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Novel *FGD4* Variants and Literature Review of Charcot-Marie-Tooth Disease Type 4H

Feixia Zhan[1#], Ruilong Ni[1,2#], Taotao Liu[1,2], Wotu Tian[1], Xiaoli Liu[3], Qingqing Jiang[1], Jieyuan Zhang[4], Zhongmin Shi[4], Li Cao[1] and Xinghua Luan[1]**

[1]Department of Neurology, Sixth People's Hospital, Shanghai Jiao Tong University, China

[2]School of Medicine, Anhui University of Science and Technology, China

[3]Department of Neurology, Shanghai Fengxian District Central Hospital, China

[4]Department of Orthopedic Surgery, Sixth People's Hospital, Shanghai Jiao Tong University, China

[#]These authors contributed equally to this work

Abstract

Background and Purpose: Charcot-Marie-Tooth Disease (CMT) is a common hereditary motor and sensory neuropathy with highly clinically and genetically hetero generous properties. The CMT4H subtype is an autosomal recessive demyelinating form of CMT due to the mutations in the *FGD4*, which encodes frabin, involving in regulating the activities of Schwann cells and maintaining the structure and function of the myelin development and homeostasis. To enhance earlier recognition and promote the pathogenic and molecularly targeted therapeutic study for this disease.

Methods: Detailed clinical evaluations, nerve biopsy, and whole-exome sequencing were performed. The sequence and co-segregation of the variants in the family was confirmed by Sanger sequencing.

Results: The proband was a 12-year-old Chinese boy from a non-consanguineous family. Clinical evaluations revealed that the patient presented with early-onset, slowly progressive gait disturbance, and pes cavus. Electrophysiological examinations showed markedly reduced conduction velocities. Nerve biopsy disclosed a demyelinating neuropathy with thickened and excessively folded myelin sheath. Exome sequencing identified two novel compound heterozygous *FGD4* variants with c.1688C>A (p.T563K) and c.1951C>T (p.Q651X).

Conclusion: We described a Chinese CMT4H patient with novel *FGD4* mutations. CMT4H is a very early onset demyelinating disease with variable phenotypes. By studying and reviewing the disorder, we summarized the phenotype, expanded the genotype spectrum. CMT4H may be a disease of various impaired signaling pathways.

Keywords: Charcot-Marie-Tooth disease; CMT4H; *FGD4*; Folded myelin

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Correspondence:
Xinghua Luan, Department of Neurology, Sixth People's Hospital, Shanghai Jiao Tong University, 600 Yi Shan Road, Shanghai, 200233, China, Tel: +86-021-24056187; E-mail: green_lxh@hotmail.com
Li Cao, Department of Neurology, Sixth People's Hospital, Shanghai Jiao Tong University, 600 Yi Shan Road, Shanghai, 200233, China, Tel: +86-021-24056187; E-mail: caoli2000@yeah.net

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Introduction

Charcot-Marie-Tooth disease (CMT), a group of clinically and genetically heterogeneous peripheral neuropathies with an overall prevalence of approximately 1-4/10,000 [1,2], are classically characterized by progressive muscular and sensory defects starting at the distal extremities with chronic weakness, skeletal deformities (pes cavus, hammer toe, or scoliosis), and loss of deep tendon reflexes [3]. Clinically, CMT can be subdivided into demyelinating (CMT1, CMT3 and CMT4) and axonal forms (CMT2) based on electrophysiological and histopathological characteristics [4]. The demyelinating neuropathies are mainly associated with reduced Nerve Conduction Velocities (NCVs; <38 m/s) due to the damage to the myelin sheath. Axonal forms of CMT are assumed to originate on the neuronal side and present with decreased compound muscle action potential amplitudes. Besides, the other CMT types with electrophysiological and histopathological presentations overlapping CMT1 and CMT2 are referred to as "intermediate CMT" (NCVs range from 38 m/s to 48 m/s) [4,5]. So far, over 80 genes are known to be a cause of CMT with autosomal dominant, autosomal recessive, or X-linked inheritance [6]. CMT4 is an autosomal recessive demyelinating form that has an earlier onset and more severe phenotypes than CMT1. In 2007, *FGD4* was first identified as the causative gene for CMT4H, which is located to chromosome 12p11.21-q13.11 in two consanguineous families of Mediterranean origin by homozygosity mapping [7,8]. *FGD4* encodes frabin, an F-actin GDP/GTP nucleotide exchange factor, specific to Cell-division cycle 42 (Cdc42)

