Proximal Dominant Hereditary Motor and Sensory Neuropathy With Proximal Dominance Association With Mutation in the TRK-Fused Gene

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**Importance:** Hereditary motor and sensory neuropathy with proximal dominance (HMSN-P) has been reported as a rare type of autosomal dominant adult-onset Charcot-Marie-Tooth disease. HMSN-P has been described only in Japanese descendants since 1997, and the causative gene has not been found.

**Objectives:** To identify the genetic cause of HMSN-P in a Korean family and determine the pathogenic mechanism.

**Design:** Genetic and observational analysis.

**Setting:** Translational research center for rare neurologic disease.

**Participants:** Twenty-eight individuals (12 men and 16 women) from a Korean family with HMSN-P.

**Main Outcome Measures:** Whole-exome sequencing, linkage analysis, and magnetic resonance imaging.

**Results:** Through whole-exome sequencing, we revealed that HMSN-P is caused by a mutation in the TRK-fused gene (TFG). Clinical heterogeneities were revealed in HMSN-P between Korean and Japanese patients. The patients in the present report showed faster progression of the disease compared with the Japanese patients, and sensory nerve action potentials of the sural nerve were lost in the early stages of the disease. Moreover, tremor and hyperlipidemia were frequently found. Magnetic resonance imaging of the lower extremity revealed a distinct pattern of muscular involvement with a clearly different pattern than patients with Charcot-Marie-Tooth disease type 1A. Particularly, endoneurial blood vessels revealed marked narrowing of the lumen with swollen vesicular endothelial cells.

**Conclusions and Relevance:** The underlying cause of HMSN-P proves to be a mutation in TFG that lies on chromosome 3q13.2. This disease is not limited to Japanese descendants, and marked narrowing of endoneurial blood vessels was noted in the present study. We believe that TFG can affect the peripheral nerve tissue.


**C**harcot-Marie-Tooth disease (CMT), which is also called hereditary motor and sensory neuropathy (HMSN), is a clinically and genetically heterogeneous disorder of the peripheral nervous system. To date, more than 50 causative genes or loci have been reported to be associated with CMT at the Inherited Peripheral Neuropathies Mutation Database (http://www.molgen.ua.ac.be/CMTMutations/Mutations/) or in other reports. However, for many patients, the genetic causes of their disease are unknown.

Hereditary motor and sensory neuropathy with proximal dominance (HMSN-P), which is characterized by predominant proximal muscle weakness and distal sensory disturbances, is a rare autosomal dominant, adult-onset, peripheral neurodegenerative disorder. Until now, HMSN-P has been reported only in Japan or in Japanese descendants. Takashima et al mapped the locus on chromosome 3q14.1-q13. Later, they suggested a narrowed locus on 3q13.1 within 3.1 cM. Maeda et al also reported a candidate locus that resides within 7.3 Mb from chromosome 3q11-q13.1.

Video available online at www.jamaneuro.com

Whole-exome sequencing is an efficient tool for identifying underlying genetic causes. It has been proven to provide potentially important contributions to reveal the genetic causes of rare human dis-
cases. Whole-exome sequencing has recently been introduced in studies of CMT and has exhibited great accuracy in identifying rare genetic causes.

The TRK-fused gene (TFG) (MIM 602498), which lies on chromosome 3q13.2, was first identified in human papillary thyroid carcinoma as a fusion partner of the NTRK1 gene (MIM 191315). Despite the fact that TFG is ubiquitously expressed across several cancerous and normal tissues, its function remains unclear. Recent studies have suggested that TFG protein is implicated in regulating cargo export at the endoplasmic reticulum and in putative metastatic melanoma tumor suppression; however, its biological function was still largely unknown. In this study, we report what we believe to be the first non-Japanese family with clinical manifestations of HMSN-P and suggest a heterozygous mutation in TFG as the cause of the disease.

**METHODS**

**PARTICIPANTS**

This study included 28 members of a Korean family with autosomal dominant CMT (family ID: FC457, 12 males and 16 females) with proximal dominant involvement (Figure 1 and eTable 1). The study also included 750 healthy controls who had no clinical features or family history of CMT. Informed consent was obtained from all participants and from the parents of participants younger than 18 years according to the protocol approved by the institutional review board for Ewha Wonsans University, Mokdong Hospital, Seoul, Korea.

