REPORT

Peripheral Nerve Demyelination Caused by a Mutant Rho GTPase Guanine Nucleotide Exchange Factor, Frabin/FGD4

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GTPases of the Rho subfamily are widely involved in the myelination of the vertebrate nervous system. Rho GTPase activity is temporally and spatially regulated by a set of specific guanine nucleotide exchange factors (GEFs). Here, we report that disruption of frabin/FGD4, a GEF for the Rho GTPase cell-division cycle 42 (Cdc42), causes peripheral nerve demyelination in patients with autosomal recessive Charcot-Marie-Tooth (CMT) neuropathy. These data, together with the ability of frabin to induce Cdc42-mediated cell-shape changes in transfected Schwann cells, suggest that Rho GTPase signaling is essential for proper myelination of the peripheral nervous system.

Charcot-Marie-Tooth (CMT) disease comprises a group of clinically and genetically heterogeneous hereditary motor and sensory neuropathies (HMSNs). With an overall population prevalence of 1 in 2,500, CMT constitutes the most common inherited neuromuscular disorder.[1] Clinical features comprise progressive distal muscle weakness and atrophy, foot deformities, and distal sensory loss. Two major subtypes have been discerned by electrophysiological and peripheral nerve biopsy studies: the demyelinating form (CMT1 or HMSN I) and the axonal type (CMT2 or HMSN II). CMT1 is characterized by reduced nerve conduction velocities (NCVs), segmental demyelination and remyelination, and onion bulb formation in nerve biopsy specimens. Patients with CMT2 present with near-normal NCVs but with reduced amplitudes of compound motor and sensory action potentials and with loss of myelinated axons and signs of axonal degeneration in nerve biopsy specimens.[2] Both types of CMT are genetically heterogeneous, with autosomal dominant, X-linked, and autosomal recessive inheritance. In recent years, considerable advances have been made in the understanding of the molecular genetics of CMT neuropathies. Mutations of genes that cause CMT are listed in the Inherited Peripheral Neuropathy Mutation Database.

