Clinical and Molecular Studies in a Family With Probable X-linked Dominant Charcot-Marie-Tooth Disease Involving the Central Nervous System

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**Objective:** To investigate the clinical and molecular characteristics of an apparently X-linked dominant form of Charcot-Marie-Tooth (CMT) disease in a family with central nervous system involvement and additional features.

**Background:** Charcot-Marie-Tooth disease may be inherited as an autosomal dominant, autosomal recessive, or X-linked trait. In the X-linked dominant form of CMT, females demonstrate milder clinical and electrophysiological features compared with male relatives.

**Methods:** Clinical and related examinations were performed in 4 affected individuals from a family with a novel form of CMT affecting males more severely than females. DNA analysis of the connexin 32 (Cx32) gene and proteolipid protein (PLP) gene was performed. We genotyped 3 members of the family to determine which regions of the X chromosome were inherited discordantly in the affected and unaffected brothers.

**Results:** Clinical studies revealed significant spasticity, hyperreflexia, and delayed central conduction, in addition to peripheral neuropathy. Nerve conduction velocities were slower in the affected males than in the affected females. Direct DNA sequencing of the Cx32 coding region and neural-specific promoter were normal. A PLP null mutation was excluded. Levels of very long chain fatty acids were normal. Genotyping studies of the X chromosome supported X-linked inheritance of the neuropathy.

**Conclusions:** This family differs from others with hereditary motor and sensory neuropathic diseases by the presence of upper motor neuron signs and additional features. The clinical features and inheritance pattern are consistent with X-linked dominant inheritance or autosomal dominant inheritance.

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**RESULTS**

**CLINICAL FINDINGS**

**Patient II-7**

The proband (patient II-7, Figure), a 56-year-old woman, was born with a foot deformity and was a clumsy child. She developed gait instability at age 20 years. At age 18 years, she completed boot camp and subsequently served 2 years in the mil-

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**CHARCOT-MARIE-TOOTH (CMT) disease is a clinically and genetically heterogeneous group of peripheral nerve disorders characterized by distal weakness, atrophy, sensory loss, and decreased tendon reflexes.**

1.2 Charcot-Marie-Tooth has been classified according to the pattern of inheritance and whether the abnormalities affect primarily myelin (CMT1) or axons (CMT2). Median motor nerve conduction velocities distinguish the 2 types.3 Genetic studies have identified mutations in several peripheral myelin genes: peripheral myelin protein 22 (PMP22), myelin protein zero (P0), and early growth response 2 (EGR2).4 The X-linked dominant form of CMT (CMTX) was mapped to Xq13.1, and subsequently, mutations in connexin 32 (Cx32) were shown to cosegregate with the phenotype.5 In CMTX families, males generally have a more severe phenotype than females, with onset of symptoms at an earlier age. Nerve conduction velocities are typically slower in affected males compared with their affected female relatives.6 More than 160 mutations in the Cx32 gene have been reported in CMTX families.7

We describe here the clinical and genetic studies in a family with an apparently novel form of X-linked dominant CMT with spasticity and central conduction delay.

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PATIENTS AND METHODS

PATIENTS

Clinical information and family history were obtained by inpatient or outpatient evaluations in the Neurology Department at Yale New Haven Hospital, New Haven, Conn, or the West Haven Veteran’s Hospital, West Haven, Conn. Clinical records from Newington Children’s Hospital, Newington, Conn, for patient IV-1 were reviewed. Additional family history was obtained through interviews with family members, one of whom is a nurse. Written informed consent was obtained from participants according to a protocol approved by the Human Investigations Committee at Yale. Genomic DNA was extracted from peripheral blood lymphocytes using standard methods. Patient III-1 twice declined to have blood drawn from herself or her son.

