



## Split Hand Syndrome in a Family with *GARS*-Associated Axonal Neuropathy

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Dear Editor,

A 21-year-old man presented with weakness in both hands that had been present for 2 years. A neurological examination revealed bilaterally symmetrical distal motor weakness (MRC grade 4+) and atrophy in both hands with no sensory loss. The atrophy was confined to the lateral side of the hands including the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles, sparing the hypothenar muscles including abductor digiti minimi (ADM) on the medial side of the hands (Fig. 1A and B), thus suggesting dissociated atrophy of the intrinsic hand muscles. Nerve conduction study (NCS) indicated reduced compound muscle action potential (CMAP) amplitudes when stimulating the median nerve, but unremarkable findings in the ulnar nerve (Fig. 1E). Electromyography revealed chronic neurogenic denervation in the APB and FDI, but not in the other C8–T1 innervated muscles including the ADM and flexor carpi ulnaris. Cervical magnetic resonance imaging (MRI) revealed Arnold-Chiari type I malformation with focal syringomyelia at the C6–C7 level. There was no radiological evidence of Hirayama disease.

The 51-year-old mother of the patient had experienced chronic muscle weakness in both hands since her early twenties (Fig. 1C and D), and presented with heel-walking difficulty followed by toe-walking difficulty since her late thirties. Her electrodiagnostic test results were similar to those of her son (Fig. 1E). Her cervical MRI finding was unremarkable. The deceased grandfather of the patient had complained of similar muscular symptoms when he was 20 years old (Fig. 1F). Whole-exome sequence analysis revealed a heterozygous missense mutation of c.632C>T (p.Ser211Phe) in the glycyl-tRNA synthetase (*GARS*) gene of the affected patient and his mother, but not in his unaffected aunt. The patient and his mother were finally diagnosed with *GARS*-associated axonal neuropathy.

A pathogenic *GARS* mutation can phenotypically present as both Charcot-Marie-Tooth disease type 2D (CMT2D) and distal spinal muscular atrophy type V (dSMA-V).<sup>1-3</sup> Our patients with *GARS*-associated axonal neuropathy can be classified as dSMA-V due to the absence of sensory symptoms or signs.<sup>2,3</sup> A *GARS* p.Ser211Phe mutation was previously reported in a 19-year-old male with dSMA-V, who presented with intrinsic hand muscle atrophy since the age of 13 years.<sup>4</sup> However, *GARS*-associated axonal neuropathy might not have a clear genotype–phenotype correlation, considering that a *GARS* p.Asp500Asn mutation presented as two different phenotypes in an Italian family.<sup>3</sup> These cases show that a pattern of dissociated atrophy of the intrinsic hand muscles, which was termed split hand syndrome (SHS) by Wilbourn,<sup>5</sup> is observed during the course of their illness. SHS is considered a peculiar sign in the early stage of amyotrophic lateral sclerosis (ALS).<sup>6</sup> The NCS performed in our cases revealed a low split-hand index and reduced CMAP amplitude ratio between the thenar and hypothenar muscles bilaterally; these findings are electrophysiologically consistent with the SHS seen in ALS.<sup>7,8</sup> However, SHS still remains in the late stage of *GARS*-associated axonal neuropathy,<sup>1</sup> which may differ from that seen in early ALS. Not every case

