

# Periaxin Mutations Cause a Broad Spectrum of Demyelinating Neuropathies

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Previous studies have demonstrated that apparent loss-of-function mutations in the periaxin gene cause autosomal recessive Dejerine-Sottas neuropathy or severe demyelinating Charcot-Marie-Tooth disease. In this report, we extend the associated phenotypes with the identification of two additional families with novel periaxin gene mutations (C715X and R82fsX96) and provide detailed neuropathology. Each patient had marked sensory involvement; two siblings with a homozygous C715X mutation had much worse sensory impairment than motor impairment. Despite early disease onset, these siblings with the C715X mutation had relatively slow disease progression and adult motor impairment typical of classic demyelinating Charcot-Marie-Tooth neuropathy. In contrast, a patient with the homozygous R82fsX96 mutation had a disease course consistent with Dejerine-Sottas neuropathy. The neuropathology of patients in both families was remarkable for demyelination, onion bulb and occasional tomacula formation with focal myelin thickening, abnormalities of the paranodal myelin loops, and focal absence of paranodal septate-like junctions between the terminal loops and axon. Our study indicates a prominent sensory neuropathy resulting from periaxin gene mutations and suggests a role for the carboxyl terminal domain of the periaxin protein.

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Charcot-Marie-Tooth neuropathy (CMT), one of the most common inherited neurological diseases, is clinically and genetically heterogeneous. At least 20 loci and nine genes have been associated with CMT and related neuropathies such as congenital hypomyelinating neuropathy (MIM 605253), Dejerine-Sottas neuropathy (DSN; MIM 145900), and hereditary neuropathy with liability to pressure palsy (MIM 162500).<sup>1</sup> Recently, we and others have identified periaxin gene (*PRX*) mutations as a cause of DSN and CMT type 4F (CMT4F).<sup>2,3</sup>

*PRX* encodes two PDZ domain proteins, L- and S-periaxin, which are required for the maintenance of peripheral nerve myelin. In murine embryonic Schwann cells, L-periaxin distributes to the adaxonal plasma membrane with the initiation of myelination and then to the abaxonal plasma membrane, Schmidt-Lanterman incisure, and paranodal membranes with the

maturation of the myelin sheath.<sup>4,5</sup> As a cytoskeleton-associated protein, L-periaxin may regulate Schwann cell shape and gene expression during axonal ensheathment by facilitating integration of extracellular signaling through the cytoskeleton.<sup>6,7</sup> The notion of such a signaling function is supported by two observations: first, L-periaxin contains a nuclear localization signal and a PDZ motif, a domain implicated in the assembly of signaling complexes at sites of cell–cell contact,<sup>5,8</sup> and second, L-periaxin binds dystroglycan-dystrophin-related protein 2 (DRP2), which is part of a complex linking extracellular matrix proteins to the cytoskeleton and cortical signaling molecules.<sup>9</sup> Confirming the necessity of periaxin for maintenance of the myelin sheath, Gillespie and colleagues<sup>10</sup> demonstrated that *Prx*<sup>-/-</sup> mice ensheath and myelinate peripheral axons normally but subsequently develop a severe demyelinating neuropathy associated with allodynia and hyperalgesia.

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To date, patients from four unrelated demyelinating neuropathy families, three manifesting DSN and one with a severe demyelinating CMT, CMT4F, have been reported to have recessive *PRX* nonsense and frameshift mutations. Each of these patients had a similar clinical phenotype, and the mutations affected only L-periaxin.<sup>2,3,11</sup>

We report on two novel *PRX* mutations causing peripheral neuropathy: homozygous C715X, which affects L-periaxin and causes an early-onset, slowly progressing CMT-like neuropathy, and homozygous R82fsX96, which affects both S- and L-periaxin and causes DSN. The two siblings with the nonsense mutation had more prominent sensory neuropathy than motor neuropathy and a milder disease course than previously reported patients with *PRX* mutations. A review of the neuropathology of these patients indicated severe demyelination or hypomyelination with occasional tomacula, or both, and abnormalities of the paranodal loops with focal absence of paranodal septate-like junctions.