**CLINICAL AND ELECTROPHYSIOLOGIC ASSESSMENTS**

The clinical evaluation was performed by 2 independent neurologists (S.-S. Lee and B.-O. Choi). Information on deceased family members was obtained from the available relatives. Strength of the flexor and extensor muscles was assessed manually using the standard Medical Research Council scale. To determine the extent of physical disability, we used a functional disability scale. Sensory impairments were assessed in terms of the level and severity of pain, temperature, vibration, and position.

Neurophysiologic studies were carried out on 5 affected individuals (4 males and 1 female). Motor nerve conduction velocities and sensory nerve conduction velocities were determined. Amplitudes of compound muscle action potentials were measured from positive to negative peak values. Amplitudes of sensory nerve action potentials (SNAPs) were measured from positive peaks to negative peaks. Electromyography was performed in bilateral proximal and distal upper and lower extremity muscles.

**HIP, THIGH, AND LEG MAGNETIC RESONANCE IMAGING STUDIES**

Four individuals (III-23, III-27, III-29, and IV-17) with TFG mutation were studied with magnetic resonance imaging (MRI).
of the hip, thigh, and leg using a 1.5-T system (Siemens Vision) equipped with a phase-array multicoil. Leg imaging was carried out in axial (field of view, 24-32 cm; slice thickness, 10 mm; and slice gap, 0.3-1.0 mm) and coronal planes (field of view, 38-40 cm; slice thickness, 4.5 mm; and slice gap, 0.3-1.0 mm). The following protocol was used in all patients: T1-weighted spin echo (repetition time/echo time [TR/TE], 570-650/14-20; 512 matrices), T2-weighted spin echo (TR/TE, 2800-4000/96-99; 512 matrices), and fat-suppressed T2-weighted spin echo (TR/TE, 3090-4900/85-99; 512 matrices).19

HISTOPATHOLOGIC STUDIES

Histopathologic analyses, including an immunohistochemistry study with anti-TFG antibody (Abcam) of the distal sural nerves, were performed in 2 patients: 1 patient (III-27) at age 50 years and the other patient (III-29) at 48 years. The density of myelinated fibers (MFs), axonal diameter, and myelin thickness were determined directly from the semithin transverse sections using a computer-assisted image analyzer (AnalySIS; Soft Imaging System). Additional analysis also was performed at lower magnification of an electron microscope (×3000) for incidence of abnormal myelin, onion bulb formation, regenerative axonal clusters, and other findings.

CHROMOSOMAL MAPPING OF 3q1 REGION AND DETERMINATION OF 17p12 DUPLICATION

For the FC457 family, linkage analysis was performed on the reported HMSN-P locus (3q1-q2) and the surrounding region by genotyping of 19 fluorescent-labeled microsatellites (eTable 2).5,9 The 1.4 × 106-base pair duplication/deletion of 17p12, which is the most frequent genetic cause of CMT, was determined by genotyping of 6 microsatellites.20 Polymerase chain reaction products were resolved on the automated genetic analyzer ABI3130xl, and data were analyzed using the GENESCAN program (Applied Biosystems).

WHOLE-EXOME SEQUENCING

Whole-exome sequencing was performed for 4 individuals (affected, III-23, III-27, and III-29; unaffected, III-25). A standard shotgun exome sequencing library was prepared using the Human SeqCap EZ Capture Array, version 2.0 (III-23 and III-27) or version 3.0 (III-25 and III-29) (Roche-NimbleGen), and sequencing was performed using the HiSeq2000 Genome Analyzer (Illumina). Paired-end sequences were first mapped to the human reference genome UCSC assembly hg19 (http://genome.ucsc.edu), and reads mapping was achieved by the BWA program (http://bio-bwa.sourceforge.net/). Variants (single-nucleotide polymorphisms [SNPs] and insertions or deletions [indels]) were detected by the SAMTOOLS program (http://samtools.sourceforge.net/) and compared with common variants registered in dbSNP135 (http://ncbi.nlm.nih.gov/) and the 1000 Genomes Project database (http://www.1000genomes.org/). Functionally significant cosegregating variants were selected from 4-sample exome sequencing data. The complementary DNA numbering was achieved with +1 corresponding to the A of the ATG initiation codon.

