A longitudinal clinicopathological study of two unrelated patients with Charcot–Marie–Tooth disease type 1E

Sir,

We document the clinical and pathological features of two patients with Charcot–Marie–Tooth disease type 1E (CMT1E) with sporadic *PMP22* point mutations who had two sural nerve biopsies 10 years apart.

Patient 1 (FC284, II-1) [Figure 1a] was not able to lift her head until approximately 7 months of age and could not even sit up alone at the age of 14 months. At the age of 24 months, she was unable to walk without support. She was wheelchair-bound and her functional disability score (FDS) was 7. At the age of 12, her muscle strength was GII in distal arms and legs and GIV in proximal arms and legs on the Medical Research Council (MRC) scale. She did not complain of any sensory symptoms; however, her vibration and position sense were reduced. Deep tendon reflex (DTR) was absent and pathologic reflex was not observed. Scoliosis, coxa valga, and pes planus were observed. At the age of 12 years, her neurological deficits had not changed and she was still wheelchair-bound. Nerve conduction study (NCS) showed no motor and sensory responses in the upper and lower limbs. Through whole-exome sequencing, p.Cys109Arg (c. 325T>C) mutation in the *PMP22* gene was identified [Figure 1c and e]. She underwent biopsies when she was 2 years of age and then at 12 years of age. The first sural nerve biopsy showed a marked reduction in the number (2295/mm^3 vs. 14170/mm^3 in normal controls) and area (3.7%, 22.3% of normal value) of myelinated fibers (MFs). MFs with onion bulbs (OBs) were observed in a density of 4452/mm^3 [Figure 2a-c]. Histogram showed a unimodal pattern and the proportion of MFs with a diameter less than 6 μm was 92.0% [Figure 2d]. The second biopsy revealed more aggravated re/demyelination [Figure 2e-g]. Compared to the first biopsy, the total number and area of MFs were remarkably reduced to 425/mm^3 and 0.7%. Moreover, the number of OBs decreased to 2275/mm^3. Most of the MFs were surrounded by Schwann cells and their cytoplasmic processes without evidence of inflammation. In the second histogram, the number of small MFs and unmyelinated fibers markedly increased [Figure 2h].

Patient 2 (FC285, II-1) [Figure 1b] could not lift his head until 6 months of age and could not sit up alone until 14 months of age. When he was 4 years old, he began to walk by leaning on a walker. His FDS was 6. At the age of 14 years, the muscle strength in the wrists and ankles was MRC GIII and that of proximal arms

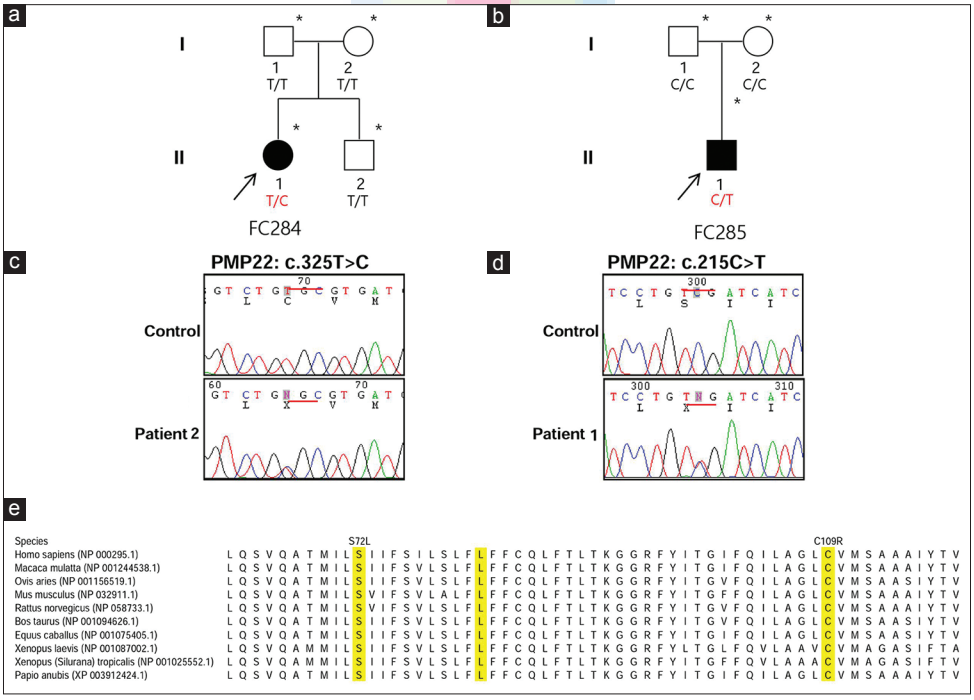

Figure 1: Two CMT1E pedigrees and identification of sporadic *PMP22* point mutations. (a) FC284, (b) FC285. Arrows (↗) indicate individuals whose exomes were used for this study, and asterisks (*) indicate individuals whose DNA was used for this study (□, ○: unaffected members; ■, ●: affected members). (c) FC284, *PMP22* c.325T>C (Cys109Arg) (d) FC285, *PMP22* c.215C>T (Ser72Leu). Confirmation of the causative mutations using the Sanger method. All causative mutations revealed by exome sequencing were confirmed using the capillary sequencing method. (e) Alignment of the amino acid sequences for mutation sites. Mutation sites are highly conserved between different species

and legs was GIV. His DTRs were absent and the pathologic reflexes were not observed. His vibration and position sense were reduced; however, pain and temperature sense were preserved. Scoliosis and pes planus were observed. He could walk with the assistance of a walker. NCS showed no motor and sensory responses in the upper and lower limbs. Through whole-exome sequencing, p.Ser72Leu (c.215C>T) in the *PMP22* gene was identified [Figure 1d and e]. Biopsies were performed at 4 and 14 years of age. In the first biopsy [Figure 3a-c], the number and area of MFs were remarkably reduced to 1491/mm^2 (14170/mm^2 in normal controls) and 2.2% (9.8% of normal value), respectively. OBs numbered 3388/mm^2. In the first histogram, the proportion of MFs with a diameter less than 6 μm was 98.5% [Figure 3d]. The second biopsy demonstrated more aggravated re/demyelination [Figure 3e-g]. The number and area of MFs were markedly reduced to 619/mm^2 and 0.9%, respectively. Profound myelination and concentric lamellation of Schwann cells around the hypomyelinated fibers without evidence of inflammation were noted. The second histogram revealed a left shift and a marked increase in small MFs and unmyelinated fibers [Figure 3h].

