Central visual, acoustic, and motor pathway involvement in a Charcot-Marie-Tooth family with an Asn205Ser mutation in the connexin 32 gene

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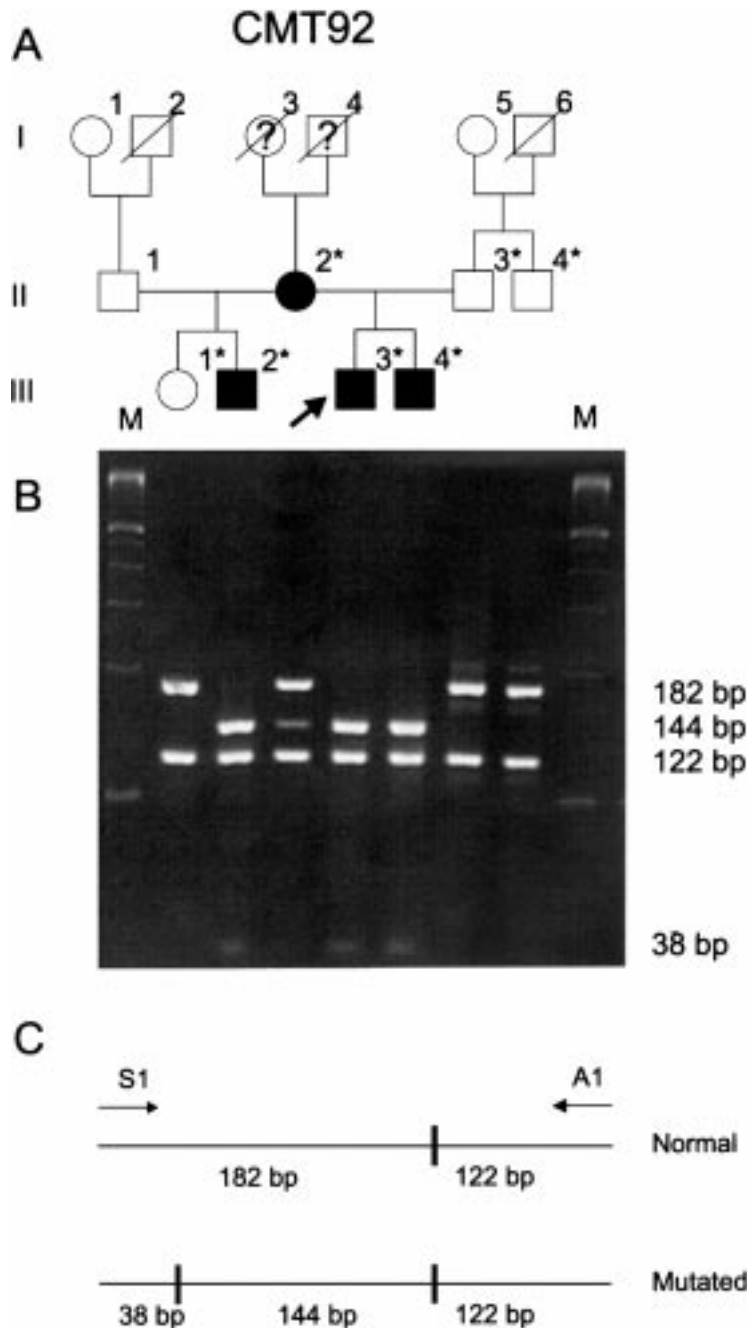E Nelis
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Abstract
Background—X linked dominant Charcot-Marie-Tooth disease (CMT1X) is an inherited motor and sensory neuropathy that mainly affects the peripheral nervous system. CMT1X is associated with mutations in the gap junction protein connexin 32 (Cx32). Cx32 is expressed in Schwann cells and oligodendrocytes in the peripheral (PNS) and in the (CNS) respectively.
Methods—A CMT1X family with a Cx32 mutation was examined clinically and electrophysiologically to determine whether PNS, or CNS, or both pathways were affected.
Results—In a CMT1X family a novel mutation (Asn205Ser) was found in the fourth transmembrane domain of Cx32. The patients showed typical clinical and electrophysiological abnormalities in the PNS, but in addition visual, acoustic, and motor pathways of the CNS were affected subclinically. This was indicated by pathological changes in visually evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs), and central motor evoked potentials (CMEPs).
Conclusions—These findings underscore the necessity of a careful analysis of CNS pathways in patients with CMT and Cx32 mutations. Abnormal electrophysiological findings in CNS pathway examinations should raise the suspicion of CMTX and a search for gene mutations towards Cx32 should be considered.
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Keywords: CMT1X; peripheral neuropathy; connexin 32; visual evoked potentials; central motor conduction velocity; transcranial magnetic stimulation

