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Identification of novel *TFG* mutation in HMSN-P pedigree: Emphasis on variable clinical presentations☆

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ABSTRACT

We aimed to identify the genetic cause of neurological disease in an Iranian pedigree whose manifestations suggested hereditary motor and sensory neuropathy with proximal predominance (HMSN-P). Identification of a p.Gly269Val mutation in *TFG*, the known HMSN-P causative gene, provided supportive evidence. Subjective, biochemical, electrodiagnostic, and imaging data were compared with previously reported HMSN-P patients, including patients of an earlier described Iranian pedigree. Although notable clinical variability was found, comparable involvement of proximal and distal muscles was observed in both Iranian pedigrees. Interestingly, the same p.Gly269Val mutation was recently reported as cause of Charcot-Marie-Tooth disease type 2 in a Taiwanese pedigree. The likelihood that the two pedigrees with the p.Gly269Val mutation are not affected with different diseases is discussed. Identification of a second Iranian HMSN-P pedigree further confirms that HMSN-P is not confined to the Far East. Furthermore, p.Pro285Leu that has been the only *TFG* mutation thus far reported in HMSN-P patients is not the only mutation that can cause the disease. It is emphasized HMSN-P is a neuronopathy.

1. Introduction

Hereditary motor and sensory neuropathy with proximal predominance (HMSN-P) is a neuromuscular disease that was described approximately two decades ago [20]. Its description emphasizes proximal dominant muscle weakness and atrophy, and also includes mild but obvious sensory dysfunction, fasciculation, decreased deep tendon reflexes, axonal degeneration in the peripheral nerves, and autosomal dominant inheritance. The disease appeared to be rare, and was originally reported only in patients of Japanese or Korean descent [3,9,11,15,17,18,20,21]. In 2015, we described a large Iranian HMSN-P affected pedigree and thus showed that the disease is not confined to individuals with Far East ancestry [1]. As suggested earlier by others, we noted that HMSN-P in other populations may have been overlooked because of erroneous diagnosis of other diseases with partially overlapping phenotypes, including Charcot-Marie-Tooth type 2, spinal and bulbar muscular atrophy (SBMA), spinal muscular atrophy (SMA), and amyotrophic lateral (ALS) [13,16]. Genetic analyses recently culminated in showing that a heterozygous mutation in *TFG* that encodes the tyrosine receptor kinase (TRK)-fused protein was the cause of HMSN-P in families from two districts in Japan, a family from Korea, and the family from Iran [1,9,11]. Although the same mutation (c.854C > T) that causes p.Pro285Leu was identified in all the families, haplotype analysis suggested at least 3 independent origins for the mutated alleles [1]. It was unclear whether association of the same mutation with three different haplotypes reflected a mutation hotspot or the unique effect of this single mutation in causing the HMSN-P phenotype.

TFG was originally identified during genetic analysis of thyroid carcinomas and other cancers [5–7]. The gene was involved in translocation events that created fusion oncogenes. With respect to neurological diseases, a homozygous mutation (c.316C > T) in *TFG* that causes p.Arg106Cys has been identified in an Indian hereditary spastic paraplegia family [2]. Two *TFG* missense mutations in sporadic ALS patients were also reported [10]. Finally, a mutation (c.806G > T) in *TFG* that causes p.Gly269Val was observed in a large Taiwanese pedigree that was diagnosed with a form of autosomal dominant Charcot-Marie-Tooth type 2 [22].

Here, we report finding p.Gly269Val in a newly identified Iranian pedigree affected with HMSN-P. We present clinical, electrodiagnostic (EDX), and muscle magnetic resonance imaging (MRI) data on the Iranian patients. We argue that the Taiwanese and Iranian patients who harbor the same p.Gly269Val mutation in *TFG* should perhaps not be diagnosed with distinct diseases.

☆ Conflicts of interest: All authors claim absence of conflicts of interest and have nothing to disclose including not receiving any payment or services from a third party at any time; no relevant financial activities outside the submitted work; no patents, whether planned, pending or issued, broadly relevant to the work; and no other relationships/conditions/circumstances that present a potential conflict of interest relationships.

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2. Materials 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.

The HMSN-160 pedigree studied here includes at least 15 affected individuals distributed in five generations (Fig. 1A). The proband (HMSN-160-IV9) who presented with an atypical motor neuron syndrome with sensory involvement was suspected of possibly being affected with HMSN-P by SN who was very familiar with the clinical features of patients of the earlier Iranian HMSN-P pedigree (HMSN-159). The two pedigrees belonged to different Iranian ethnic groups and geographic regions. The common features of patients in the two pedigrees are described below. The proband of HMSN-160 and several affected and non-affected family members were referred to us for genetic analysis. Inheritance was autosomal dominant. Individuals HMSN-160-II2 and HMSN-160-II7 had died in separate accidents at ages 22 and 24 years. Presumably, they would have manifested disease had they lived longer.

All exons of *TFG* were polymerase-chain reaction (PCR) amplified from the DNA of peripheral leukocytes of proband HMSN-160-IV9, and the amplicons were sequenced by the Sanger protocol. Sequences were analyzed with Sequencher 5.4 software (Gene Codes Corporation, Ann Arbor, MI). *TFG* reference sequences used were NC_000003.12, NM_001007565.2, and NP_001007566.1. The identified putative disease causing mutation was screened for segregation with disease status in 11 available affected and 3 available unaffected family members by direct sequencing. Many asymptomatic members of the family declined to participate in genetic analysis. The mutation was also screened in 300 Iranian control individuals by an allele specific PCR protocol. Sequences of all primers used are available upon request.