ELECTROPHYSIOLOGICAL EVALUATION

All nerve conduction studies were performed by one of us (J.M.G.) using Dantech (Counterpoint MK2 or Neuroview, Minn) equipment. Standard techniques were applied to measure nerve conduction. Visual evoked potentials were obtained by pattern reversal to monocular full-field stimulation using 30-minute checks, reversing at a rate of 1.9 Hz. Brainstem auditory evoked potentials were performed using monaural stimulation with rarefaction clicks with a 100-ms duration at a rate of 11.1 Hz. Somatosensory evoked potentials were elicited by unilateral percutaneous stimulation of the median nerve at a threshold just above motor threshold, and recorded from the brachial plexus (Erb potential), cervical spine at C2 (N13), and the contralateral parietal area (N19) with a frontal (F2) reference.

ANALYSIS OF Cx32

The Cx32 gene coding region (exon 2) was amplified by polymerase chain reaction (PCR) using previously published primer sets. The reaction mixture (25 µL) contained 100 ng of genomic DNA, 10mM Tris-HCl (pH, 8.3), 60mM KCl, 7 pmol of each primer, 1.25mM MgCl2, 2.5 U of AmpliTaq DNA polymerase (Applied Biosystems, Foster City, Calif). After an initial denaturation step at 95°C for 5 minutes, PCR was performed for 35 cycles at 95°C for 1 minute, 60°C for 1 minute, and 72°C for 1 minute, followed by a final extension step of 72°C for 5 minutes. The PCR products were analyzed on a 1% agarose gel, purified by Qiagen columns (Qiagen, Valencia, Calif) and directly sequenced using an automated 373A sequencer (Applied Biosystems). Sequence comparisons were done manually and with BLAST software (National Center for Biotechnology Information, Bethesda, Md).

ANALYSIS OF THE Cx32 PROMOTER REGION

The Cx32 gene promoter P2 region was amplified using primers P7 and P11 and conditions previously reported in a 50-µL reaction containing 100 ng of genomic DNA. The size of the product was verified by electrophoresis on a 2% agarose gel, and sequenced using an Applied Biosystems 373A sequencer. In addition, a new primer, P9, was designed (antisense, −397 to −417), 5’ CACCCAGACAGTGCTCCCCATG 3’, and used with the published primer P16 (antisense, −745 to −725) to amplify a 348-base pair (bp) product for restriction digestion. Restriction digests were performed at 37°C with 10 µL of the PCR product and 20 U of BanII (New England Biolabs, Beverly, Mass) for 2 hours.

ANALYSIS OF THE PROTEOLIPID PROTEIN GENE

We excluded the G-4 deletion described by Garbern et al and other mutations in exon 1 of the proteolipid protein (PLP) gene by using the PCR-directed site-specific mutagenesis test developed by Sistermans et al. Briefly, a mutated forward primer was used with an intron 1-specific reverse primer to introduce a Ncol site into the resulting 114-bp PCR fragment. Restriction digestion with Ncol from a wild-type allele results in 85-bp and 29-bp fragments; an exon 1 mutation will prevent this digestion.