Gene mutations causing demyelinating CMT1 affect the development, maintenance, and function of the Schwann cells, which effect myelination in the peripheral nervous system (PNS).[3–5] Schwann cells are highly specialized cells that need to exert a multitude of tightly regulated cellular activities, such as proliferation, migration, adhesion, polarization, and vesicle and membrane trafficking.[6,7] All these processes involve the actin cytoskeleton and the microtubule network of the cell. Both actin and microtubule dynamics are controlled through small GTPases of the Rho family.[8] Like all GTPases, Rho proteins cycle between an inactive (GDP-bound) and an active (GTP-bound) conformational state. Interconversion and accessibility of these two forms are temporally and spatially regulated in a variety of ways.[9] Guanine nucleotide exchange factors (GEFs) stimulate the exchange of GDP for GTP, to generate the activated form, which then modulates the activity of downstream targets and effector molecules. GTPase-activating proteins (GAPs) accelerate the intrinsic GTPase activity of Rho family members and terminate the signal-transduction process. Finally, guanine nucleotide dissociation inhibitors (GDIs) control cycling of GTPases between membranes and cytosol. Overall, Rho GTPases and their regulators are promising candidates for molecules that control several aspects of Schwann cell biology, including those associated with the ensheathment and myelination of axons. Interestingly, a missense mutation in the gene for a putative Rho GTPase GEF, ARHGEF10, is associated with a dominant trait of slowed NCVs and thin myelin sheaths, without clinical CMT phenotype in humans.[10]
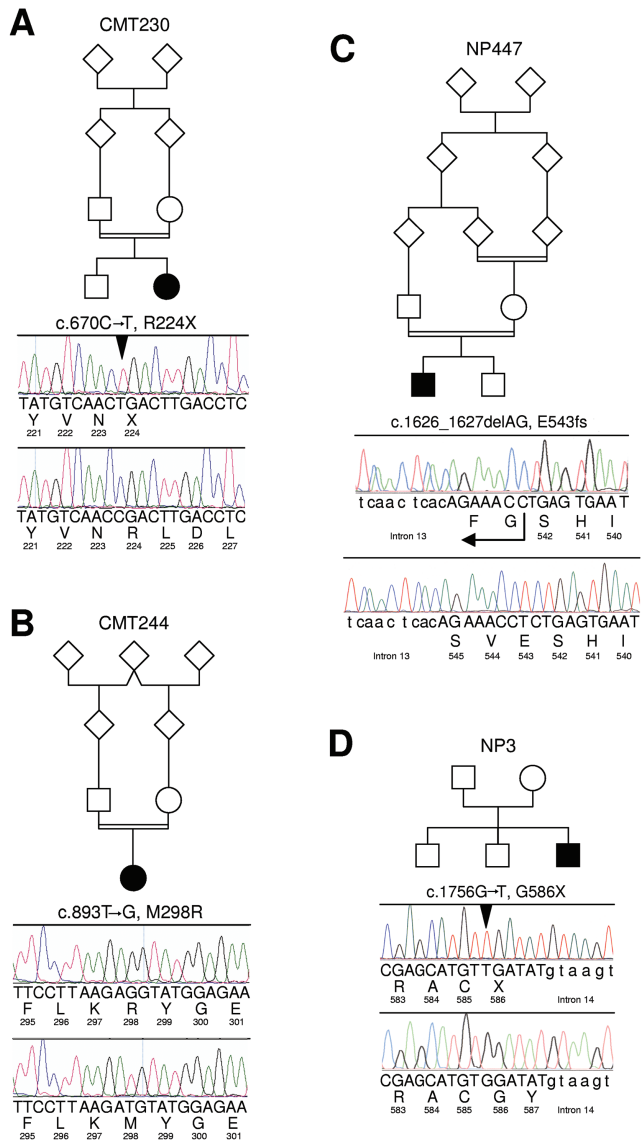
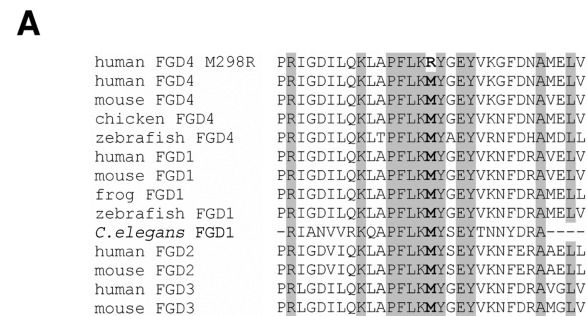To increase the understanding of the role of Rho

Figure 1. *FGD4* mutations in the four families with CMT4H. Arrowheads in the electropherograms indicate the disease-causing mutations. The wild-type sequence is shown in the lower electropherogram in each panel. *A,* Homozygous nonsense mutation c.670C→T, R224X. *B,* Homozygous missense mutation c.893T→G, M298R. *C,* Homozygous frameshift mutation c.1626_1627delAG, E543fs. The reverse sequence is shown. An arrow indicates the frameshift. *D,* Homozygous nonsense mutation c.1756G→T, G586X.

striking candidate was the *FGD4* gene (GenBank accession number NM_139241), which was identified within the 11.5-cM critical interval for CMT4H on chromosome 12p11.21-q13.11. The *FGD4* gene encodes frabin, a GEF for the Rho GTPase cell-division cycle 42 (Cdc42).[11,12] CMT4H is an autosomal recessive demyelinating form of CMT that was initially mapped in Lebanese and Algerian consanguineous families.[13] All patients had early disease onset but slowly progressive sensorimotor neuropathy, and most of them presented with severe scoliosis. NCVs were invariably slow, and sural nerve biopsy specimens displayed a severe loss of myelinated fibers, thinly myelinated axons, and outfoldings of myelin sheaths. To establish the causative role of *FGD4* in CMT4H, we selected a series of 63 patients with demyelinating sensorimotor neuropathy with onset in the 1st decade, absence of clinical symptoms and neurophysiological signs in the parents, and at least one of the following features: (i) parental consanguinity or at least one other affected sibling, (ii) severely slowed NCVs (<15 m/s for the motor median nerve), (iii) prominent scoliosis, and (iv) myelin outfoldings in nerve biopsy specimens.