## Patients and Methods

### Patients

All patients referred to this study by their primary physician or neurologist signed an informed consent form approved by the Institutional Review Board of the University of Antwerp. We isolated DNA from the peripheral blood of each patient.

### Mutation Screening

Mutation screening was performed as previously described.<sup>2</sup> We numbered the *PRX* complementary DNA sequence beginning with the adenine of the presumed initiating methionine and described mutations according to den Dunnen and Antonarakis.<sup>12</sup>

### Sural Nerve Pathology

Sural nerve biopsies, performed when Patient PN-44.1 was 40 years of age and when Patient PN-761.3 was 3 years of age, were analyzed according to standard morphological procedures for light and electron microscopy.<sup>13</sup>

### Immunohistochemistry

Frozen sections (5 $\mu$ m) of sural nerve biopsy embedded at an optimal cutting temperature were collected on 3-aminopropyltriethoxysilane-subbed slides. The sections were fixed in a 4% paraformaldehyde solution. Immunofluorescence for L-periaxin and myelin basic protein was performed as previously described.<sup>8</sup>

### Families

FAMILY PN-44. The proband (PN-44.1; Fig 1) was the sixth child of healthy, consanguineous parents. One brother died at age 3 months of heart failure, two sisters were healthy, and one sister and one brother had a similar neurological phenotype. The affected sister died at age 48 years because of a cardiomyopathy; detailed neurological informa-

tion was unavailable. The affected brother (PN-44.4) is described later in this article.

Beginning in the 1st year of life, Patient PN-44.1 had difficulty sitting and delayed acquisition of motor milestones. She developed scoliosis in puberty. A neurological examination at age 50 years showed hearing loss; weakness of the intrinsic hand (5-/5), foot (5-/5), and distal leg muscles (5-/5); atrophy of the thenar and foot muscles; a steppage and ataxic gait; absent tendon reflexes; s-curved scoliosis; and pes cavus. Her proximal strength was normal. Coordination tests showed slight dysmetria on the finger-nose test. She had severely decreased sensitivity to touch, position, vibration, pinprick, and temperature distally to the level of the knees and elbows. Electrophysiological studies of the median and ulnar nerves showed slow motor nerve conduction velocities (NCVs; 3m/sec), reduced compound muscle action potential (CMAP; median, 1.1mV; ulnar, 0.45mV; control, >6mV), and undetectable median sensory nerve action potential (SNAP). The discrepancy between the severely reduced CMAP and the well-preserved strength can be explained potentially by the marked temporal dispersion of the CMAP, which make the peak-to-peak measurements less reliable.

Patient PN-44.4 had gait problems from childhood and developed severe scoliosis at age 10 years. On examination at age 54 years, he had hearing loss; absent reflexes; weak foot and distal leg muscles; and atrophy of the hands, distal forearms, and calves. His proximal muscle strength was normal. His sensation in response to touch, position, vibration, and pinprick was severely reduced in both arms and legs.

FAMILY PN-761. Patient PN-761.3 was the first child of healthy, consanguineous parents (see Fig 1). She had delayed motor development; she sat at age 10 months, crawled at age 17 months, stood with support at age 4 years, and took her first steps at age 5 years. At age 6 years, she was able to walk 20 to 30m with a broad-based gait and marked sensory ataxia. On examination at age 2 years, she had absent deep tendon reflexes, weakness of her lower legs and hands, atrophy of the distal lower leg muscles, incomplete foot dorsal flexion, pes planus, and scoliosis. When last seen at age 6 years, she had weak proximal muscles, could not rise from a squat, walked with locked knees, and was unable to hop on two legs or stand on one leg. Her sensation in response to vibration was diminished in the distal lower legs and hands, and her tongue showed fasciculations. Her electrophysiological studies at age 20 months showed a normal sensory NCV (53m/sec), latency (1.3msec), and action potential (SNAP; 21 $\mu$ V) but undetectable peroneal and tibial CMAP (stimulus, 100mA for 0.5sec). When the patient was 5 years of age, electrophysiological studies showed undetectable CMAP and decreased sensory NCV (46.3m/sec) in the median nerve and an undetectable SNAP in the sural nerve. Her visual evoked potential was normal, and her auditory evoked potential showed a slight delay of wave I.