GENOTYPING

X-chromosomal microsatellite markers were tested by use of primers available from Research Genetics (Huntington, Ala). Details regarding primer sequences and PCR conditions are available from the Genome Database (http://gdbwww.gdb.org). Locations and genetic distances were obtained from a Marshfield chromosome map (http://research.marshfieldclinic.org/genetics/), the Integrated X-Chromosome Database, version 2.3 (http://ixdb.molgen.mpg.de/), and the Cooperative Human Linkage Center (http://cgap.nci.nih.gov/CHLC). Polymerase chain reaction amplifications were performed in a 25-µL reaction containing 10 to 100 ng of genomic DNA, 10mM Tris-HCl (pH, 8.3), 50mM KCl, 2.5mM MgCl2, 7 pmol each of sense and antisense primer, 250 µM of dNTPS, and 0.25 U of Taq polymerase (Perkin-Elmer). Ten to 25 ng of PCR product was diluted to 6 µL with denaturing solution (94% formamide, 0.05% xylene cyanol solution, and 0.04% bromophenol blue), and heat denaturated at 95°C for 5 minutes. Samples were separated at 5°C or 20°C on 12.5% polyacrylamide gels (GeneGel Excel 12.5/24; Amersham Pharmacia Biotech AB, Uppsala, Sweden) from the manufacturer using the GenePhor Electrophoresis Unit (Amersham Pharmacia Biotech). Following the separation, the DNA was stained using the Hoefer Automated Gel Stainer with the PlusOne DNA SilverStaining Kit (Amersham Pharmacia Biotech).
nuclear antibody, C-reactive protein, folate, and vitamin B12 levels; brain computed tomography scan; myelogram; and phytanic acid level. Results of commercial DNA testing (Athena Diagnostics, Worcester, Mass) for spinocerebellar ataxia 1 (SCA1), SCA2, SCA3, Friedreich ataxia, the peripheral myelin protein 22 (PMP22) duplication, and Cx32 mutations were normal. Cerebrospinal fluid protein level was elevated on 2 occasions (89 mg/dL and 69 mg/dL [normal range, 15-45 mg/dL]). A magnetic resonance imaging (MRI) scan of the brain and spine at age 47 years showed bilateral increased signal in the white matter, with a normal corpus callosum, mild atrophy of the distal thoracic cord, and conus medul- laris. Evoked potentials were performed at age 42 years. Visual evoked potential showed normal response on the right side, and small amplitude and delayed potentials on the left side. There was a history of childhood amblyopia. Somatosensory evoked potentials showed grossly delayed, small-amplitude spinal and cerebral potentials. Brain stem auditory evoked potentials showed normal eighth-nerve volleys, but central potentials were delayed and of reduced amplitude. In summary, these sug- gested both central and peripheral conduction delay. Nerve conduction studies for the 4 affected individuals are summarized in Table 1. Results were consistent with demyelinating and axonal sensorimotor neuropathy. Significantly, nerve conduction velocities were slower in the males than the females, and were near normal in an obligate gene carrier female (patient III-1).

**Patient III-4**

The proband’s son is a 33-year-old man who was born after a complicated forceps delivery with face presentation and had a childhood learning disability. He had bronchi- tis as an infant, talked at age 3 years, and walked at age 9 years with long leg braces. His clinical features included mental retardation, a total of 3 seizures, nystagmus, se- vere kyphoscoliosis, hip dislocation, and contractures of the hips, knees, and wrists by his late 20s. His examina- tion was remarkable for limited and dysarthric speech, nys- tagmus, peripheral neuropathy, distal atrophy, pes cavus, spasticity, increased patellar reflexes, absent ankle re- flexes, and plantar responses. He is confined to bed and stretcher because of the scoliosis and contractures, is fed by a gastrostomy tube, and lives in a group home. He had the following normal test results: SCA1 and SCA3; very long chain fatty acid (VLCFA) and lactate levels; and hexos- aminidase A and B, arylsulfatase A, galactocerebrosidase, and β-mannosidase activities. Urine sulfatide level was mildly elevated in one test. Results of a retinal exami- nation were normal. Audiometry results were normal.

**Patient III-1**

The proband’s daughter is a 36-year-old woman with a normal early history. She walked at 14 months. She began to have episodes of twisting her ankles and occa- sional falls as a teenager. On examination at age 23 years, she had pes cavus, distal leg atrophy, normal muscle strength including peroneals, claw toes, and mild spasticity of the legs. Levels of VLCFA were normal. At age 27 years, visual and brainstem auditory evoked potentials were done. The P100 latencies were normal (left, 98 ms; right, 89 ms) but with an interocular latency difference of 9 ms (+2 SD). Brainstem auditory evoked potential showed a prolonged wave III-V interpeak interval of 2.44 ms and a wave I-V interpeak interval of 4.60 ms following right ear stimulation. This suggests a con-duction defect between the lower pons and the midbrain and abnormal latency intensity function of wave V bilaterally, suggesting possible associated conductive hearing loss. Formal audiometry was not performed.