We used primers (generated with Primer3 software) flanking the 15 coding exons of the *FGD4* gene, to amplify

Figure 2. *In silico* characterization of the consequences of the c.893T→G mutation in the *FGD4* gene. *A,* Multiple sequence alignment, generated with ClustalW, of the protein region surrounding the site of the putative M298R mutation. Conserved residues are shown on a gray background. M298R (*in bold*) is conserved through evolution in members of the FGD protein family. *B,* Scores from different splice-site prediction algorithms (i.e., WebGene, NNSplice, FSPLICE, and SPL). The putative donor splice site created by the c.893T→G change reaches scores similar to the genuine intron 7 donor splice site.

GTPase signaling in the PNS, we combined positional and functional cloning strategies. Using the UCSC Genome Browser, we systematically investigated critical linkage intervals of CMT forms for which no disease genes had been identified so far (CMT2B2 [MIM %605589], CMT4H [MIM %609311], HMSNR [MIM %605285], CMTDIA [MIM %606483], CMT2G [MIM %608591], and CMT2C [MIM %606071]), to search for the presence of genes encoding Rho GTPases or Rho GTPase regulatory proteins. The most

Table 1. Clinical, Electrophysiologic, and Morphological Data in CMT4H

Patient	Sex	Ethnic Origin	Consanguinity	Mutation	Age at Walking (mo)	Age at Diagnosis (years)	Age at Last Examination (years)	Distal Weakness[a]	Distal Muscle Atrophy[b]	Foot Deformity[c]	Distal Sensory Loss[d]	Scoliosis[e]	Reflexes[f]	Motor NCV[g] (m/s)			Sensory NCV[h] (m/s)		Nerve Biopsy
														Median	Ulnar	Tibial	Median	Sural	
CMT244	F	Lebanese	+	M298R	12	4	13	+++	++	+	++	++	−/−	...	7	NR	...	NR	Myelin outfoldings
CMT230	F	Turkish	+	R224X	Delayed	Infancy	30	+++	++	+	+	−	+/−	5	...	...	NR	NR	...
NP447	M	Turkish	+	E543fs	26	2	8	++	+	−	−	−	−/−	10	6.6	...	NR	...	Myelin outfoldings
NP3	M	Tamil	−	G586X	16	9	11	+	+	−	−	−	−/−	12	...	NR	NR	...	...

a − = Not affected; + = mild in the lower extremities; ++ = marked in the lower extremities; +++ = also affecting the hands and forearms. No patient had involvement of proximal muscles.
b − = Not affected; + = mild; ++ = severe. No patient had involvement of proximal muscles.
c − = No deformity; + = pes cavus and hammer toes; ++ = clubfoot deformity; +++ = surgery required.
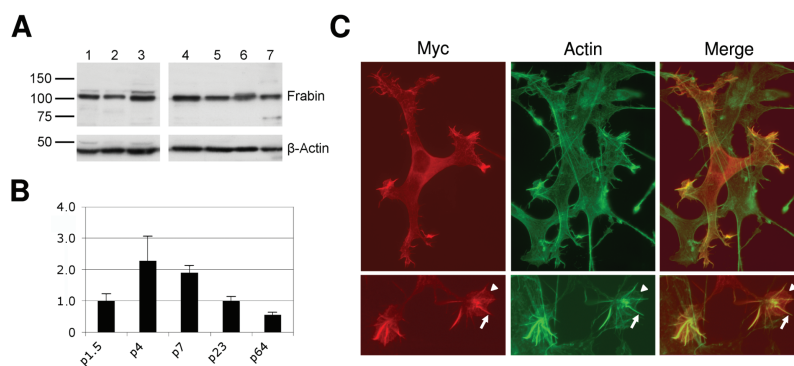d − = No deficit; + = decreased sensibility; ++ = absent sensibility.
e − = None; + = mild; ++ = severe; +++ = surgery required.
f In upper/lower extremities. − = Absent; + = normal.
g Normal values: median and ulnar nerve >45 m/s; tibial nerve >40 m/s. NR = not recordable.
h Normal values: median nerve >45 m/s; sural nerve >40 m/s. NR = not recordable.