Charcot-Marie-Tooth disease (CMT) is an inherited peripheral neuropathy causing a progressive neuromuscular impairment in both children and adults. The main clinical features are progressive distal muscle weakness and atrophy of the lower limbs, particularly of the peroneal muscles, and progression to the arms. High arched feet or pes cavus are often present. There is a wide variation in severity and the disease usually starts during the first or second decade. More than 90% of affected people show clinical signs by the age of 27 years.[1] Historically, hereditary motor and sensory neuropathies were classified into several clinical subtypes which now include previously described entities such as CMT, Dejerine-Sottas syndrome, and several other peripheral neuropathies with pyramidal tract, optic nerve, auditory or retinal involvement.[2 3] X linked, autosomal dominant and recessive forms of CMT1, as well as sporadic patients were identified.[2]

X linked CMT has been considered to be relatively rare or non-existent,[4] probably due to the fact that the dominant inherited nature of the disease can easily be overlooked as the transmitting mothers are often clinically asymptomatic. Furthermore, it was shown that about 20% of the CMT1 families are X linked.[5] Mutations involving several myelin genes including peripheral myelin protein 22 (PMP22; CMT1A), myelin protein zero (MPZ; CMT1B) and connexin 32 (Cx32; CMT1X) were found in patients with CMT1. Recent genetic analyses showed at least 65 different Cx32 mutations in 99 unrelated CMT1X families.[6] The Cx32 gene encodes a gap junction protein which is incorporated into cell membranes as a subunit of a hemichannel called the connexon. One connexon comprises six subunits and allows rapid exchange of ions and small nutrients between cells.[7] In the peripheral nervous system, Cx32 is expressed in Schwann cells at the Schmidt-Lantermann incisures and the paranodal regions. The Cx32 protein is also present in the central nervous system where it is expressed in neurons and oligodendrocytes.[8–10]

In this study we describe a CMT1X family with a mutation (Asn205Ser) in the fourth transmembrane domain of the *Cx32* gene. The patients in this family had subclinical abnormalities in the central nervous system pathways.

Material and methods

GENETIC ANALYSIS
Single strand conformation polymorphism analysis was used as a standard procedure to screen for mutations in the coding sequence of Cx32. The polymerase chain reaction (PCR) samples were subjected to electrophoresis on a 1×MDE (FMC BioProducts, Rockland, ME, USA) gel at 15 W for 17 hours at room temperature and silver staining was carried out according to a standard protocol.[11] Direct sequencing of Cx32 exon 2 (part 3) was performed with the primers Cx32-S1 and Cx32-A1[11] using ThermoSequenase (Amer-

sham, England, UK) and the Dye Terminator Cycle Sequencing kit (Perkin Elmer, Belgium). The PCR products were loaded on a polyacrylamide sequencing gel and electrophoresed on the ABI automated DNA sequencer 377