**Patient IV-1**

The 12-year-old (current age) grandson of the proband has motor and sensory neuropathy, bilateral hip dysplasia, and spasticity. He had peripheral neuropathy as well as spasticity by age 4 years. He underwent eye surgery for strabismus and had multiple leg operations, including adductor tenotomies, lengthening of the Achilles tendons, and femoral osteotomies. He walks with leg braces and a walker. He uses a wheelchair for long distances. He is in special education for reading and math, and takes regular classes for other subjects. Test results included normal lactate and pyruvate levels in blood and CSF, and normal ammonia and VLCFA levels. Cerebral spinal fluid protein level was elevated at 54 mg/dL (normal range, 15-45 mg/dL). Brainstem auditory evoked potential was abnormal with no wave V recorded on the right and a reproducible wave V on the left. The left wave I-III interpeak latency was 2.76 ms, the left wave I-V interpeak latency was 4.34 ms, and the right wave I-III interpeak latency was 3.10 ms, which was consistent with conduction delay between the eighth nerve and lower pons.

**MOLECULAR STUDIES OF Cx32 AND THE PLP GENES**

Direct DNA sequencing of the coding region (exon 2) of Cx32 in patient II-7 by both commercial and research testing, and of patient III-4 by research testing did not de- tect any mutations. By sequencing the neural-specific pro- moter region (exon 1b) in these 2 individuals, we
The essential clinical features of this family are peripheral sensorimotor neuropathy, spasticity, hyperreflexia, central conduction delay, and an X-linked dominant pattern of inheritance. Elevated cerebrospinal fluid protein was observed in 2 family members. A brain MRI scan showed leukodystrophy in the proband. The 2 male patients had early motor disability and hip dysplasia. One male patient has mental retardation, but this could be unrelated since he may have suffered birth injury. His nephew, aged 12 years, has essentially normal intelligence, with only mild learning delays. The central manifestations in this family led to extensive investigations, including neurometabolic studies and exclusion of several of the inherited ataxias. Evoked potentials documented central involvement in 3 family members; however, MRI was performed in only one subject. Patient III-4 had an elevated urine sulfatide level which could indicate metachromatic leukodystrophy, but this seems very unlikely since metachromatic leukodystrophy is inherited as an autosomal recessive condition, which is not consistent with the pedigree. Leukocyte arylsulfatase A activity was normal. The observed inheritance pattern in this family could be consistent with either autosomal dominant or X-linked inheritance. Male-to-male transmission, which would exclude X-linked inheritance, is not observed in this family. The clinical picture, however, is more suggestive of X-linked dominant inheritance because the 2 affected males had earlier onset, more severe symptoms, and slower nerve conduction velocities than the affected female relatives.

There are several previously reported conditions that overlap with the features in our family. X-linked adrenoleukodystrophy is known to show considerable phenotypic variability, which may include cerebral demyelination, spastic paraparesis, peripheral neuropathy, Addison disease, and relatively slow progression. This condition was excluded by normal VLCFA levels in plasma in 3 subjects. The later onset forms of Krabbe disease can show leukodystrophy, elevated CSF protein, and peripheral nerve dysfunction in 2 family members. A brain MRI scan showed leukodystrophy in the proband. The 2 male patients had early motor disability and hip dysplasia. One male patient has mental retardation, but this could be unrelated since he may have suffered birth injury. His nephew, aged 12 years, has essentially normal intelligence, with only mild learning delays. The central manifestations in this family led to extensive investigations, including neurometabolic studies and exclusion of several of the inherited ataxias. Evoked potentials documented central involvement in 3 family members; however, MRI was performed in only one subject. Patient III-4 had an elevated urine sulfatide level which could indicate metachromatic leukodystrophy, but this seems very unlikely since metachromatic leukodystrophy is inherited as an autosomal recessive condition, which is not consistent with the pedigree. Leukocyte arylsulfatase A activity was normal. The observed inheritance pattern in this family could be consistent with either autosomal dominant or X-linked inheritance. Male-to-male transmission, which would exclude X-linked inheritance, is not observed in this family. The clinical picture, however, is more suggestive of X-linked dominant inheritance because the 2 affected males had earlier onset, more severe symptoms, and slower nerve conduction velocities than the affected female relatives.