Figure 3. Expression analysis and overexpression of *Fgd4*/frabin in Schwann cells. *A,* Western-blot analysis of lysates from rat tissues, Schwann cell lines, and cultured primary Schwann cells. *Upper panel,* Mouse monoclonal anti-frabin antibody (BD Transduction Labs) detecting a band of the expected size in all lysates analyzed. *Lower panel,* Blot probed with mouse monoclonal anti–β-actin antibody (Sigma-Aldrich) to ensure similar loading. *Lane 1,* Spinal cord; *lane 2,* sciatic nerve; *lane 3,* whole brain; *lane 4,* primary rat Schwann cells; *lane 5,* primary rat oligodendrocytes; *lane 6,* RN22; and *lane 7,* RT4-D6P2T. *B,* Quantitative RT-PCR analysis of *Fgd4* (GenBank accession number NM_139232) expression in the developing mouse sciatic nerve. Measurements were normalized against *Gapdh* levels. p = Postnatal days. *C,* Frabin-induced cell-shape changes of primary rat Schwann cells. *Upper panel,* overview; *lower panel,* detail of cell processes. pCMV-Myc full-length frabin was transfected by use of the liposome-mediated gene transfection. *Left,* Transfected cells identified by staining with a mouse monoclonal anti-myc antibody (Roche Diagnostics) and a Cy3-conjugated goat anti-mouse antibody (*red*) (Jackson ImmunoResearch). *Middle,* Actin cytoskeleton, visualized with Alexa Fluor 488 phalloidin (*green*) (Molecular Probes). *Right,* Merge. Arrows indicate filopodia; arrowheads indicate lamellipodia. Note that untransfected cells, visible in the middle and right columns, are virtually devoid of filopodia and lamellipodia.

genomic DNA of affected individuals, and products were subjected to direct sequencing. We identified homozygous mutations in the *FGD4* gene in three consanguineous families and in one patient with sporadic disease (fig. 1). Three of the identified mutations are clearly pathogenic, because they result in premature stop codons at amino acids 224 and 586 and in a frameshift at amino acid 543. The fourth mutation is also most likely pathogenic, since it is predicted to result in a nonconservative substitution of an evolutionarily conserved amino acid at position 298. Alternatively, according to *in silico* splice-site predictions, it may create a new donor splice site that would remove part of exon 7 from the mature cDNA and result in a frame shift (fig. 2). Unfortunately, no fresh blood sample was obtainable for mRNA isolation, for the further pursuit of this possibility. We confirmed cosegregation of the DNA changes with the phenotype in all four families. The parents carried these mutations in the heterozygous state, whereas unaffected siblings also carried one mutation or were homozygous for the wild-type alleles. These mutations have not been described previously in the National Center for Biotechnology Information dbSNP database, in which information on human genome variation is deposited, and none of these changes was detected in the DNA of healthy control samples (100 control DNA samples of western European origin for the truncating mutations and 300 western European and 160 ethnically matched control samples for the putative missense change). Clinical, electrophysiologic, and morphological data of patients with identified *FGD4* mutations are summarized in table 1.