## Results

### Periaxin Gene Mutation Analysis

By DNA sequencing, we screened each coding exon of *PRX* for mutations in 29 peripheral neuropathy pa-

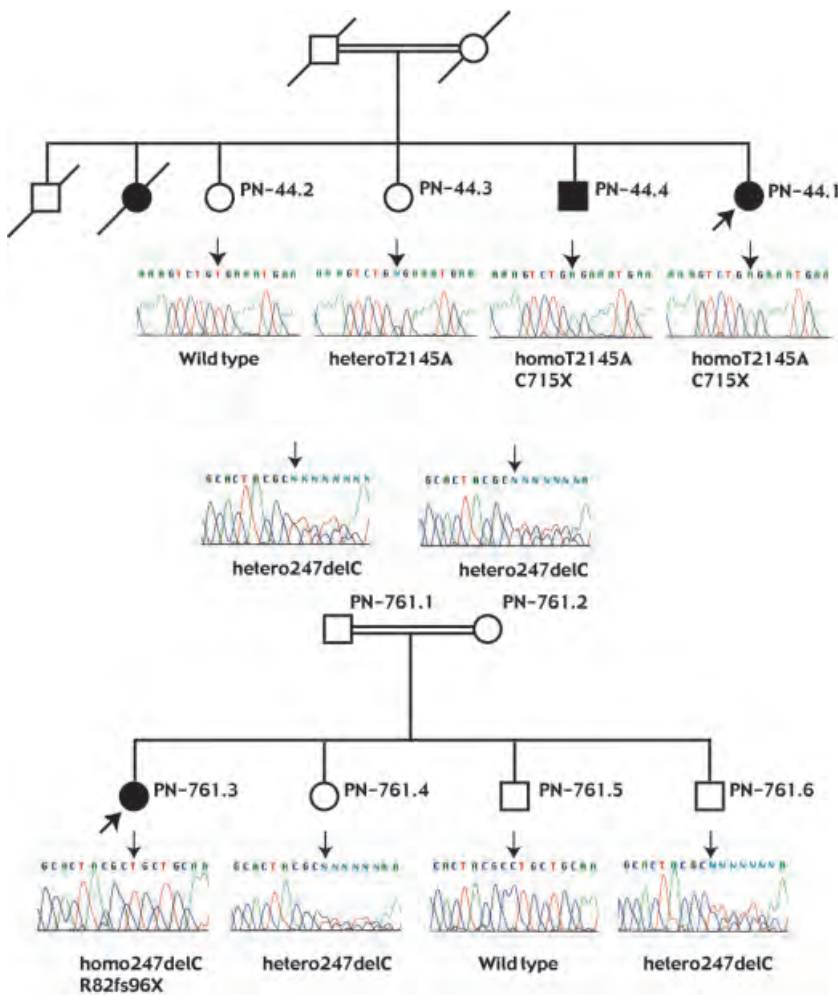


Fig 1. Chromatograms of PRX alterations identified in two families. Standard pedigree symbols are used; males are represented by squares, and females are represented by circles. Black, filled symbols indicate patients with Charcot-Marie-Tooth (CMT) neuropathy or Dejerine-Sottas neuropathy (DSN). Families PN-44 and PN-761 exhibited autosomal recessive inheritance. Below each individual, the DNA sequence chromatogram is shown, with the specific mutation (vertical arrows) given under the chromatogram. PN-44.1 and PN-44.4 were homozygous, and their unaffected sister PN-44.3 was heterozygous for the C715X mutation. PN-761.3 was homozygous and her parents and unaffected brother were heterozygous for the R82fsX96 mutation.