and Rac1, which belong to the members of the Rho family of small GTP-binding proteins (Rho GTPases), to control several aspects of Schwann cell biology and function [9,10]. All patients described to date, with mutations in *FGD4* are affected with early-onset and slowly progressive demyelinating CMT, presenting severely reduced motor NCVs and loss of myelinated fibers companion with focally folded myelin [8,11,12]. With the widespread use of molecular genetics technology, more CMT4H cases with a broad phenotypic spectrum have been reported. Due to a strong clinical variability and progressive course, the current information concerning frabin function is limited. Herein, a Chinese patient with novel *FGD4* mutations was described and a further overview of CMT4H was made to summarize the clinical and genetic spectrum, as well as the current pathogenesis progress of the disease to discuss genotype-phenotype correlations, and shed light on the pathogenic and molecularly targeted therapeutic study for this disease.

Materials and Methods

Patients

Extensive clinical evaluation including medical history, physical and electrophysiological examination was performed in a 12-year-old Chinese male patient. This study was approved by the ethics committee of Sixth People's Hospital, Shanghai Jiao Tong University Shanghai, China. Written informed consent, which also included the consent for the publication of medical information, was obtained from the guardians.

Sural nerve biopsy

The right sural nerve biopsy was performed on the proband after obtaining informed consent. Tissue sections were stained using conventional histologic methods for hematoxylin and eosin, modified Gomori Trichrome, and Congo Red. Separate portions of specimen was fixed in 2% PFA/2.5% glutaraldehyde in phosphate buffer, processed, and embedded in Epon. Transverse, semithin sections were stained with Toluidine Blue for evaluation by light microscope. Ultrathin sections were contrasted with uranyl acetate and lead citrate for examination by electron microscope to ultrastructural studies (PHI LIP CM-120).

Genetic analyses

Genomic DNA was extracted from peripheral blood using the standardized phenol/chloroform extraction protocol; exome sequencing was conducted in the proband. The screened variants were analyzed as follows: The related database including 1000 Genomes Project (http://www.internationalgenome.org), dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP), and gnomAD (https://gnomad.broadinstitute.org/) were used as references to exclude all variants present in the population at greater than 5% frequency. In addition, MutationTaster (http://www.mutationtaster.org), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2) and SIFT (http://sift.jcvi.org) were used to predict the pathogenicity of the mutation. Then the pathogenic of the variant was interpreted and classified following the American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines [13]. Putative pathogenic variants were further confirmed by Sanger sequencing of both the forward and reverse strands among family members.

Results

Clinical findings

The index patient was a 12-year-old boy from a non-consanguineous family referred to our neurology department with a complaint of 1-year history of progressive gait disturbance, toe walking. Through detailed medical history tracking, the boy had slow running with occasional falls since middle school when at exercise training time. The patient had normal developmental milestones, and there were no similar affected family members. Neurological examination showed a toes walking, bilateral mild pes cavus deformities, and deep tendon are flexia. Cranial nerve examination was normal, and Babinski signs were not elicited. No weakness, amyotrophy, sensory deficits, and scoliosis were observed. Motor conduction studies revealed slightly reduced amplitudes (1.08 mV to 4.0 mV), prolonged distal motor latencies, and severely reduced velocities (17.6 m/sec) at bilateral median nerve, while no motor or sensory action potentials could be obtained in the lower limbs. Needle electromyography examination found no abnormalities. The X-ray showed bilateral foot deformities with pes cavus (Figure 1A).

Neuropathological findings

Electron micrographs from transverse sections of sural nerve revealed a moderate decrease in density of myelinated fibers, scattered thinly myelinated fibers, accompanied by a small amount of thickened, grossly distorted, and excessively folded eccentric myelin (Figure 1B).