TRANSCRIPTOME SEQUENCING

The RNA-sequencing data were generated from a patient (III-29, a 48-year-old woman [F/48]) and 2 individuals serving as healthy controls (F/37 and F/38). The complementary DNA library was prepared using the TruSeq RNA library kit (Illumina). The sequencing protocol consisted of total RNA extraction from the biopsy of distal sural nerve and polyA RNA extraction, RNA fragmentation, random hexamer primed reverse transcription, and 100nt paired-end sequencing by HiSeq2000. To estimate expression levels and identify alternative spliced transcripts, the RNA-Seq reads were mapped to the human genome using TopHat (version 1.3.3; http://www[tophat.cbcb.umd.edu). The transcript levels were calculated and the relative transcript abundances were measured in FPKM (fragments per kilobase of exon per million fragments mapped) using Cufflinks. To discover gene fusion from RNA-seq data, the defuse program (version 0.4.3; http://sourceforge.net/apps/mediawiki/defuse/) was used.

CAPILLARY DNA SEQUENCING AND IN SILICO ANALYSIS

The candidate variants considered to be causative mutations were confirmed by the capillary sequencing method using the automatic genetic analyzer ABI3130xl with the BigDye terminator cycle sequencing kit (Applied Biosystems). In silico predictions were performed using SIFT (http://sift.jcvi.org/) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/).

LOCALIZATION AND CYTOTOXICITY OF TFG

Mammalian-expressible TFG plasmids were constructed using pcDNA 3.1 vector. For mutant TFG, Pro-285 residue (CCT) was substituted with Leu (CCT) by oligonucleotide-directed mutagenesis. Immunoblot assays were performed with routine methods using anti-TFG antibody (Abcam) after expression of TFG in HEK 293T cells. The cytotoxic effects of TFG mutant on the NSC-34 cells were determined by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay kit (Invitrogen) in the NSC-34 cells, following the manufacturer’s instructions. To determine the localization of TFG, wild-type and mutant-type pEGFP-N1-TFG were transfected into the NSC-34 cell line and Lipofectamine 2000 (Invitrogen). Location of TFG protein was visualized by N-terminal–fused green fluorescent protein in the differentiated NSC-34 cells under fluorescent microscope.

RESULTS

CLINICAL MANIFESTATIONS

The clinical manifestations are summarized in Table 1. The ages at onset ranged from 27 to 48 years for 5 affected individuals. In 3 patients (III-23, III-27, and III-29), cramping as well as fasciculation were noted, and all 3 of them experienced hand tremor and rapid disease progression compared with patients in previous reports.6,7,21 In the fourth generation, patient IV-11 reported proximal lower limb weakness at 29 years, and patient IV-19 felt frequent fasciculations at 27 years. However, no symptoms were noticed in participants IV-9 (F/32), IV-10 (F/33), IV-12 (F/28), and IV-17 (M/23).

Physical examination revealed no pes cavus in any affected individuals. In addition, dysphagia, dysarthria, and bulbar symptoms were not observed. Hip abduction (Medical Research Council, G0/5 [no power] to G2/5 [mild power]) was markedly weaker than hip adduction (G1/5 [low power] to G5/5 [full power]) and extension (G1/5 to G3/5). Vibration and position senses were more severely disturbed than were pain and tempera-
tured senses. Areflexia was noted in the very early stages of the disease, but pathologic reflexes were not found. The frequency of hyperlipidemia was high (80% [4 patients]) but that of hyperglycemia was low (20% [1 patient]) compared with the frequency in Japanese patients.6,21 Elevated serum creatine kinase levels were noted in patients III-27 and III-29.

Sensory nerve action potentials of the sural nerves were lost in the early stage of the disease. Although compound muscle action potentials in the tibial motor nerves of patient III-29 were within the normal range, SNAPs in sural nerves were not elicited. Needle electromyography showed abundant fasciculation potentials and neurogenic motor unit action potentials.