tients who had tested negative for mutations in PMP22 (peripheral myelin protein), MPZ (myelin protein zero), GJB1 (connexin 32), and EGR2 (early growth response 2 protein). Sibling patients PN-44.1 and PN-44.4 were homozygous for the mutation 2145T>A, which by conceptual translation substitutes a nonsense stop codon for cysteine at amino acid 715 (C715X). Patient PN-761.3 was homozygous for 247ΔC, which results in frameshift mutation R82fsX96. The unaffected parents, sister, and brothers either were heterozygous carriers or did not carry the mutation (see Fig 1). We did not observe either 2145T>A or 247ΔC in 180 control chromosomes.

### Histopathology

PATIENT PN-44.1. Light microscopy indicated a severe loss of myelinated axons of all diameters and increased connective tissue (Fig 2A). Although some remaining myelinated fibers were normal, many showed tomacula formation or small onion bulb formations.

Some onion bulbs had a central axon, but many were denervated. There was no evidence of axonal regeneration. Endoneural and perineural vessels were normal. On electron microscopy, the tomacula consisted of concentric or eccentric thickenings of the myelin sheath with focally folded myelin surrounding a constricted axon. The onion bulbs were made up of concentrically arranged Schwann cell processes with or without a central axon. Multiple paranodal abnormalities were identified, including a reduced number of myelin loops and an absence of septate-like junctions between the paranodal myelin and the axon (see Fig 2F).

PATIENT PN-761.3. Light microscopy (see Fig 2B) indicated a severe deficiency of large, myelinated fibers. Numerous fibers were demyelinated or thinly remyelinated. Atrophic axons with relatively thick myelin sheaths (tomacula) were occasionally seen (see Figs 2B and C). Typical onion bulb formation was minimal. At the electron microscopic level, basal lamina onion