CMT1E, which is a rare subtype of CMT1 caused by *PMP22* point mutation, shows a more heterogeneous spectrum of phenotypes from mild demyelinating to severe demyelinating or dysmyelinating forms such as Dejerine–Sottas disease in comparison with CMT1A.[1,2] Clinically, our patients with *PMP22* point mutations (p.Cys109Arg and p.Ser72Leu) had early-onset disease, developmental delays, distal motor and sensory deficits, foot deformities, and hyporeflexia in common. NCS showed no motor and sensory responses in the upper and lower limbs. The patients presented with a severe, early-onset demyelinating neuropathy, which was similar to those seen in previous reports.[1,2] The genetic loci of S72L and C109R have been reported to be associated with an early-onset, severe demyelination, or dysmyelination neuropathy.[3-5] Our cases displayed profound demyelination with abundant OB formation of Schwann cell processes. In the present longitudinal and comparative analysis, we identified distinct demyelination as the essential pathology that CMT1E patients had in common. Furthermore, we performed a follow-up sural nerve biopsy in two CMT1E patients one decade after the first biopsy. Our results showed that the demyelinating process was not static, but ongoing.

Though many years have passed, our patients' functional disabilities have not been significantly exacerbated. As there was no worsening of disability in our cases, we assumed that their pathology did not deteriorate. Contrary to our expectations, the follow-up biopsy showed a marked aggravation of the demyelinating process and reduction in the number and area of MFs. Our study suggests that the extent of pathological change is not a major factor in determining functional disability. Unidentified components, including developmental differences and environmental factors influencing the growth process, may contribute to the extent of the functional disability. Therefore, supportive care, including proper exercise and nutritional supplementation, might play an important role in preventing the clinical progression of hereditary neuropathy.

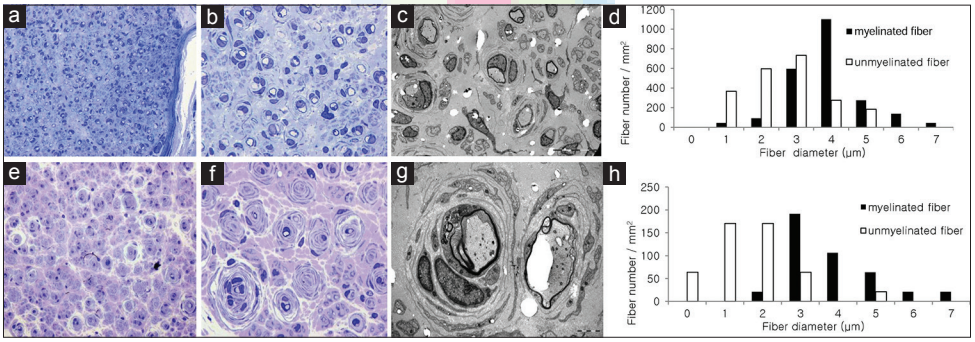

Figure 2: Transverse semi-thin sections and electron micrographs of the distal sural nerve of FC284. (a-c) First biopsy, (d) Histograms of the first biopsy showing the distribution of MFs and unmyelinated axons, (e-g) Second biopsy, (h) Histograms of the second biopsy showing the distribution of the MFs and unmyelinated axons (a and d: ×400, b and e: ×1000, c: ×4000, f: ×10000)

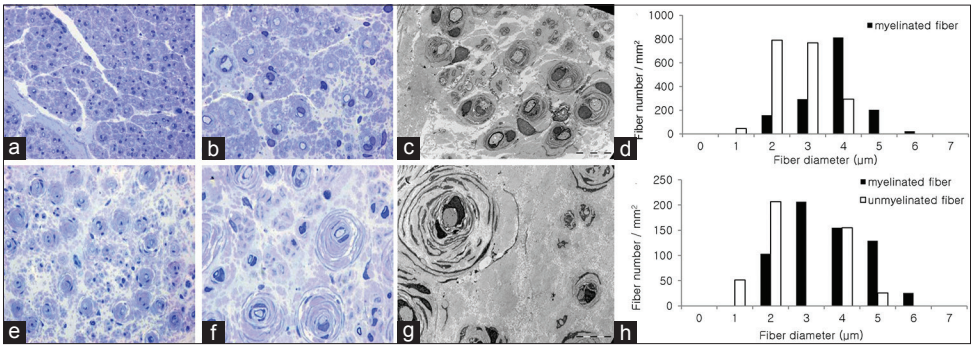

Figure 3: Transverse semi-thin sections and electron micrographs of the distal sural nerve of FC285. (a-c) First biopsy and (d) histograms of the first biopsy showing distribution of MFs and unmyelinated axons; (e-g) second biopsy; (h) histograms of the second biopsy showing distribution of MFs and unmyelinated axons (a and d: ×400, b and e: ×1000, c and d: ×3000)

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Conflicts of interest

There are no conflicts of interest.

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