The *FGD4* gene product, frabin, is a 766-aa protein with a molecular mass of 105 kDa.[11] Frabin has, in order from the N- to the C- terminus, one F-actin binding (FAB) domain, a Dbl homology (DH) domain in tandem with a pleckstrin homology (PH) domain, a FYVE finger (FYVE) domain, and a second PH domain. The adjacent DH and PH domains are the typical signatures of GEFs for Rho GTPases. Therefore, it is not surprising that frabin was found to act as a GEF for the Rho GTPase Cdc42.[12] In line with this observation, overexpression of frabin in various cell types results in Cdc42-mediated cell-shape changes.[11,12,14–16] Its domain structure and composition place frabin in the small family of orthologues of the FGD1 protein. FGD1 is mutated in faciogenital dysplasia (also known as Aarskog syndrome [MIM #305400]), a form of syndromic X-linked mental retardation.[17] FGD1 also acts as a GEF specific to Cdc42,[18] but patients with Aarskog syndrome do not have peripheral neuropathy, and the mental status of patients with CMT4H is normal. This highlights the fact that different FGD proteins are not interchangeable and that sets of cooperating Rho GTPases and FGD proteins may be tissue- or cell-type specific.

To establish the role of frabin in the PNS, we studied its expression in developing and adult rodent sciatic nerve, in rat Schwann cell lines, and in rat primary Schwann cell cultures. Frabin is expressed during early postnatal development of the PNS. Expression persists in adult sciatic nerve, and both Schwann cell lines (RT4-D6P2T and RN22) as well as primary cultures of Schwann cells express frabin (fig. 3). These expression data are consistent with the tissue and the cell population involved in a demye-
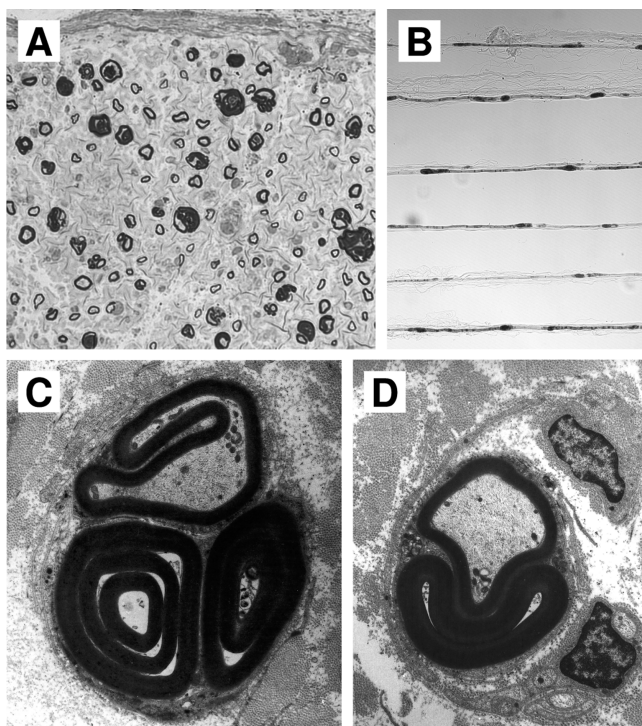
Figure 4. Sural nerve biopsy specimens of patients with *FGD4* mutations. *A,* Transverse section of the sural nerve biopsy sample of patient CMT244 with the *FGD4* M298R mutation. There is a moderate decrease in density of myelinated fibers, particularly affecting the large fibers. Many of the remaining fibers are thinly myelinated, whereas others are surrounded by thickened, grossly distorted, and excessively folded myelin. Toluidine blue staining; 400 × magnification. *B,* Teased fiber preparation of the sural nerve biopsy sample of the same patient. There are demyelinated segments and myelin thickenings on virtually every fiber. 100 × magnification. *C* and *D,* Electron micrographs of the sural nerve biopsy specimen of patient NP447 with the *FGD4* E543fs mutation. Complex folding of the myelin sheath outside the axon (*C* and *D*) and a loop extending toward the axon (*C*) are shown. Semithin sections stained with uranyl acetate and lead citrate; 6,500 × magnification.

