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# A Novel HNPP Phenotype in Charcot-Marie-Tooth Type 2E With c.1319C>T Missense Mutation in the NEFL Gene

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Dear Editor,

Charcot-Marie-Tooth (CMT) disease is the most common cause of hereditary motor sensory neuropathy, with an estimated prevalence of about 1 in 2500 people.[1] Mutation in neurofilament light chain gene (*NEFL*) on chromosome 8q21 is related to inherited peripheral neuropathy for axonal-type CMT type 2E (CMT2E), demyelinating-type CMT type 1F (CMT1F), intermediate-type CMT, or the early-onset, severe phenotype of Dejerine-Sottas syndrome.[2] Hereditary neuropathy with liability to pressure palsy (HNPP) is a recurrent sensory and motor neuropathy caused by the deletion of the chromosome 17p11.2-p12 region including the peripheral myelin protein-22 gene (*PMP22*), whereas CMT 1A is due to duplication of *PMP22*. Here we report a noble mild HNPP phenotype in CMT 2E associated with the c.1319C>T missense mutation in *NEFL*.

A 39-year-old male presented with the sudden onset of continuous left-arm paresthesia for 1 day after taking a nap while resting on his left arm for 30 minutes. Initially he felt tingling in his left fourth and fifth fingers and on the medial side of the left forearm, as well as in the left medial thigh and left lateral ankle. Most of the tingling had disappeared several hours later without treatment, but that on the distal part of his left medial forearm persisted. He was diagnosed with thoracic spine kyphoscoliosis at the age of 14 years. He could perform the routine activities of daily living independently, including working as a restaurant manager without significant back pain. His family history was unremarkable. Physical and neurologic examinations revealed hypoesthesia to light tactile and pinprick stimuli in the area dominated by the left ulnar nerve. He had no muscle weakness or atrophy, and showed a normal flexor response. His deep tendon reflexes were normal. Neither pes cavus nor cerebellar sign was observed. Cervical spine x-ray revealed fusions and clefts that were probably attributable to congenital abnormality (Fig. 1A).

Chest computed tomography revealed kyphoscoliosis in the thoracic vertebrae (Fig. 1B and C). An electrophysiologic study indicated that the median motor nerve conduction velocity (MNCV) was more than 38 m/s on the left side, whereas the median MNCV was mildly decreased on the unaffected right side, and the amplitude for the sural nerve was markedly reduced. The ulnar MNCV was decreased and distal motor latency was slightly increased (Table 1). Deletion or duplication in *PMP22* was not detected, but targeted next-generation sequencing (NGS) including of 85 genes associated with CMT (Supplementary Material in the online-only Data Supplement) revealed that he had a heterozygous likely pathogenic variant of c.1319C>T (NM_006158.4) in *NEFL* that leads to the p.Pro440Leu (Fig. 1D), which has previously been reported in association with CMT2E or CMT1F. During a 1-year follow-up period, most of the patient's symptoms on the left hand and leg completely recovered, with only the mild tingling on the left forearm persisting.

This patient experienced the sudden onset of ulnar sensory mononeuropathy-like symptoms after possible physical compression, with an electrophysiologic study indicating periph-



 

