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Brief communication

# HMSN-P caused by p.Pro285Leu mutation in *TFG* is not confined to patients with Far East ancestry

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ABSTRACT

Hereditary motor and sensory neuropathy with proximal predominance (HMSN-P) is a rare disease so far identified only in individuals of Far East ancestry. Here, genome-wide linkage analysis and exome sequencing in an Iranian pedigree with 16 members affected with a neuromuscular disease led to identification of a mutation in TFG that causes p.Pro285Leu as cause of disease. The very same mutation was reported as cause of HMSN-P during the course of the study. Phenotypic analysis in conjunction with genetic data revealed that the Iranian patients were also affected with HMSN-P. Therefore, HMSN-P is not confined to the Far East and may simply not have been diagnosed in other populations. Haplotype analysis suggests at least 3 independent origins for mutated alleles that cause p.Pro285Leu. The phenotypic data gathered included subjective, biochemical, nerve conduction, electromyography, and muscle magnetic resonance imaging data. Comparison with patients with same disease in previous publications showed that clinical variability exists, sensory nerves are prominently affected, and proximal and distal muscles are involved.


## 1. Introduction

Hereditary motor and sensory neuropathy with proximal predominance (HMSN-P) is the name given to a recently described and apparently rare neuromuscular disease. Its present description emphasizes proximal dominant muscle weakness and atrophy and also includes mild sensory dysfunction, fasciculations, absence of deep tendon reflexes, and axonal degeneration in the peripheral nerves (Takashima et al., 1997). The condition has been described in families of Japanese descent and 1 Korean family (Campellone, 2013; Ishiura et al., 2012; Lee et al., 2013; Miura et al., 2008; Patroclo et al., 2009; Takahashi et al., 2007; Takashima et al., 1997, 1999). Recently, genetic analyses showed that a heterozygous mutation in *TFG* that encodes the tyrosine receptor kinase (TRK)-fused protein was the cause of HMSN-P in 2 families from Okinawa in Japan, 2 families from Kansai in Japan, and the 1 family from Korea (Ishiura et al., 2012; Lee et al., 2013). The same mutation that causes p.Pro285Leu was identified in all the families. Genetic analysis in 1 HMSN-P family from Kumamoto in Japan showed absence of linkage to the locus wherein *TFG* is positioned (Miura et al., 2008). Another mutation in *TFG* that causes p.Arg106Cys was identified in an Indian hereditary spastic paraplegia family (Beetz et al., 2013). Two *TFG* missense mutations in sporadic amyotrophic lateral sclerosis (ALS) patients were recently reported (Kawarai et al., 2013).

*TFG* was originally identified during genetic analysis of thyroid carcinomas and other cancers (Greco et al., 1995; Hernández et al., 1999; Hisaoka et al., 2004). The gene was involved in translocation events that created fusion oncogenes. In studies with *Caenorhabditis elegans*, it was shown that the homolog of the human TFG affects Golgi assembly and is localized at endoplasmic reticulum (ER) exit sites in various tissues including muscle and is involved in secretory processes (Witte et al., 2011). With respect to HMSN-P, the p.Pro285Leu mutation may also affect protein homeostasis and ER and Golgi functions (Ishiura et al., 2012; Yagi et al., 2014). The genes of several hereditary neurologic disorders including ALS and Charcot Marie Tooth diseases have roles in ER functions (Ito and Suzuki, 2007, 2009; Kanekura et al., 2006, 2009; Lin and Popko, 2009; Rossor et al., 2013; Roussel et al., 2013; Walker and Atkin, 2011; Yagi et al., 2011).

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Here, we report identification of the same p.Pro285Leu mutation in a large Iranian HMSN-P pedigree. To the best of our knowledge, this is the first report of HMSN-P in patients whose ancestry is not in the Far East. We gathered detailed clinical, electrodiagnostic (EDX), and muscle magnetic resonance imaging (MRI) data on the Iranian patients and compared these with previously reported HMSN-P patients.

## 2. Subjects and methods

This research was performed in accordance with the Declaration of Helsinki and with approval of the ethics board of the University of Tehran.

### 2.1. Subjects

The HMSN-159 pedigree studied here includes at least 16 affected individuals distributed in 4 generations (Fig. 1). The patients, who were diagnosed with an atypical motor neuron syndrome with sensory involvement, were referred to us for genetic analysis. Mutation screening of the 3 most common ALS-causing genes failed to identify mutations (Sabatelli et al., 2013). Inheritance was autosomal dominant. Genetic analysis and medical examination as described in the following revealed that HMSN-159 patients are affected with HMSN-P.

