myopathy [13]. Accumulation of desmin-positive material is the hallmark of most of the surplus protein myopathies probably because of defective protein catabolism, but different mutant proteins are sometimes involved in aggregate formation by accruing together with desmin within muscle fibres [13]. Despite the wide phenotypic heterogeneity, distal muscle involvement is a common feature of protein surplus myopathies [14].

Most *SORD* mutations are frameshift or splicing mutations suggesting a loss of function of sorbitol dehydrogenase [5], but the c.404A > G (p.His135Arg) variant of *SORD* has been associated with aggregate formation of sorbitol dehydrogenase with low protein solubility in *in vitro* cell functional studies with human fibroblasts [15]. Electron microscopic characterization of the deposits in our patient's muscle fibres could therefore be interesting.

As recently reported by Li L. et al. [12], mutations in *SORD* could be responsible for both motor neuropathy and myopathy. Having found no other genes potentially responsible for myopathy, neither with WES nor with a panel for distal and myofibrillar myopathies containing 43 genes, we believe that *SORD* may be the cause of the patient's myopathy. However, this is currently an associative finding that needs to be replicated in other families to be considered causative.

The recent finding of subclinical muscle involvement in some patients is intriguing. Li L. and colleagues suggest that the underlying mechanism of muscle involvement in SORD neuropathy is still to be elucidated and hypothesize that there may be an accumulation of sorbitol with increased osmolarity at the muscle level [12]. However, further studies on skeletal muscle cells and animal models are certainly needed to understand the molecular mechanisms better. The development of new animal models would also be essential since the C57BL/LiA mice and *Drosophila melanogaster* models of SORD deficiency cannot fully mimic the pathogenesis of *SORD*-related disorders [1,5,16,17].

Conclusions

This is an isolated case report of compound heterozygosity for two *SORD* mutations associated with histological signs of myopathy, suggesting a possible further enlargement of the phenotypic spectrum related to *SORD* mutations. Given the potential for treatment (with aldose reductase inhibitors) [1], searching for pathogenetic variants of *SORD* in patients with slowly progressive distal myopathy of unknown etiology could be useful.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Author contributions

SM, MG, CF: draft preparation, writing; MG, SM, CG, AS, CF: data collection and interpretation; TM, CF: interpretation of the muscle biopsy; EB, PM, MT, AG: interpretation of the genetic analysis; MG, AS, TM, EF, ES, CF, SB: review of the manuscript; SM, MG: submission of the manuscript.

Ethical consideration

This study was performed in line with the principles of the Declaration of Helsinki. The approval of the Ethics Committee was not necessary as no procedures other than those routinely performed were employed.

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