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Table 1. Clinical Features and Peripheral Nerve Conduction Studies*

<table>
<thead>
<tr>
<th>Patient†</th>
<th>Sex</th>
<th>Age at Onset, y</th>
<th>Current Age, y</th>
<th>Nerve</th>
<th>Motor Nerve Studies</th>
<th>Sensory Nerve Studies</th>
<th>Disability Scale</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Distal CMAP Amplitude, mV</td>
<td>Distal Latency, ms</td>
<td>NCV, m/s</td>
</tr>
<tr>
<td>II-7</td>
<td>F</td>
<td>20</td>
<td>56</td>
<td>Median</td>
<td>7.8</td>
<td>5.6</td>
<td>38.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ulnar</td>
<td>10.8</td>
<td>4.1</td>
<td>40.0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Peroneal</td>
<td>0.23</td>
<td>8.6</td>
<td>18.4</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Sural</td>
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<tr>
<td>III-1</td>
<td>F</td>
<td>16</td>
<td>36</td>
<td>Median</td>
<td>8.1</td>
<td>3.1</td>
<td>46.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Peroneal</td>
<td>2.7</td>
<td>4.9</td>
<td>34.0</td>
</tr>
<tr>
<td>III-4</td>
<td>M</td>
<td>&lt;10</td>
<td>33</td>
<td>Ulnar</td>
<td>3.8</td>
<td>6.2</td>
<td>33.3</td>
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<td></td>
<td>Peroneal</td>
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<td>26.9</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Tibial</td>
<td>5.9</td>
<td>8.4</td>
<td>24.4</td>
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<td></td>
<td></td>
<td></td>
<td>Sural</td>
<td>.</td>
<td>.</td>
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</tr>
<tr>
<td>IV-1</td>
<td>M</td>
<td>&lt;3</td>
<td>12</td>
<td>Median</td>
<td>5.0</td>
<td>3.5</td>
<td>31.0</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Peroneal</td>
<td>2.7</td>
<td>4.9</td>
<td>34.0</td>
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<td></td>
<td></td>
<td>Sural</td>
<td>.</td>
<td>2.4</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*CMAP indicates compound muscle action potential; SNAP, sensory nerve action potential; ellipses, data not available; and NR, no response on stimulation.
†Median nerve conduction velocity (NCV) study could not be performed in patient III-4 because of severe flexor contraction at the wrists.

Table 2. Sequence Variants in the Connexin 32 Promoter Region

<table>
<thead>
<tr>
<th>Intron or Exon</th>
<th>Location*</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intron −21 to −22</td>
<td>T insertion</td>
<td></td>
</tr>
<tr>
<td>Intron −103</td>
<td>T→G</td>
<td></td>
</tr>
<tr>
<td>Intron −135</td>
<td>C→T</td>
<td></td>
</tr>
<tr>
<td>Exon 1b −544</td>
<td>A→C</td>
<td></td>
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</tbody>
</table>

*Numbering is based on the A of the ATG initiator methionine codon designated as +1.

The 4 sequence variants (Table 2) were identified and compared with the published sequence (Genbank L47127). An A-to-C transversion at −544 bp from the ATG start site resulted in a new BanII restriction fragment-length polymorphism. All 4 sequence variants were confirmed by sequencing or restriction digestion of the product of separate PCR reactions. Each variant was found in 16 of 16 healthy controls, with no evidence of CMT or spasticity on neurologic examination. The PCR-directed site-specific mutagenesis test did not detect mutations in the small (4 nucleotides) coding region of exon 1 of the PLP gene in patients II-7, III-4, and III-5.