Family members reported that the proband’s deceased grandfather (I-1), father (II-9), and 2 sisters (III-20 and III-22) had proximal muscle weakness. The initial symptoms started after their fourth decade, and they became bedridden 6 to 8 years later.

HIP, THIGH, AND LOWER LIMB MRI FINDINGS

Results of an MRI were normal in an asymptomatic individual (IV-19), but hypertensive signal abnormalities were observed in the lower limb muscles of 3 symptomatic individuals (III-23, III-27, and III-29). The T1-weighted images demonstrated marked signal changes and atrophies in the hip muscles rather than the thigh or leg muscles; therefore, MRI findings of fatty infiltrations were more affected proximally (Figure 2A, E, I, and M). It is noteworthy that gluteus minimus and medius muscles were initially involved and revealed the most severe fatty hypertensive signal changes, but tibialis anterior muscles were spared in the later stages.

We observed a sequential pattern of muscle involvement associated with disease duration and severity. In the early disease stage, diffuse fatty infiltration was observed in the gluteus minimus and to a lesser degree in the gluteus medius; in later stages, the infiltration was...
present in the gluteus maximus (Figure 2B, F, J, and N). At the thigh level, there was selective severe involvement of the semitendinosus muscles, but the adductor muscles, vastus medialis, and intermedius muscles were relatively spared (Figure 2C, G, K, and O). In the legs, gastrocnemius and peronei muscles showed initially equal involvement; however, tibialis anterior muscles were not involved until the later stages (Figure 2D, H, L, and P).

HISTOPATHOLOGIC FINDINGS

The sural nerve biopsy of III-29 revealed the absence of large MFs, with remaining medium and small MFs (4653/mm²), and showed the unimodal distribution pattern with loss of large MFs (Figure 3A). Ultrastructural micrographs showed MFs with an irregular thickness of myelin, thick MFs, and occasional regenerating axonal clusters (Figure 3B and C). The histopathologic features of patient III-27 were similar to those of patient III-29 but became more severe in its degree of changes. Immunohistochemical analysis with anti-TF2G antibody showed similar TFG protein distribution between 2 control cases (37- and 38-year-old women) and 2 patients (III-27 and III-29) (data not shown).

ENDONEURAL BLOOD VESSEL WITH SWOLLEN VESICULAR ENDOTHELIAL CELLS AND NARROWED LUMEN

One patient’s (III-29) endoneural blood vessels displayed marked narrowing of the lumen with swollen vesicular endothelial cells (Figure 3E) compared with the healthy control (Figure 3D, F/38). In particular, patient III-27 revealed extensive edematous changes of endothelial cells with a nearly obstructed lumen (Figure 3F). Concentric multilamella collections of basal lamina were prominent in both patients.

IDENTIFICATION OF LINKAGE DISEQUILIBRIUM IN THE 3q12-q25 REGION

Chromosomal mapping of the 3q region revealed a linkage disequilibrium region in the 3q12-q25 from D3S3652 to D3S3531, which spans 52.2 megabase pairs (Mbp) (Figure 1 and eFigure 1). Although the linkage region could not be narrowed into a short distance, it overlaps with the Japanese HMSN-P locus6,7 between D3S1592i and D3S1083i (4.8-Mbp interval) but slightly deviates from the narrow locus (eFigure 1).9