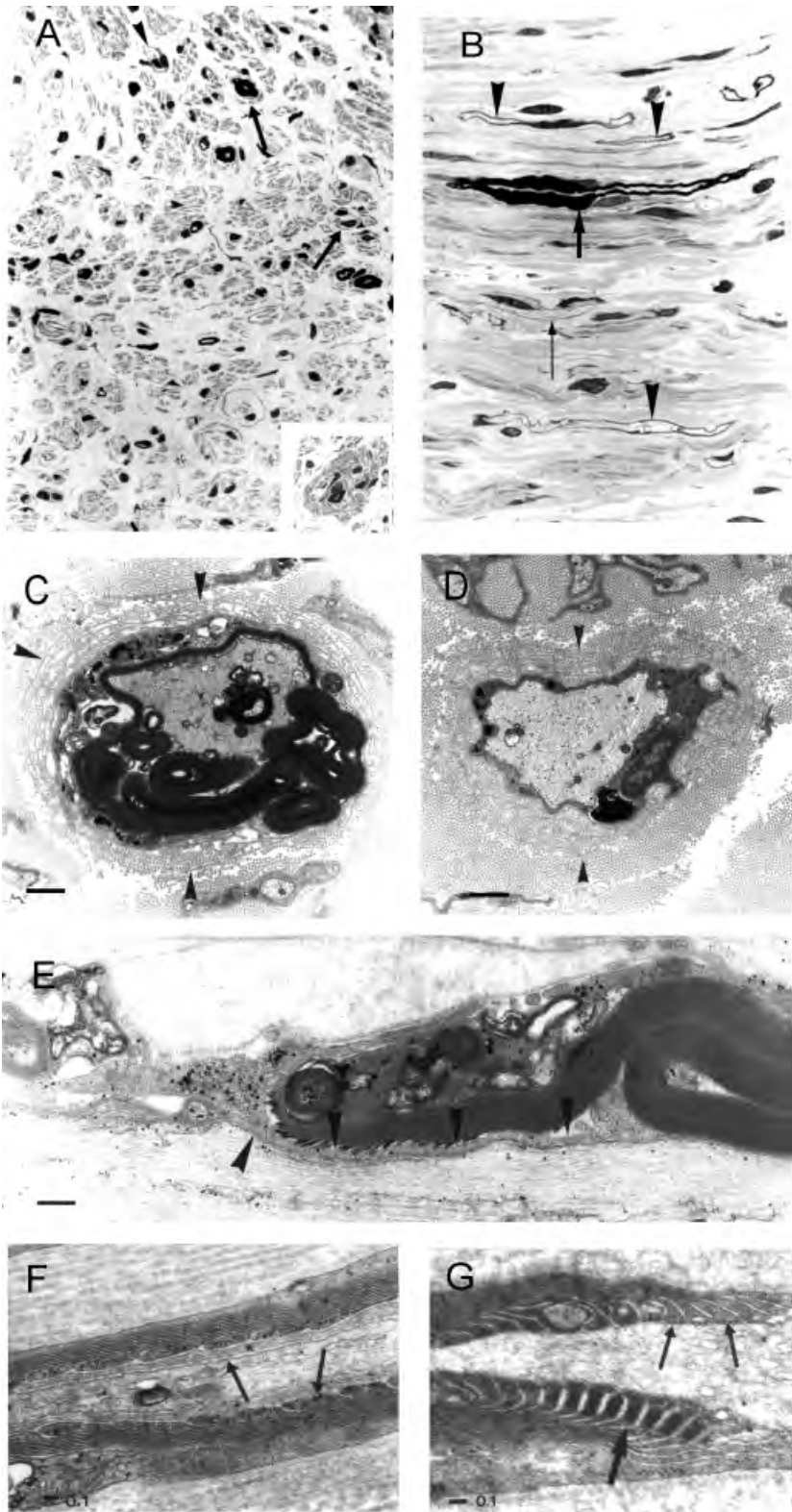


Fig 2. (A, B) Light microscopy. (A) Patient PN-44.1: a transverse, semithin section of the sural nerve biopsy shows loss of myelinated fibers of all sizes; onion bulbs (arrows), which were sometimes denervated (arrowheads); and tomacula formations. A complex of grouped, proliferated Schwann cell processes surrounded a myelinated axon (inset) ( $\times 637$  before 7% reduction). (B) Patient PN-761.3: a tomaculous fiber (thick arrow), a demyelinated axon (thin arrow), and thinly remyelinated fibers (arrowheads). The connective tissue is increased in amount ( $\times 900$  before 7% reduction). (C–G) Electron microscopy. (C) Patient PN-761.3: a relatively large axon with numerous neurofilaments is surrounded by a focally folded, newly formed, disproportionately thin myelin sheath and by one to seven concentrically arranged empty basal laminae (arrowheads). Adjacent fibroblastic processes and Schwann cell processes with or without an unmyelinated axon are also seen ( $\times 10,000$  before 7% reduction). (D) Patient PN-761.3: typical basal lamina onion bulb formation with one to eight layers of empty basal laminae (arrowheads) surround a large, demyelinated axon with an increased density of neurofilaments, indicating some degree of shrinkage. The collagen fibrils between the layers are slightly thinner than in the surrounding endoneurium. Glycogen granules are accumulated at several sites in the cytoplasm of the Schwann cell ( $\times 11,500$  before 7% reduction). (E) Patient PN-761.3: this heminode shows paranodal myelin folds and a Schwann cell process separating terminal myelin loops from the axon. Scale =  $1\mu\text{m}$ . (F) Patient PN-44.1: abnormalities of paranodal myelin loops and the absence of septate-like junctions or transverse bands (arrows). The myelin loops and axon are separated by a Schwann cell process (asterisk). There were no abnormalities of the myelin packing. Scale =  $0.1\mu\text{m}$ . (G) Control sural nerve: note the well-developed septate-like junctions or transverse bands (arrows) of normal paranodal myelin loops. Also note the adherens junctions (big arrow). Scale =  $0.1\mu\text{m}$ .

bulbs (see Fig 2D) with up to eight layers were frequently encountered. The paranodes of nerve fibers showed incomplete myelination or demyelination and separation of multiple terminal myelin loops from the axon at the paranode, sometimes with intervening Schwann cell processes (see Fig 2E). The unmyelinated axons were of uneven size and surrounded by Schwann cell processes that showed degenerative changes (data not shown).