GENOTYPING

A total of 35 X chromosome markers that cover the entire X chromosome at intervals of 10 to 25 centimorgans were analyzed in genomic DNA from the proband (patient II-7) and her 2 sons (patients III-4 and III-5). Affected patients III-1 and IV-1 were not available for study. Data on the concordant or discordant inheritance of markers are presented in Table 3. The 2 brothers (one affected, the other unaffected) have discordantly inherited markers DXS1047, DXS1105, DXS6789, GATA144D04, DXS1061, DXS999, and DXS 996 distributed along the X chromosome. The remaining markers were uninformative because the 2 maternal alleles could not be distinguished.
involvement. This is inherited as an autosomal recessive disorder, in contrast with the inheritance observed in this family. Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive disorder of widespread central nervous system dysmyelination, spasticity, ataxia, and optic atrophy caused by mutations in the PLP gene. Although Pelizaeus-Merzbacher disease typically spares peripheral nerves, mutations involving the first exon of the PLP gene may result in a milder Pelizaeus-Merzbacher disease phenotype with demyelinating peripheral neuropathy.10,11

Central nervous system involvement has been reported in patients with complicated variants of CMT. Thomas et al13 described 3 patients with peripheral myelin protein 22 (PMP22) duplications and associated pyramidal signs, including bulbar and cerebellar involvement. A PMP22 duplication was excluded in our family by DNA testing. Recently, families with CMTX1 and Cx32 mutations but atypical signs, such as severe neuropathy or central nervous system involvement, have been described, thus expanding the phenotype of Cx32-associated neurological conditions.15-17 Some families with CMTX1 have been shown to have mutations in the neural-specific (P2) promoter region. In the family reported here, sequencing of the neural-specific promoter and the coding region did not show any of the previously reported mutations. Our family meets the criteria for “probable CMTX” proposed by Nicholson et al,18 with clinical and electrophysiologic characteristics of CMTX, including a brainstem auditory evoked potential I-V interpeak delay of greater than 4.6 ms. In their study of 23 probable CMTX families, 21 (91%) had I-V interpeak delays of greater than 4.6 ms. We identified 2 informative markers along the X chromosome that were inherited discordantly by patients III-4 and III-5. Linkage mapping to rule out discordant regions of the X chromosome is indicated in boldface. The CMTX1 locus is indicated by the dagger (†).

This family is too small for conventional linkage analysis, but if additional families are reported, then exclusion mapping to rule out discordant regions of the X chromosome in affected patients could be used to narrow the candidate loci. Exclusion mapping was proposed by Romeo et al19 as an approach to small families with rare, X-linked disorders such as Rett syndrome. This disorder is nearly always sporadic, but a few families with 2 or 3 affected members have been described and were crucial to mapping and cloning the Rett syndrome gene.25-29 Elucidating the molecular basis of the condition in this and other families with X-linked neuropathy complicated by additional features shows that in the family reported by Cowchock et al,21 males develop severe distal weakness, sensory loss, and areflexia in the first few years, with increased risk of social or intellectual delay. Obligate heterozygous females, however, are asymptomatic. Linkage to markers in the Xq24-26 region was demonstrated.22 Three families described by Ionasescu et al23 showed linkage to Xp22.2 or Xq26 markers. Their clinical features included neuropathy and mental retardation, tremor, or spastic paraparesis. All of these families differed from the one in the present report by an X-linked recessive inheritance pattern. Whether one of these conditions, or Cx32-negative X-linked dominant CMT, is allelic to the condition reported here remains to be determined.

We performed genotyping of 35 markers on the X chromosome to determine if the inheritance of the X chromosome in this family supported the hypothesis of X-linked inheritance and to identify possible candidate regions containing the disease-causing locus. Genotyping studies showed that 7 informative markers distributed along the X chromosome were inherited discordantly by the affected and unaffected brothers, supporting X-linked inheritance.

These markers are located at Xp22.1 to Xp22.3 (DXS996, DXS999, DXS1061), Xp11.4 to Xp11.3 (GATA144D04), Xq21.33 to Xq22.33 (DXS6789, DXS1105), and Xq25 (DXS1047).

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