Figure 2. Hip, thigh, and leg magnetic resonance images (MRIs) of a clinically unaffected individual (IV-17, A-D) and 3 symptomatic individuals (III-29, E-H; III-27, I-L; and III-23, M-P) with TFG mutation. A 23-year-old man (IV-17) did not experience any symptoms, and MRIs of the hip (A and B), thigh (G), and leg (D) revealed normal findings. A 48-year-old woman (III-29) with 2 years’ disease duration showed atrophy and fatty changes in gluteus minimus and medius muscles (arrow, E) but relatively preserved gluteus maximus muscle (arrowhead, F). At the thigh level (G), the semitendinosus muscle (open arrowhead) was severely damaged, and vastus lateralis and sartorius muscles (arrowhead) were involved. On the leg (H), we found mild fatty changes in the gastrocnemius muscle (arrow); however, the tibialis anterior muscle (arrowhead) was not involved. A 51-year-old man (III-27; I-L) with 3 years’ disease duration had more progression of fatty infiltrations than his younger sister (III-28). In a 56-year-old man (III-23; M-P) with 11 years’ disease duration, we observed diffuse severe atrophy and fatty change of his whole lower limb muscles, including the hip (N). Very minimal muscle fiber remained in the adductor longus on his thigh (O), and the muscle fiber was relatively intact in the anterior compartment, especially the tibialis anterior muscles on the leg (P).
FILTERING OF NONSYNONYMOUS VARIANTS FROM WHOLE-EXOME DATA

The exome sequencing data of 4 samples are summarized in Table 2. The mean total sequencing yield was approximately 8.79 giga base pairs/sample, and the coverage rate of targeted exon regions (≥10×) was 92.6%. The average number of observed variants per sample was 70,645 SNPs and 8,427 indels, respectively. Of these, functionally significant variants (e.g., missense, frameshift, stop-gain, stop-loss, and coding indel) were 9,856.8/sample. When the nonsynonymous variants were eliminated by the dbSNP135 and 1000 Genomes Project databases, each sample exhibited 165 to 348 variants. Finally, we filtered cosegregating variants from the exome data of 4 individuals (e.g., present in 3 affected individuals [III-11, III-14, and III-16] but absent in the unaffected individual [III-6]), and then only 22 functionally significant variants remained (Table 3). Except for a nonsense mutation (c.753G>A, W251X) in the PAICS gene, all other variants were missense mutations.

IDENTIFICATION OF A P285L MUTATION IN TFG

When the 22 nonsynonymous variants were examined in all family members, a c.854C>T (P285L) mutation in TFG variants was cosegregated only with the affected members (Figure 1). The TFG is located within the link-
age disequilibrium region between D3S1592i and D3S3652 (eFigure 1). It is located on the HMSN-P linkage maps by Maeda et al7 and Takashima et al8; however, it is deviated from the 1-cM–narrowed map.9

Specifically, the P285L mutation in TFG was confirmed by the Sanger sequencing method (Figure 4A). It was completely cosegregated with affected individuals of second and third generations in the FC457 family (eTable 1 and Figure 1). Although the mutation was also identified in 4 unaffected individuals of the fourth generation (IV-9, IV-10, IV-12, and IV-17), they are younger than the age at onset (23-33 years), whereas the affected individuals' mean age at onset was 39 years.

The TFG mutation was not found in 750 healthy controls, and the mutation site was well conserved between different animal species (Figure 4B). In silico analysis also predicted that the mutation may affect protein function, with scores of 0.01 (SIFT) and 2.25 (PolyPhen-2).

In addition to the TFG-P285L mutation, a Y317H mutation in GPR128 was identified within the linkage disequilibrium region (eFigure 1). The GPR128 is located on chromosome 3q12.12 near the equilibrium region between D3S1592i and D3S3652; however, the Y317H mutation was found in an elderly unaffected woman (II-6, 89 years old) who revealed no symptoms of HMSN in careful clinical examinations. The GPR128 mutation site was not conserved in different species, and in silico analysis also predicted toleration of the mutation site. Therefore, the GPR128 mutation was not considered the genetic underlying cause, although it was not found in 500 controls. All functionally significant variants in the CMT-relevant genes could be excluded from the causative mutation. Exome data from the proband (III-14) revealed 15 nonsynonymous variants in 10 CMT genes; however, no variant was cosegregated with affected individuals (eTable 4). The 17p12 duplication that is the underlying cause of CMT type 1A disease was also excluded by pretesting before the exome sequencing.

RNA-seq data revealed TFG expression in the peripheral nerves but with no significant difference in the affected individuals compared with the healthy controls (eFigure 2). Although the TFG was first reported to be a fusion partner of the NTRK1 gene,13 the RNA-seq data revealed no TFG fusion with other genes, including NTRK.