Genetic findings

Exome and Sanger sequencing identified the patient carried the

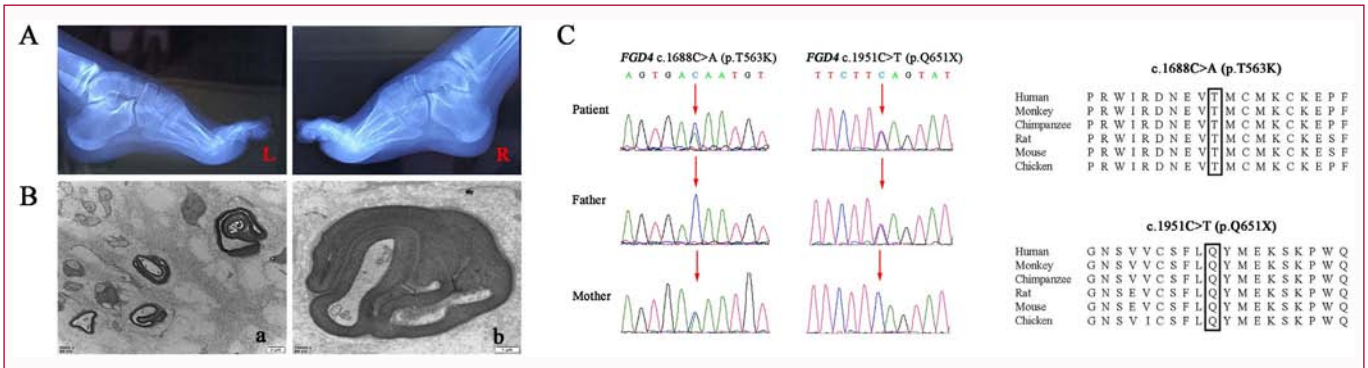

Figure 1: A) The X-ray showed bilateral foot deformities with pes cavus. L: Left; R: Right. B) Transverse section of the sural nerve biopsy viwed by electron microscopy. (a) There is a moderate decrease in density of myelinated fibers, scattered thinly myelinated fibers, with a small amount of thickened and excessively folded myelin; 5000x magnification. (b) The excessive myelination with eccentric myelin out folding; 15000x magnification.
C. Sanger sequencing: The patient had the compound heterozygous *FGD4* mutations with c.1688C>A (p.T563K) and c.1951C>T (p.Q651X), which came from his heterozygous state mother and father, respectively. Both two mutations were highly functional conservative.