### 2.2. Genome-wide linkage analysis

Genome-wide single-nucleotide polymorphism genotyping was carried out using HumanCytoSNP-12v2-1_C BeadChips (Illumina, San Diego, CA, USA). Merlin was used to attain logarithm of odds scores under assumption of autosomal dominant inheritance and disease-allele frequency of 0.0001 (Abecasis et al., 2002; Takashima et al., 1997). An affected only analysis with 7 affected individuals was performed (Fig. 1).

### 2.3. Exome sequencing

Exome sequencing Illumina HiSeq 2000 system (Illumina) was done on the DNAs of 1 unaffected individual (HMSN-159-IV26) and his 2 affected sons (HMSN-159-V14 and HMSN-159-V16). Sequence alignment and variant calling were performed against human reference genome UCSC NCBI37/hg19. Preliminary filtering of sequence variations was done to identify all heterozygous changes present in both affected siblings that were absent in their father and that were positioned within the locus identified by linkage analysis. Subsequently, single-nucleotide polymorphisms with a reported minimal-allele frequency in the dbSNP database (http://www.ncbi.nlm.nih.gov/), the 1000 Genome project (www.1000genomes.org), or the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/), or observed in the exomes of 25 unrelated healthy Iranians or Iranians affected with nonneurologic diseases were removed. Finally, variations that did not affect amino acid change or splicing were filtered out.

### 2.4. Screening of c.854C>T in TFG and c.1324T>C in ZBTB11

Exon 8 of *TFG* that contains nucleotide c.854 and exon 4 in *ZBTB11* that contains nucleotide c.1324 were polymerase-chain reaction (PCR) amplified from the DNAs of 8 affected and 5 asymptomatic individuals. The amplicons were sequenced using the Sanger method. The variations were also screened in 420 Iranian control subjects by a PCR-restriction fragment length polymorphism protocol or an allele specific PCR protocol.

### 2.5. Electrodiagnostic and muscle MRI studies

EDX that included nerve conduction studies (NCS) and needle electromyography (EMG) was done according to standard procedures (Dantec Keypoint G4, Natus, CA, USA). Pelvic, thigh, and calf MRI studies were performed using a 1.5-T system (MAGNETOM Avanto 1.5 Tesla, Siemens, Germany). Leg imaging was performed in axial and coronal planes. T1-and T2-weighted spin echo protocols were used.

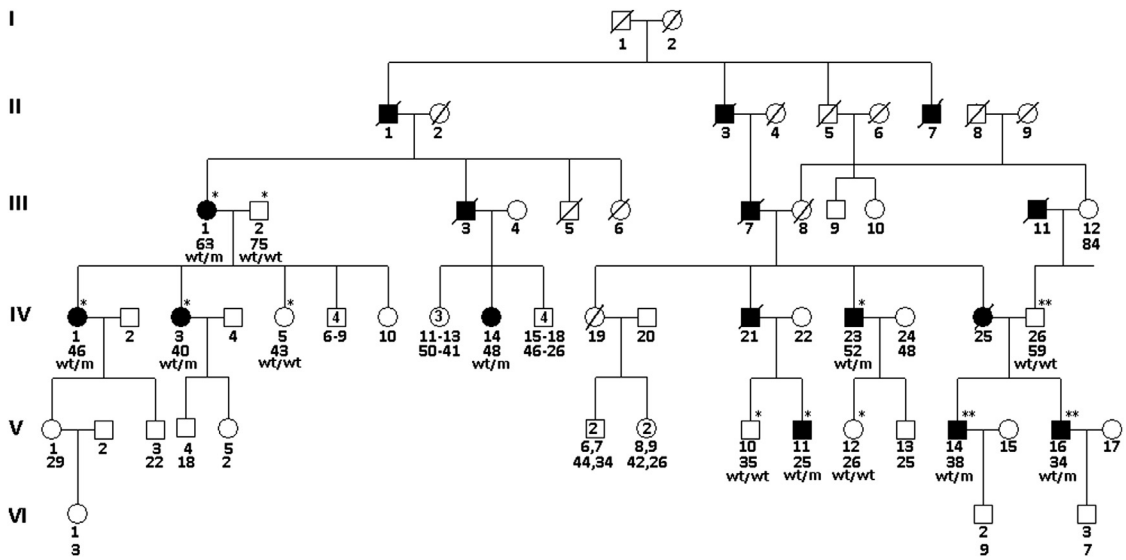


**Fig. 1.** Iranian HMSN-P pedigree with p.Pro285Leu mutation in *TFG*. Present age (years) of some individuals is indicated under their ID numbers. *TFG* genotypes of individuals tested are presented. Filled circles and squares, HMSN-P affected; unfilled circles and squares, not HMSN-P affected; asterisk (*) indicates included in linkage analysis; double asterisks (**) indicate included in linkage and exome-sequence analysis. Abbreviations: HMSN-P, hereditary motor and sensory neuropathy with proximal predominance; m, mutated *TFG* allele; wt, wild-type *TFG* allele.