In the literature,6-8 HMSN-P has been described only in Japanese descendants; however, we could not find any record of a blood relationship between the present Korean and Japanese patients. Therefore, to our knowledge, this is the first report of a family with HMSN-P outside of Japan who are not Japanese descendants. Through whole-exome sequencing of 4 individuals, we identified a novel heterozygous P283L mutation in TFG as the underlying cause of HMSN-P. The TFG locus is in accordance with previous reports.11-12 On completion of the present study, Ishiura et al21 independently reported a TFG mutation as a cause for HMSN-P in a Japanese family. Interestingly, the mutation is the same as in our cases.

Figure 4. Sequencing chromatograms and conservation analysis of c.854C>T (Pro285Leu) in TFG. A, Confirmation of the mutation by capillary sequencing. The heterozygous c.854C>T mutation was cosegregated in the affected individuals but was not found in the controls. B, Conservation analysis. The mutation site (arrow) and surrounding amino acid sequences are well conserved between the different species.

Clinical heterogeneities were revealed between Korean and Japanese patients. In our group of patients, hand tremors were present in the early stages of the disease, but this had not been recorded in the Japanese patients.6,7,21 The disease duration from symptom onset until a bedridden state was relatively short in the Koreans (6-8 years) compared with the Japanese (10-25 years).6,21 Furthermore, Ishiura et al21 suggested that SNAPs of the sural nerve were lost in the later stage of this disease, but the present study revealed it in the early stage. Even though patient III-29 had normal compound muscle action potentials in the tibial motor nerve, she showed no SNAPs in the sural nerve. Furthermore, SNAPs in patient IV-19 showed a low limit of the normal range in the very early stage of the disease. The frequency of hyperlipidemia was high (80%) in the Korean patients compared with that of the Japanese individuals (38%).21 Moreover, hyperlipidemia was observed in the clinically asymptomatic individual (IV-17); thus, it may be useful as a biomarker to evaluate presymptomatic evidence of HMSN-P.

Detailed MRI analysis revealed a distinct pattern of muscular involvement in HMSN-P. Marked hypertensive signal changes in the hip muscles compared with those in the thigh or the leg muscles were well related to the proximal dominance; however, those signal changes were clearly different from the ones in patients with CMT having length-dependent neuropathy.9,22 Because the earliest and most severe changes were seen in the gluteus minimus and medius muscles, the present group of patients showed a waddling gait (video). Furthermore, leg
MRI showed that tibialis anterior muscles were not involved until the later stage of the disease. Those were very different from the MRI features of CMT type 1A\textsuperscript{19,22} and might explain why all reported patients with HMSN-P did not have pes cavus, which usually is seen in CMT.

The endoneural blood vessels in the sural nerve of the patients clearly revealed moderate to marked narrowing of the lumen and enlarged endothelial cells with swollen vesicular appearance (Figure 3D-F). Although the significance of the blood vessel change is uncertain and further studies are needed, the narrowing of the endoneural blood vessels may explain the proximal dominant weakness.

The in vitro expression of wild-type \textit{TFG} revealed that \textit{TFG} proteins can be expressed in the neurites of the NSC-34 motor neuron cells (Figure 5A). However, the P285L mutation did not affect the cellular localization of the \textit{TFG} protein (not shown) and viability of the transfected cells (Figure 5B). In addition, the length of the neurites and size of soma in cells with P285L-\textit{TFG} were unchanged compared with those of the wild type (data not shown). In HEK 293T cells, expression levels were not different between wild-type \textit{TFG} and P285L-\textit{TFG} (Figure 5C). Some cells with P285L-\textit{TFG} transfection showed punctate or inclusion-like structures. However, this was also observed in cells with wild-type \textit{TFG} (Figure 5D). These data may indicate that simple transient expression of mutant \textit{TFG} in neuronal or easily transfectable mammalian cells is not enough to demonstrate the neurodegeneration in vitro.

The present study suggests that a missense mutation in \textit{TFG} provides the underlying cause of HMSN-P with dominant inheritance. We also suggest that \textit{TFG} could play an important role in the peripheral nervous system.

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