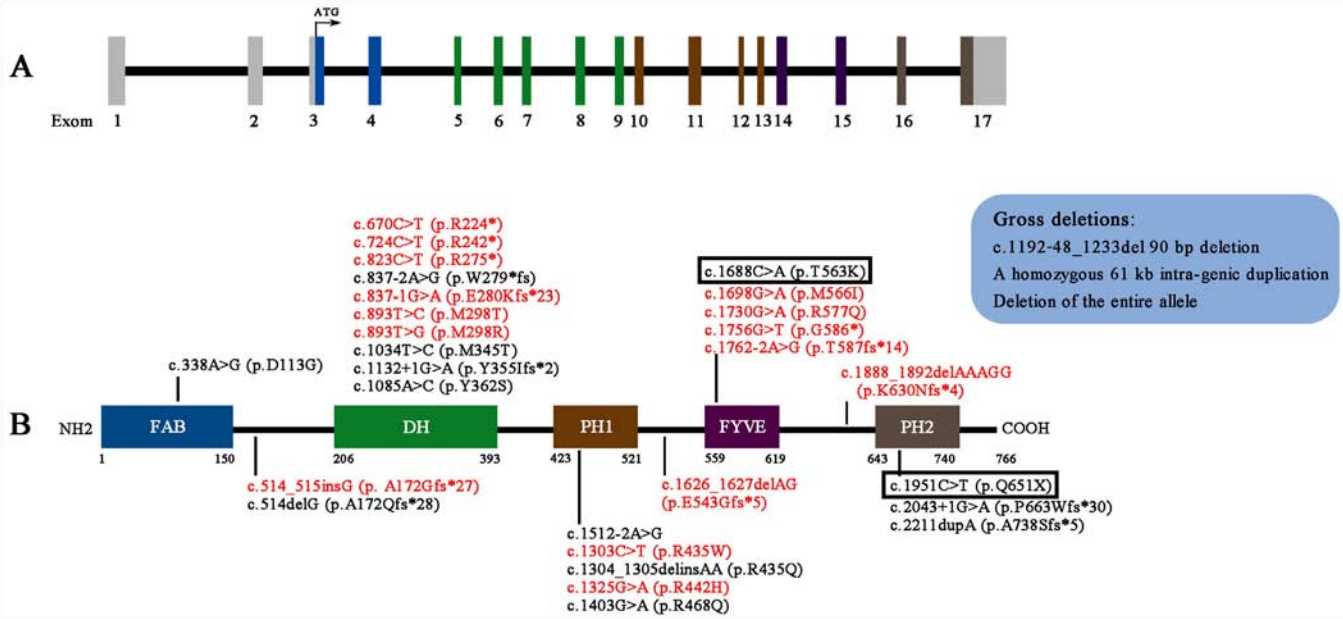

Figure 2: A) Schematic drawing of the *FGD4* gene. B) Diagram of *FGD4* protein structure with reported mutations (NM_139241). Five functional domains are represented for *FGD4,* the FAB (F-actin binding), DH (Dbl homology), PH (Pleckstrin homology) and FYVE (Fab 1, YOTB, V ac 1, and EEA1zinc finger) domains. The novel mutations detected in this paper are marked in black box. The previously reported homozygous mutations are marked in red and heterozygous mutations in black. The three gross deletion mutations, including c.1192-48_1233del 90bp deletion, a homozygous 61 kb intra-genic duplication, encompassing exons 3-14, and deletion of the entire allele.

compound heterozygous *FGD4* mutations with c.1688C>A (p.T563K) and c.1951C>T (p.Q651X), which were from his heterozygous state mother and father (Figure 1C), respectively. Both two variants are novel, which were not found in 1000 Genomes Project, dbSNP, and ExAC database, and pathogenicity assessment according to the ACMG revealed that both the mutations are likely pathogenic.

Discussion

In our study, we described a Chinese case with a genetically confirmed diagnosis of CMT4H. The patient displayed marked demyelinating peripheral nerve, from clinical manifestations to electrophysiological and neuropathological features. Since the first two families with CMT4H were described, this condition has been regarded as a very early onset demyelinating disease with a severe phenotype that involves delayed walking, pes cavus, kyphoscoliosis, and an early loss of ambulation [11,14,15]. To date, 40 cases from 24 families with CMT4H have been reported, the average age of onset is 5.5-year-old, ranging from early infancy to the late second decade, and the disease course is chronic and progressive [8,11,12,14-18]. Individual CMT4H cases have recently been reported with pupil asymmetry [17,19], multiple cranial nerve involvement [20], sensory ataxia [15,21], spinal syringomyelia [22], autonomic neuropathy [17], and cauda equina thickening [17], hence gradually broadening the known CMT4H phenotype. However, the significant clinical variability even among siblings with identical *FGD4* genotype, suggesting a high clinical heterogeneity among individuals [17,23]. Including the present case, almost all the affected patients were showed severely reduced velocities in electromyogram. In addition, nerve biopsies disclosed a demyelinating neuropathy characterized by myelin thickening, redundant myelin loops, and numerous infoldings and outfoldings of the myelin sheath [10], which were taken as the striking pathological hallmarks of the disease, although these features can also be found in other CMT4 subtypes (CMT4B or CMT4F) [24].

The responsible gene *FGD4* contains 17 exons, of which 15 are coding exons (Figure 2A). The encoding protein frabin is a 766-amino acids GDP/GTP Guanine Nucleotide Exchange Factor (GEF), a member of the Rho GTPases, and plays a role in Cdc42-mediated cell shape changes [9,25]. The ubiquitously expressed protein contains, in order from the N- to the C-terminus, five functional domains: One F-Actin Binding (FAB) domain, one Dbl Homology (DH) domain, two Pleckstrin Homology (PH) domains, and one cysteine-rich FYVE domain (Figure 2B). DH domain plays a vital role in the catalysis of GDP-to-GTP exchange, whereas PH and FYVE domains are mainly involved in interactions with different forms of phosphoinositides and activation of c-Jun N-terminal kinase [8,26]. As a GEF, frabin stimulates the exchange of GDP for GTP to generate the activated form, which then modulates the activity of downstream targets and effect or molecules. It was demonstrated that frabin likely has a key role in proliferation, polarization, endocytosis, and survival of Schwann cells, all of which are distinctively required for correct nerve development and accurate myelin maintenance [8,10]. In cultured Schwann cells, the normal form of frabin colocalized with F-actin and induced the formation of microspikes, whereas the expression of truncated frabin significantly inhibited this effect [8,27]. What's more, lack of frabin causes dysmyelination in mice in early peripheral nerve development, followed by profound myelin abnormalities at later stages [10]. Besides, the Frabin-Cdc42 axis exerts a crucial effect on developmental Schwann cells and myelination. When frabin was over expressed in cultured cells, it can enhance GTP-loading of GTPases, then Rho GTPases function as molecular switches that are implicated in a wide variety of downstream signal-transduction pathways, including regulation of the actin and microtubule cytoskeleton during cell migration, morphogenesis, polarization, and proliferation [9]. Previous studies have demonstrated that Cdc42 and Rac1 are required for Schwann cells migration and proliferation, and regulate Schwann cells process extension and stabilization, allowing