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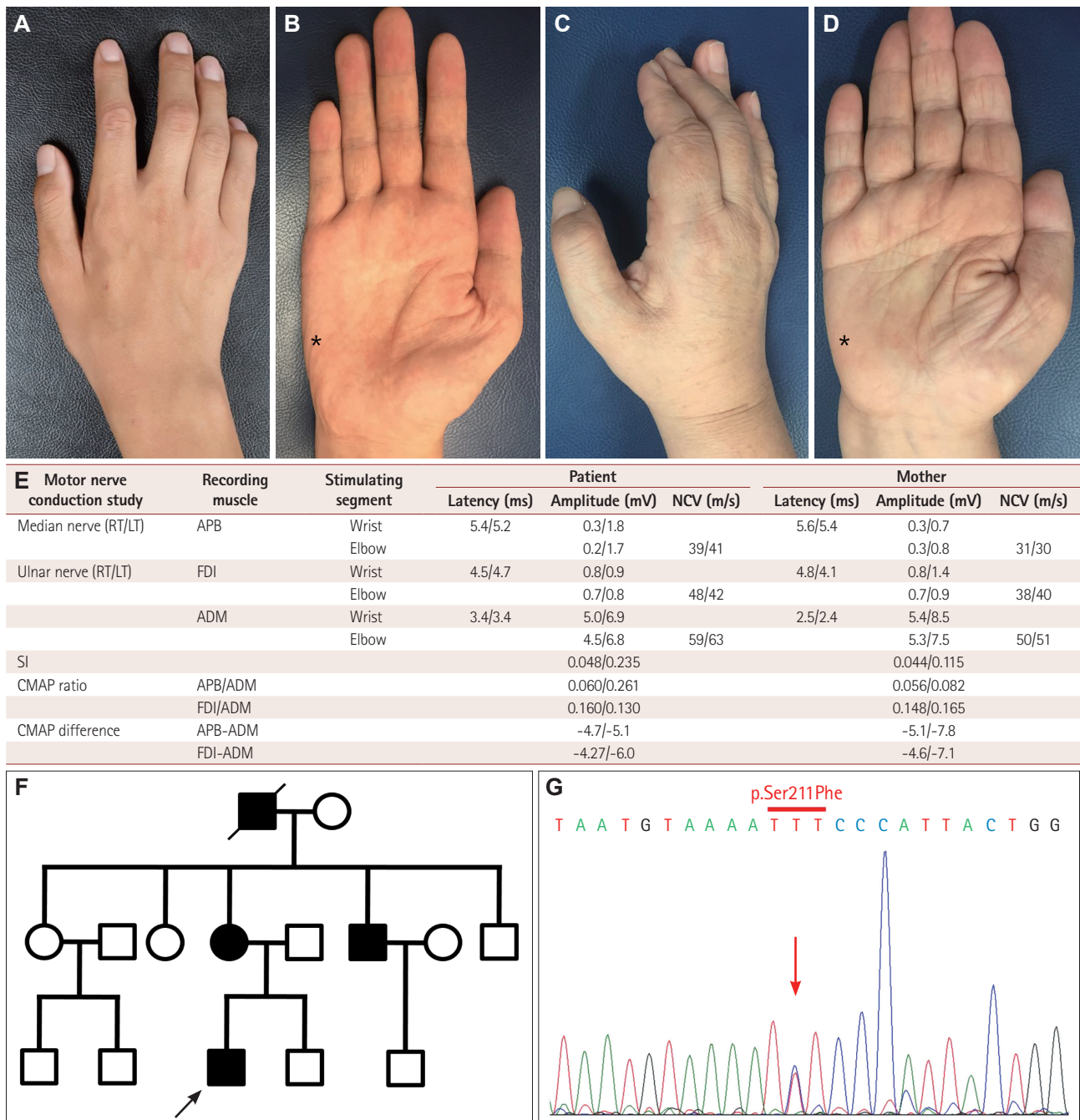
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of dSMA-V shows SHS during the course of illness,<sup>3,4</sup> but it may be more common in dSMA-V-like phenotype than in CMT2D.<sup>2</sup>

These observations indicate that SHS can be seen in GARS-associated axonal neuropathy, especially in a dSMA-V-like phenotype. Further studies are needed to explain the mecha-



**Fig. 1.** Clinical and electrodiagnostic features, pedigree, and electropherogram. The patient (A, B, and arrow in F) and his mother (C and D) showed atrophy in the APB and FDI muscles, with the sparing of the hypothenar eminence (asterisks) including the ADM muscle (E). NCSs in the patient and his mother showed that CMAP amplitudes were reduced in the APB and FDI muscles but relatively preserved in the ADM muscle. The electrophysiological parameters of split hand syndrome consist of the SI, and the ratio and difference between the thenar and hypothenar muscles. The SI was calculated by multiplying the CMAP amplitudes recorded in the APB and FDI muscles, and dividing that value by the CMAP amplitude recorded in the ADM muscle. The detailed electrodiagnostic results including electromyography in the patient and his mother are presented in the Supplementary Tables 1 and 2 (in the online-only Data Supplement). F: Pedigree of affected individuals shown as solid symbols. G: Mutational analysis revealed a nonsynonymous heterozygous missense mutation (c.632C>T, p.Ser211Phe, red arrow) in exon 7 of the GARS gene. ADM: abductor digiti minimi, APB: abductor pollicis brevis, CMAP: compound muscle action potential, FDI: first dorsal interosseus, LT: left, NCS: nerve conduction study, NCV: nerve conduction velocity, RT: right, SI: split-hand index.

nism underlying SHS in *GARS*-associated axonal neuropathy.

### Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2019.15.4.566>.

### Author Contributions

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### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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