#### Periaxin Immunofluorescence Analysis

Immunofluorescence analysis of a normal human sural nerve biopsy detected both myelin basic protein and L-periaxin (anti-N-terminal, anti-repeat, and anti-C-terminal). In Patient 44.1, there was staining for the N-terminal and repeat region antibodies but not for the anti-C-terminal antibody, even though there was myelin basic protein-positive staining (Fig 3).

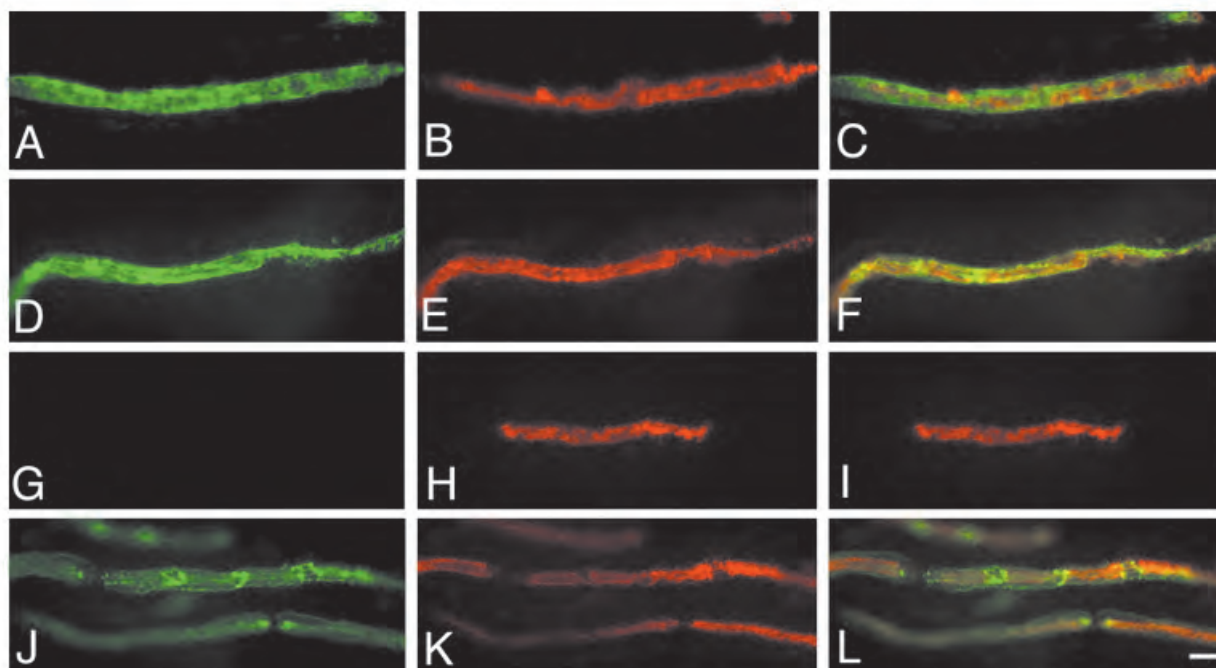
#### Discussion

Our analyses of these two families confirm that putative loss-of-function mutations in *PRX* cause autosomal recessive neuropathies and broaden the spectrum of *PRX*-associated peripheral neuropathies. Consistent

with the phenotype of *Prx*<sup>-/-</sup> mice<sup>10</sup> and previously reported patients,<sup>2,3</sup> all three patients reported in this study had marked sensory involvement. Such severe sensory involvement is rare among patients with mutations in other CMT-associated genes such as *PMP22*, *MPZ*, *GJB1*, and *EGR2* and, therefore, may be a signature clinical feature of neuropathy arising from *PRX* mutations. Interestingly, the sensory involvement observed in Patients PN-44.1 and PN-44.4 was more severe, and their motor neuropathy less severe, than previously reported for patients with *PRX* mutations (Fig 4).<sup>2,3,11</sup>