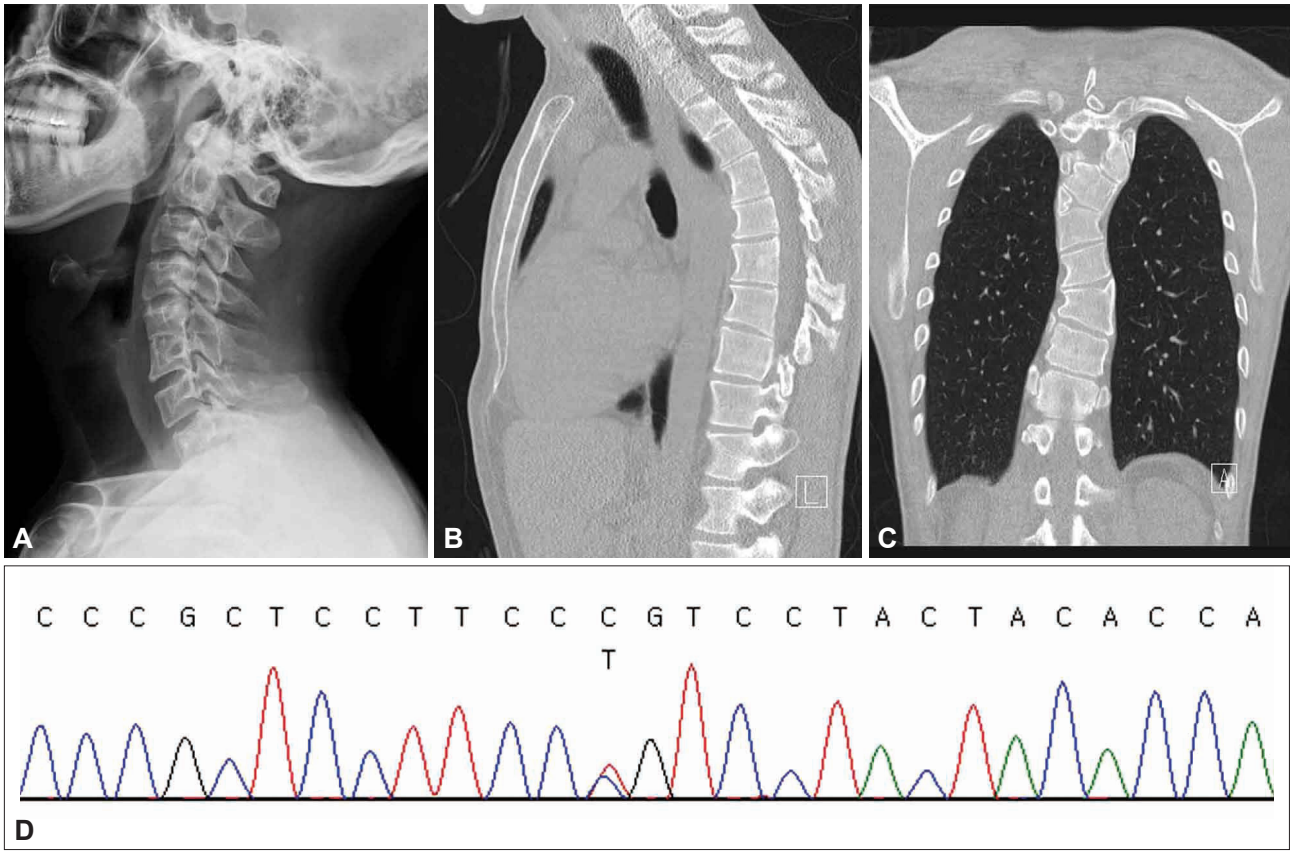


**Fig. 1.** Image study and Sanger sequencing of patient. A: C-spine x-ray. The C-spine x-ray revealed anterior and posterior element fusion of C5-6 and sagittal vertebral clefts of C6, C7 and T1 probably from congenital segmentation abnormality. B, C: Chest CT scan. Chest CT scan revealed benign looking, 4 mm of small nodule in RLL and kyphoscoliosis in his thoracic vertebrae. D: The Sanger sequencing showed heterozygous missense variant c.1319C>T (p.Pro440Leu) in *NEFL* gene.

eral polyneuropathy. Based on the discrepancy between the mild clinical presentation and moderate-to-severe findings in the nerve conduction study, the pressure-sensitive onset and almost-recovered neuropathy on his left arm could be a type of HNPP, and hence the genetic cause was examined. NGS targeting 85 genes related to CMT revealed the previously reported pathologic c.1319C>T heterozygous missense mutation in *NEFL*. To our best knowledge, only two CMT cases have been reported in association with the c.1319C>T mutation to date, with phenotypes of axonal-type CMT2E with limb muscle weakness and wasting,[3] and CMT1F with sensory deficit and pes cavus.[4] The CMT type has been classified into two major clinical subtypes of CMT2E and CMT1F in association with *NEFL* mutation based on the following simple and widely used measurements of the median MNCV in current practice: 1) a median MNCV of >38 m/s is considered as axonal-type CMT2E, whereas 2) MNCV of <38 m/s is considered as demyelinating CMT1F.[5] However, patients with CMT2E can have low MNCVs within the typical range of CMT1 with or without the early onset of severe disease.[5] In our patient, the median MNCV exceeded 38 m/s on the affected side, while additionally the sensory amplitudes were markedly reduced in all tested nerves. Therefore, it is reasonable to conclude that the CMT phenotype of our patient is axonal type 2E.