efficient radial sorting and myelin sheath folding [28]. A significant reduction in active Cdc42 was found in *FGD4* knockout mice. Genetic disruption of Cdc42 in Schwann cells of myelinated nerves resulted in demyelination similar to those observed in frabin-deficient mice [10], while axon sorting deficits in Schwann cells lacking laminins were improved after forced activation of Cdc42 and/or Rac1 [29]. Overall, it is strongly suggested that CMT4H is a disease of various impaired signaling pathways.

Up to now, about 29 *FGD4* mutations have been reported in patients with CMT4H, most of them predicted to result in truncated or absent protein (nonsense, frame shift, or splicing mutations) [17,18,23,30]. The mutations mainly affect the DH domain, two PH domains, and FYVE domain (Figure 2B). It seems that patients homozygous for nonsense or splicing mutations may be related to an infantile-onset and delayed motor milestones. However, there is no notable trend between the disease progression, phenotypic severity and the mutations of different types or in different domains. Previous studies suggested that a nonsense variant might translate a truncated protein since the affected mRNA wasn't degraded [19]. Additionally, reduced microspike formation was found in cell cultures transfected with truncated forms of frabin [8,27]. The two novel mutations described here were highly functional conservative and located in domains FYVE and PH2, which were interacted with polyphosphoinositides and implicated in morphogenesis, membrane trafficking, signal transduction, and cytoskeleton dynamics [8,26]. In addition, the nonsense mutation c.1951C>T (p.Q651X) in our study resulted in a prematurely truncated protein. Thus, we can speculate that the rapid protein degradation and resulting haploinsufficiency caused by the mutations may consequently result in the impaired Rho GTPase signaling and dysregulation of membrane-transport processes, which subsequently perturb Schwann cell morphology, polarity, or proliferation, and impel the formation of myelin outfoldings, causing aberrant myelination in peripheral nerves [8,10]. Further detailed molecular mechanism underlies the signaling is warranted to be explored. Since the relative rarity and progressive course, affected patients with autosomal recessive or sporadic early-onset, slowly progressive CMT disease should be considered to screen the *FGD4* mutations. Currently, there is no therapy progress for this hereditary peripheral neuropathy. Individuals with CMT4H are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical therapists. Rho GTPases and the frabin-Cdc42 axis are promising candidates for molecules that are involved in several aspects of Schwann cell biology, including those associated with myelin development and homeostasis [31]. The knowledge about the involvement of Rho GTPase signaling in an inherited neuropathy provides a direction to a better understanding of the development, degeneration, and regeneration of the peripheral nervous system. It is noteworthy that complicated signaling pathways leading to the pathology remain to be elucidated, which may shed light on the pathogenetic studies and achieve a breakthrough in therapeutic approaches [32,33].

Conclusion

In conclusion, we described a Chinese CMT4H patient with novel *FGD4* mutations. CMT4H is a very early onset demyelinating disease with variable phenotypes. By studying and reviewing the disorder, we summarized the phenotype, expanded the genotype spectrum. However, we are still far from a comprehensive picture of the information concerning frabin function and the following molecular signaling. Identification of the underlying mechanisms of Schwann cell damage in inherited neuropathies may hold promise for the development of therapies not only for these rare entities but also for a broad spectrum of more acquired demyelinating disorders of the peripheral and central nervous system.

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