Patient PN-761.3 is the only patient reported to have a *PRX* mutation affecting both L- and S-periaxin; all other patients had mutations involving only L-periaxin (see Fig 4). A thorough evaluation of her symptoms and nerve histopathology did not identify features that were distinct from those observed in other patients; therefore, no specific pathology could be attributed to the frameshift mutation in S-periaxin. Because the frameshift mutation occurs in exon 6 (the penultimate exon of L-periaxin), we predict that this mutation will result in complete loss of L-periaxin expression by nonsense-mediated RNA de-

Fig 3. Immunofluorescence analysis of a sural nerve biopsy from Patient PN-44.1. (A–C) Nerve fibers from the patient show staining with N-terminal *PRX* antibody (A) and myelin basic protein (MBP) (B), which colocalize (C). (D–F) Nerve fibers from the patient show staining with repeat region *PRX* antibody (D) and MBP (E), which colocalize (F). (G–I) Nerve fibers from the patient show no staining with C-terminal *PRX* antibody (G) but staining with MBP (H), indicating that a truncated *PRX* protein is formed. (J–L) Nerve fibers from a normal control subject show staining with the C-terminal *PRX* antibody (J) and MBP (K), which colocalize (L). Note the organized staining of *PRX* in the Schmidt-Lantermann incisures, which is not present in the patient. Scale = 5  $\mu$ m.



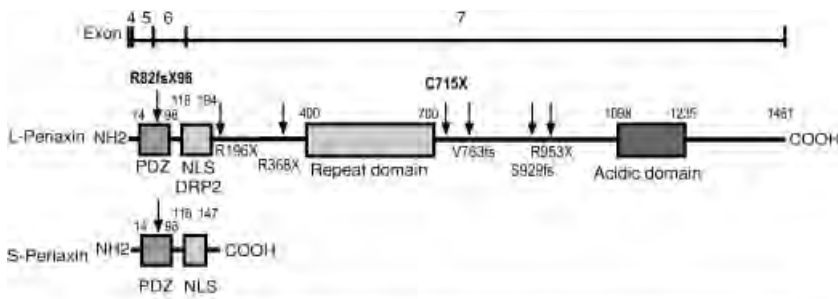


Fig 4. Summary of all reported mutations identified in PRX.<sup>2,3</sup> The top panel depicts exons encoding the periaxin proteins. Exons 1, 2, and 3 are noncoding. The middle panel of horizontal shaded boxes illustrates the various domains of L- and S-periaxin. Previously reported mutations are given below, with the mutations reported herein shown above. The locations of mutations are indicated by the vertical arrows. The mutation C715X affects only L-periaxin, and the mutation R82fsX96 affects both S- and L-periaxin. The table at the bottom lists all reported PRX mutations and their associated disease phenotypes. PDZ = PDZ domain; NLS = nuclear localization signal; DRP2 = dystroglycan-dystrophin-related protein 2 binding domain.

Patient	Phenotype	Pathogenic Allele 1	Frequency	Pathogenic Allele 2	Frequency
PN44.1	CMT	C715X	0/180	C715X	0/180
PN44.4	CMT	C715X	0/180	C715X	0/180
PN761.3	DSN	R82fsX96	0/190	R82fsX96	0/190
851	DSN	R953X	0/190	S929fsX957	0/190
1461	DSN	R368X	0/178	V763fsX774	0/178
1136	DSN	S929fsX957	0/190	S929fsX957	0/190
CMT4F	DSN	R196X		R196X	

cay.<sup>14</sup> In contrast, because exon 6 is the last exon of S-periaxin, we predict that S-periaxin may be expressed as an altered protein but fulfill the function of S-periaxin.