(A) Pedigree of CMT1X family (CMT-92). Symbols: males=squares; females=circles; affected=filled symbol; unaffected=empty symbol; diagnosis unknown=?; arrow = proband; asterisk = DNA available. (B) DdeI restriction pattern of the Asn205Ser Cx32 mutation in CMT1X family members (*). The size marker M represents a 100 bp ladder (Gibco BRL: Life Technologies, Belgium). In the unaffected males (II.3 and II.4) and female (III.1), two PCR fragments are obtained of 182 and 122bp. In the three affected males (III.2, III.3 and III.4), the 144 and 38 bp fragments result from an additional DdeI restriction site due to the Asn205Ser mutation. The affected female (II.2) is heterozygous for the mutation and transmits the mutation to her three sons (III.2, III.3 and III.4). (C) Normal and mutated Cx32 PCR products. The vertical bars represent the DdeI restriction sites. The total length of the Cx32 PCR product amplified with primers Cx32-S1 and Cx32-A1 is 304 bp (Bergoffen et al[12]; Nelis et al[11]). In the normal Cx32 PCR fragment DdeI creates two fragments of 182 and 122bp, whereas in the mutated Cx32 gene the presence of an additional DdeI restriction site creates three fragments; 38, 144, and 122bp.

(Applied Biosystems Inc Foster City, CA, USA). The data were collected and analysed using the ABI DNA sequencing analysis software.

The Cx32 mutation at codon 205 creates a *Dde*I restriction site that can be detected by restriction analysis of the PCR product (see figure C). For this purpose, part 3 of Cx32 exon 2 was PCR amplified with primers sequences Cx32-S1 and Cx32-A[11] [12] with Taq DNA polymerase and PCR buffer (Gibco BRL-Life Technologies, Belgium). A 15 µl aliquot of the PCR amplification product was digested with 10 U of *Dde*I restriction enzyme (New England Biolabs, England, UK). The restriction digest was loaded on to a 4% agarose gel (Gibco BRL-Life Technologies) which was stained with ethidium bromide and photographed on a UV transilluminator.

ELECTROPHYSIOLOGICAL AND PATHOLOGICAL EVALUATIONS

Visually evoked potentials (VEPs) and brainstem auditory evoked potentials (BAEPs) were recorded with standard techniques. VEPs were obtained by simulating at a 3° angle to specifically assess demyelination of maculofoveal pathways. BAEPs in response to 1024 10 Hz click stimuli were measured bilaterally focusing on interpeak latencies I-III and III-V (for detailed methods and normal values see Stöhr et al[13]).

Electromyography of the M tibialis anterior was performed with concentric needle electrodes. Abnormal spontaneous activity as well as motor unit potential morphologies and recruitment patterns were assessed. Transcranial magnetic stimulation to the M tibialis anterior and M abductor hallucis brevis was performed with a circular shape coil (inner diameter 5 cm) and a MagStim 200 stimulator (Magstim Company) to measure the motor evoked potential latency. The central motor conduction time was calculated by subtracting the peripheral motor conducting time (CMCT (ms)=cortical MEP–(F wave latency+distal CMAP)/2)) from the total latency of the MEP. Lumbar stimulation was performed in patients in whom no reliable F wave was obtained (CMCT (ms)=cortical MEP−radicular MEP−3 ms).

NERVE BIOPSY

A sural nerve biopsy was performed in the proband III-3, freshly frozen or fixed in glutaraldehyde or formalin. The biopsy samples were then processed for light and electron microscopy, after embedding in Araldite.

Results

MOLECULAR GENETIC RESULTS

An altered SSCP pattern of the Cx32 part 3 PCR fragment of exon 2 was detected in the mother (II-2) and her three affected sons (III-2, III-3, and III-4) whereas a normal pattern was found in the half sister III-1 (figure A) suggesting the presence of a mutation in the coding region of Cx32. SSCP analysis of the other two regions of Cx32 exon 2 was normal. The altered SSCP pattern was absent in normal controls and a large group of patients