linating peripheral neuropathy. We next addressed the question of whether frabin also exerts its known functions in Schwann cells. To this end, we transiently expressed myc-tagged frabin (a kind gift from Y. Takai) in Schwann cell lines and primary Schwann cells. Frabin was capable of altering the cell shape in Schwann cells and induced the formation of prominent filopodia and lamellipodia (fig. 3), similar to the effect of a constitutive active form of Cdc42 (also a kind gift from Y. Takai).[11,12] These results suggest that frabin is biologically active in Schwann cells. The particular relevance of Rho GTPase signaling through Cdc42 for myelinating glial cells has very recently been shown in oligodendrocytes, the counterparts of Schwann cells in the CNS. Oligodendrocyte-specific conditional gene ablation of Cdc42 in mice results in severe myelin abnormalities in the CNS.[19] Moreover, the phenotype of

the conditional knockout of Cdc42 activity in Schwann cells indicates that Cdc42 is necessary for Schwann cell proliferation and the correct myelination of axons in the murine PNS (J.B.R. and U.S., unpublished data). These data strongly support our conclusion that CMT4H is a disease of impaired Rho GTPase signaling.

The presence of FYVE and PH domains in frabin suggests cooperation of frabin with another group of CMT proteins, the myotubularin-related proteins MTMR2 (MIM *603557) and SET binding factor 2 (SBF2/MTMR13 [MIM *607697]). MTMRs are a family of phosphoinositide phosphatases that are believed to control spatial and temporal phosphoinositide phosphate (PIP) pools on cellular membranes.[20–23] FYVE and PH domains are known to bind to PIPs, and it has been shown that localization and nucleotide-exchange activity of Rho GTPase GEFs are regulated by their association with specific PIPs.[24–26] Thus, it is possible that binding to MTMR substrates and products regulates the spatial and temporal activity of frabin and, by extension, Cdc42 in Schwann cells. Confirmation of this hypothesis will require measurement of interactions between PIPs and frabin PH domains, to identify those PIPs to which frabin binds preferentially. Interestingly, the hypothesis of a functional relationship between RhoGTPase signaling and MTMRs is further supported by the occurrence of similar myelin abnormalities in the nerve biopsy samples of affected patients. Patients with *MTMR2* and *SBF2/MTMR13* mutations consistently display irregular folding and redundant loops of myelin—so-called myelin outfoldings[27]—and we observed similar irregularities of the myelin sheaths in the nerve biopsy specimens of two patients with *FGD4* mutations (fig. 4). The formation of myelin outfoldings suggests dysregulation of membrane-transport processes in the diseased Schwann cells, probably related to impaired Rho GTPase signaling.

Overall, our study reveals a new disease-related mechanism in hereditary peripheral neuropathies. Our discovery will aid genetics testing and counseling for patients with CMT. Moreover, the knowledge about the involvement of Rho GTPase signaling in an inherited neuropathy provides a direct path to a better understanding of the development, degeneration, and regeneration of the PNS. Identification of the underlying mechanisms of Schwann cell damage in inherited neuropathies may also hold promise for the development of therapies not only for these rare entities but also for a broad spectrum of more frequent acquired demyelinating disorders of the PNS and the CNS. In this way, our data are relevant for patient and family care, basic science, and, we hope, future treatment options.

Web Resources

Accession numbers and URLs for data presented herein are as follows:

ClustalW, http://www.ebi.ac.uk/clustalw/

dbSNP, http://www.ncbi.nlm.nih.gov/SNP/

FSPLICE, http://softberry.com/berry.phtml?topic=fsplice&group=programs&subgroup=gfind

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *Homo sapiens FGD4* [accession number NM_139241] and *Mus musculus Fgd4* [accession number NM_139232])

Inherited Peripheral Neuropathy Mutation Database, http://www.molgen.ua.ac.be/CMTMutations/

NNSplice, http://www.fruitfly.org/seq_tools/splice.html

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for CMT2B2, CMT4H, HMSNR, CMTDIA, CMT2G, CMT2C, faciogenital dysplasia/Aarskog syndrome, MTMR2, and SBF2/MTMR13)

Primer3, http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi

SPL, http://softberry.com/berry.phtml?topic=spl&group=programs&subgroup=gfind

UCSC Genome Browser, http://genome.ucsc.edu/

WebGene, http://l25.itba.mi.cnr.it/~webgene/wwwspliceview.html

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