In conclusion, this is the first report of the mild HNPP phenotype in CMT2E due to the c.1319C>T heterozygous missense mutation in *NEFL*. This case provides novel insight into an unknown, different phenotype variant regarding the manifestation of the c.1319C>T heterozygous missense *NEFL* mutation.

## Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.2.244.

### Ethics Statement

Written informed consent was obtained from the patient.

### Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

**Table 1.** Findings of the electrophysiologic study

| Motor | DL (ms) | CMAP (mV) | NCV (m/s) | Sensory | SNAP (μV) | NCV (m/s) |
|---|---|---|---|---|---|---|
| R median | | | | R median | | |
| Wrist | 4.38 (<3.6) | 9.9 (>5) | | F-W | 4.3 (>10) | 27.8 (>41.26) |
| Elbow | 10.0 | 7.5 | 35.2 (>49.96) | W-E | 9.3 | 39.8 |
| L median | | | | L median | | |
| Wrist | 4.06 (<3.6) | 10.8 (>5) | | F-W | 6.3 (>10) | 28.9 (>41.26) |
| Elbow | 8.8 | 8.6 | 42.2 (>49.96) | W-E | 8.8 | 43.3 |
| R ulnar | | | | R ulnar | | |
| Wrist | 3.02 (<2.51) | 14.7 (>5) | | F-W | 2.9 (>8) | 25.6 (>39.26) |
| Elbow | 10.05 | 12.2 | 31.3 (>50.61) | W-E | 3.2 | 32.7 |
| L ulnar | | | | L ulnar | | |
| Wrist | 2.92 (<2.51) | 12.8 (>5) | | F-W | 2.5 (>8) | 24.8 (>39.26) |
| Elbow | 8.65 | 10.4 | 39.3 (>50.61) | W-E | 3.4 | 35.6 |
| R peroneal | | | | | | |
| Ankle | 4.58 (<4.78) | 6.8 (>4) | | R superficial peroneal | 1.2 (>4) | 34.9 (>40.5) |
| Fibular head | 16.67 | 4.8 | 27.9 (>41.85) | | | |
| L peroneal | | | | | | |
| Ankle | 5.26 (<4.78) | 2.7 (>4) | | L superficial peroneal | 1.2 (>4) | 34.4 (>40.5) |
| Fibular head | 16.09 | 2.3 | 31.6 (>41.85) | | | |
| R tibial | | | | | | |
| Ankle | 4.27 (<5.11) | 12.1 (>5) | | R sural | 0.5 (>6) | 26.4 (>34.6) |
| Knee | 15.16 | 7.5 | 34.3 (>40.63) | | | |
| L tibial | | | | | | |
| Ankle | 4.27 (<5.11) | 12.7 (>5) | | L sural | 0.65 (>6) | 26.4 (>34.6) |
| Knee | 14.74 | 9.6 | 35.5 (>40.63) | | | |

CMAP, compound motor action potential; DL, distal motor latency; E, elbow; F, finger; L, left; NCV, nerve conduction velocity; R, right; SNAP, sensory nerve action potential; W, wrist.


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Conceptualization: Jung Hwan Lee. Data curation: Ko-Eun Choi, Jisook Yim. Formal analysis: Ko-Eun Choi, Jisook Yim, Jung Hwan Lee. Methodology: all authors. Supervision: Jung Hwan Lee. Validation: Ko-Eun Choi, Jisook Yim. Visualization: Ko-Eun Choi, Jisook Yim. Writing—original draft: Ko-Eun Choi. Writing—review & editing: all authors.

## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.


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