An unusual observation in PN-761.3 was the discordance between the sensory clinical findings and electrophysiology. Electrophysiological studies showed normal or mildly decreased sensory NCV in sural or median nerves, whereas clinical and pathological examinations suggested severe sensory nerve involvement. This finding probably indicates the preservation of some myelinated fibers and suggests that a normal sensory NCV in early childhood does not exclude a PRX mutation, again illustrating the difficulty in differentiating and diagnosing various forms of peripheral neuropathy by electrophysiology alone.<sup>1,15-17</sup>

The peripheral nerve pathology observed in our patients included demyelination with minor remyelination, typical or basal lamina onion bulb formation with occasional tomacula, focally folded myelin, and detached terminal myelin loops. To the best of our knowledge, detachment of terminal paranodal myelin loops from the axon with loss of septate-like junctions and transverse bands has not previously been reported in human inherited peripheral neuropathies with known mutations, although such observations have been made in some animal models.<sup>18-20</sup> The formation of axoglial junctions at the paranode has been shown to require at least three proteins: contactin and Caspr on the axonal surface and an isoform of neurofascin, NF155, on the glial surface, which together

form an adhesion complex.<sup>21</sup> Therefore, the description of the axoglial junctions in our patients might suggest that L-periaxin is necessary for the formation or maintenance of the adhesion complex.

L-periaxin is an integral constituent of a DRP2 complex and possibly other plasma membrane complexes, where it presumably interacts with the basal lamina surrounding the Schwann cell.<sup>9</sup> The importance of such complexes for stabilizing the axon-Schwann cell unit is illustrated by periaxin-null mice, which show a late-onset peripheral demyelinating neuropathy,<sup>10</sup> and by CMT4F and Dejerine-Sottas disease among patients with PRX mutations.<sup>2,3</sup> However, although the interaction between periaxin and DRP2 may be essential for complex formation, the disruption of the interaction between these two proteins does not appear to be essential for causation of demyelinating CMT. Immunofluorescence studies of the nerve biopsy from Patient PN-44.1 showed that this patient made a stable, truncated periaxin protein containing the DRP2 binding domain. This suggests that the truncated protein can still interact with DRP2 and that interaction with DRP2 is not sufficient for L-periaxin's function. In addition, we screened 168 patients with CMT and related neuropathies for DRP2 mutations but did not identify any nucleotide sequence variants segregating with disease (H.T., C.F.B., and J.R.L, unpublished data).

Genotype-phenotype correlations among patients with PRX mutations are limited by the small number of patients; nevertheless, some conclusions are suggested by a comparison of our Patient PN-44.1 and

the patient described by Guilbot and colleagues.<sup>3</sup> In contrast to PN-44.1, the patient of Guilbot and colleagues had both severe motor and sensory neuropathy and no detectable L-periaxin. This suggests that patients with severe motor and sensory neuropathy do not produce detectable L-periaxin, whereas those with milder motor neuropathy and more prominent sensory neuropathy produce a truncated form of L-periaxin. Whether this difference in phenotype is caused by partial loss of L-periaxin function or gain of function in Patient PN-44.1, as opposed to a complete loss of L-periaxin function, is unclear; the C-terminal domain truncated in Patient PN-44.1 was responsible for targeting the protein for ubiquitin-mediated proteolysis (S. Vasiliou and P.J.B., unpublished data, 2002). Therefore, in addition to any loss of function caused by the absence of the C-terminal domain, this truncated protein may have enhanced stability and thereby gain-of-function effects that disrupt interactions of the Schwann cell with basal lamina.

Similar to the spectrum of phenotypes observed with the mutation of other genes associated with CMT and related inherited peripheral neuropathies, the clinical phenotypes manifested in patients with *PRX* mutations include CMT myelinopathies and DSN. However, in contrast to the mutation of other neuropathy genes, the mutation of *PRX* causes a prominent sensory neuropathy. These observations on peripheral neuropathy due to recessive *PRX* mutations add to a growing body of evidence implicating specific genes and proteins in peripheral nerve function and delineating the pathological consequences of their dysfunction.

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Electronic Database Information: Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim>

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