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# Unusual upper limb features in *SORD* neuropathy

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Dear Editor,

We read with interest the recent study by Grosz *et al* demonstrating the use of long read sequencing in their genetically undermined Charcot-Marie-Tooth (CMT) cohort to confirm compound heterozygous variants in *SORD*.[1] Since it was first reported, the phenotype of *SORD*-related CMT has consistently been found to be an uncomplicated length-dependent neuropathy; either distal hereditary motor neuropathy (dHMN) or a motor-predominant CMT2 phenotype, occasionally with intermediate conduction velocities. Patients typically develop walking difficulties in the second decade and the disease is slowly progressive, with distal weakness and wasting.[2,3] However, the patient identified in the study reported by Grosz *et al* exhibited an additional median neuropathy at the wrist and ulnar neuropathy not localised to the elbow, accompanied by positive, fluctuating sensory symptoms.

At our centre we have 12 patients with biallelic pathogenic variants in *SORD.* Their phenotype is either dHMN or CMT2. However, 92% (11/12) have either reduced upper limb sensory nerve action potentials (SNAPs) or borderline SNAP amplitudes for age. In contrast, only 50% (6/12) have abnormal lower limb SNAPs. In nine patients (75%) the upper limb SNAPs are unusually more severely attenuated than in the lower limbs (Table 1). Sensory symptoms were only reported in three of our cohort. Interestingly, upper limb conduction slowing in the intermediate range (25-45 m/s) in either median or ulnar nerves, was observed in 50% (6/12) of our patients, without any median entrapment at the wrist. Allowing for reduction in motor action potentials (MAPs), conduction slowing in the lower limbs was seen in only one patient, with a right common peroneal velocity of 29 m/s (MAP 3.3 mV, Patient 2, Table1). Unusual motor features were seen in five patients. Patient 1 has proximal denervation on EMG in tongue and masseter muscles, and developed a right

common peroneal nerve palsy without compression injury. Patient 5 has severe non-compressive median neuropathies and had successful bilateral tendon transfers. They also have pectoral wasting and mild scapular winging. Patient 6 has striking bilateral ulnar motor conduction block (CB) localised to the forearms and Patient 8 has almost 50% reduction in median motor responses proximally suggesting CB. Patient 11 has proximal ulnar conduction block with dispersion. Additionally Patient 10 has brisk upper limb reflexes and denervation in facial muscles but also has a second molecular diagnosis of Kennedy's disease.

We conclude that although mutations in *SORD* typically cause a motor-predominant, length-dependent neuropathy, there are some unusual but consistent features suggestive of a non-length-dependent process particularly involving upper limbs, with reduction of SNAPs and motor conduction slowing and block. There is a suggestion that patients are susceptible to mononeuropathy and mechanistic parallels with diabetic mononeuropathy should be considered, with elevated sorbitol levels potentially being implicated in pathogenesis. Finally, this distinctive phenotype should prompt clinicians to test for variants in *SORD*.

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**Conflict of Interest Statement**

There are no conflicts of interest to declare

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| Patient number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age at assessment | 34 | 43 | 39 | 28 | 55 | 23 | 18 | 48 | 18 | 45 | 36 | 71 |
| Genotype | Homo c.757del | Homo c.757del | c.757del ;c.298C>T | Homo c.757del | Homo c.757del | Homo c.757del | Homo c.757del | Homo c.757del | c.757del ;c.458C>A | Homo c.757del | Homo c.757del | Homo c.757del |
| Median motor conduction velocity (m/s) | 65 | 58 | 50 | 56 | 47 | 55 | 51 | 37 | 46 | 44 | 55 | 43 |
| Ulnar motor conduction velocity (m/s) | 59 | ND | 58 | 67 | 45 | 62 (33)$^{++}$ | 47 | 44 | 45 | 48 | 56 | 54 |
| Median SAP (μV) | 6 | 10 | 7 | 7 | absent | 4 | 6 | 2 | absent | 1 | 5 | absent[a] |
| Ulnar SAP (μV) | 4 | ND | 4 | 6 | absent | 2 | 5 | 2 | absent | absent | 6 | 4 |
| Radial SAP (μV) | 18 | 21 | 25 | 31 | 15 | 17 | 22 | 5 | 5 | 10 | 9 | 21 |
| Sural SAP (μV) | 12 | 24 | absent | 14$^{+}$ | 7 | 13 | 10 | 3 | 15 | 2 | 19 | 5 |
| Superficial peroneal SAP (μV) | 9 | 4[b] | absent | 11$^{+}$ | 2 | 10 | 16 | absent | 9 | 4 | 14 | 3 |
| Median MAP (mV) | 8.5 | 8.0 | 8.5 | 5.1 | 1.0 | 5.8 | 4.5 | 4.3* | 4.2 | 7.3 | 5.2 | 1.7 |
| Ulnar MAP (mV) | 8.4 | ND | 10.2 | 3.4 | 8.2 | 4.2^ | 12.6 | 6.1 | 3.9 | 4.9 | 6.9[c] | 7.2 |
| Common peroneal MAP (mV) | 1.8 | 3.3 | 1.5 | 0.3 | absent | 4.3 | 2.2 | absent | 0.3 | absent | 1.6 | 1.2 |
| Posterior tibial MAP (mV) | 3.0 | 4.1 | 0.6 | 8.3 | 0.2 | 4.5 | 2.0 | ND | 1.5 | 1.2 | 0.9 | 2.5 |

**Table 1 Neurophysiology** Median conduction velocity from wrist to elbow, motor amplitudes all recorded from most distal stimulation point. Sensory electrode on extensor digitorum brevis for common peroneal. All studies performed on right side apart from patient 4 and 7 upper limbs, and patient 10 (radial and upper limb motor) patient 12 radial. Radial responses are antidromic. *SAP* sensory action potential, *MAP* motor action potential, *Homo* homozygous, *ND* not done/available, *LL* Lower limb, *TA* tibialis anterior, $^{+}$studies performed one year later aged 29 yrs ^ above the wrist there was conduction block with dispersion bilaterally, $^{++}$reduced velocity more proximally (proximal value in parenthesis), *slowing in UL studies but normal

conduction velocities in LL and right median proximal conduction block, [a] compressive median neuropathy [b] common peroneal nerve palsy [c] proximal ulnar conduction block with dispersion. Corresponding protein changes: c.757del p.(Ala253Glnfs*27); c.298C>T p.(Arg100Ter); c.458C>A p.(Ala153Asp).

Patient gender is omitted from the table to maintain anonymity.