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.

3. Results

Four sequence variations were observed upon sequencing *TFG* exons in the DNA of the proband of HMSN-160. Two of the variations (c.184 + 39A > T, rs9824942; c.185-35A > G, rs60550917) are intronic, and one (c.846T > C, rs11353) creates a synonymous (p.Pro282) codon. None of these three variations were considered candidate disease causing mutations; each had reported minimum allele frequencies of at least 0.28, and none were predicted to affect splicing. The fourth variation, c.806G > T that causes p.Gly269Val, was immediately suspected of being the cause of the proband's neurological disease as the same mutation had been recently reported to be cause of dominant axonal CMT in a Taiwanese pedigree (Fig. 1B) [22]. The mutation co-segregated with disease status in the large Taiwanese pedigree, affected an evolutionarily conserved amino acid residue, was novel and absent in the chromosomes of approximately 500 ethnically matched control individuals [22]. Elegant cell transfection studies further confirmed that the mutation disrupts functions of the encoded protein [22]. The p.Gly269Val causing sequence variation (c.806G > T) in *TFG* that was observed in the heterozygous state also segregated with disease status in pedigree HMSN-160, and it was absent in the chromosomes of 300 Iranian control individuals. Given all this, earlier association of *TFG* with HMSN-P, and overlapping clinical presentations of classically defined CMT2 and HMSN-P, the mutation was considered the definitive cause of the neurological disease of pedigree HMSN-160.

Clinical information and blood chemistry laboratory findings on seven HMSN-160 patients are presented in Table 1. Presentations that portrayed telling commonalities with patients of the Iranian pedigree earlier diagnosed with HMSN-P (pedigree HMSN-159) included considerable proximal and distal muscle weakness, asymmetry at onset, notable fasciculation and cramps in trunk and limbs, tremor, paroxysmal dry coughing, and occasional urinary dysfunction (Table 1) [1]. Except for patient HMSN-160-V1 in whom disease duration has been less than one year, muscle force examinations in both families confirmed that proximal and distal muscles are involved. In HMSN-160-V1 with very short disease progression, only mild proximal muscle involvement was detected (Table 1). The average age at onset in HMSN-160 patients

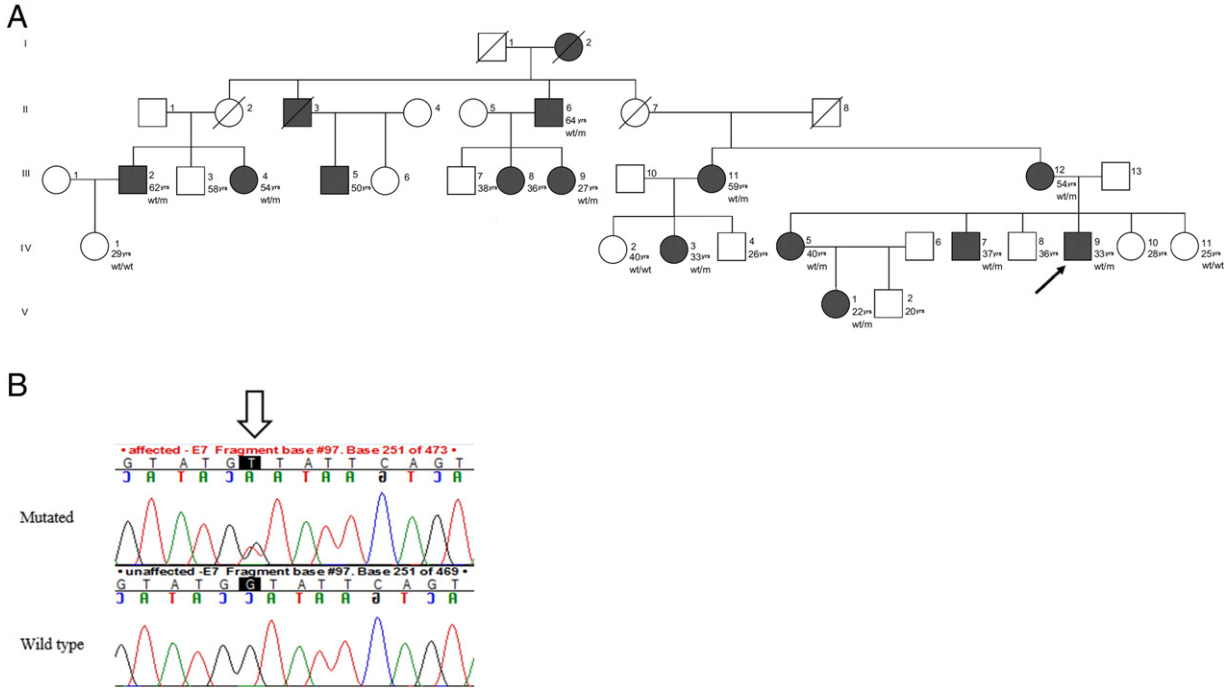

Fig. 1. Iranian HMSN-P pedigree (HMSN-160) with p.Gly269Val mutation in *TFG*. A- *TFG* genotypes of individuals tested are presented. Present age of individuals is provided when known. Filled circles and squares, HMSN-P affected; unfilled circles and squares, asymptomatic at time of examination; m, mutated *TFG* allele; wt, wild-type *TFG* allele. B- DNA sequence chromatograms showing the heterozygous c.806G > T mutation in *TFG*, and the wild type sequence.