Table 1 Peripheral nerve conduction studies

Patient (sex, age)	Nerve	Motor NCS			Sensory NCS	
		Distal CMAP amplitude (mV)	Distal latency (m/s)	NCV (m/s)	SNAP amplitude (µV)	NCV (m/s)
II–2 (F, 46 y)	Median	13	5.2*	49	2.6*	38*
	Tibial	6.3	4.2	39*		
	Sural				6.5*	36*
III–1 (F, 25 y)	Median	19.5	4.3*	54	5.8*	42*
	Tibial	20.2	3.4	50		
	Sural				25.3	51
III–2 (M, 21 y)	Median	8.5	5.1*	35*	0.5*	24*
	Tibial	3.0*	5.1	32*		
	Sural				4.8*	32*
III–3 (M, 19 y)	Median	2.2*	7.9*	28*	0.9*	31*
	Tibial	2.6*	5.3*	31*		
	Sural				0.7*	34*
III–4 (M, 13 y)	Median	ND	ND	ND	ND	ND
	Tibial	8.6	4.5	30*		
	Sural				NR	NR

*Pathological values; ND=not done; NR=no response upon stimulation; CMAP=compound muscle action potential; SNAP=sensory nerve action potential; NCV=nerve conduction velocity.
Although not clinically affected, the transmitting mother (II-2) showed slight abnormalities in sensory and motor NCVs. The unaffected daugther (III-1) has subtle signs of a (clinically asymptomatic) carpal tunnel syndrome, which is not related to the CMTX mutation. The carriers of the mutation show pathological motor and sensory NCVs .

with CMT1 screened for other Cx32 mutations. Direct DNA sequencing analysis was performed in the index patient III-3 and disclosed an A to G transversion mutation at codon 205 (AAT−AGT) resulting in an amino acid change from Asn to Ser (data not shown). This mutation creates a *Dde*I restriction site that allows the detection of the mutation by PCR amplification of Cx32 part 3 followed by *Dde*I digestion and agarose gel electrophoresis (figure B and C).

CLINICAL, ELECTROPHYSIOLOGICAL, HISTOPATHOLOGICAL, AND MRI CHARACTERISTICS
The pedigree of the CMT1X family (CMT-92) with the Asn205Ser *Cx32* mutation is shown in the figure A. No clinical information regarding the maternal grandparents could be obtained as both died years before our study. The fathers (II-1 and II-3) of the patients were asymptomatic on clinical examination. Electrophysiological examination of one of the fathers (II-3) was normal. No data could be obtained from the other father (II-1) because he refused to participate in this study.

Foot drop, steppage gait, and pes cavus were noted in the proband III-3 when he was 19 years old. The muscle strength for the peroneal muscles was 4 on the MRC scale. At the age of 21 years, peroneal weakness had only slightly progressed but involvement of the hand muscles was apparent. Distal hypoaesthesia for touch, proprioception, and vibration sense was more pronounced in the feet than in the hands. Perception for pain and temperature were normal. The Romberg sign was negative. Deep tendon reflexes could only be obtained after facilitation and the triceps surae reflex could not be elicited. Besides peripheral sensory and motor NCV abnormalities (table 1), severe abnormalities of VEPs (table 2), BAEPs (table 3) and central motor NCVs (table 4) were found. Similar clinical and electrophysiological findings occured in his younger brother III-4 at the age of 13 years. Furthermore, the cranial nerve tests of these clinically affected males III-3 and III-4 were normal and no optic nerve atrophy or hearing loss were noted at ages 13 and 19 years respectively. The sural nerve biopsy of index patient III-3 showed a reduced

Table 2 Visually evoked potentials

Patient	Stimulus	Latencies (ms)		Amplitudes (mV)	
		L	R	L	R
11–2	Foveal	110	117	4	4
	Pattern-reversed transient (22.5')	115	112	16	11
	Pattern-reversed steady state	116	115	19	16
III–1	Foveal	105	Nr*	3	—
	Pattern-reversed transient (22.5')	112	103	7	8
	Pattern-reversed steady state	115	110	13	13
III–2	Foveal	140*	140*	3	1*
	Pattern-reversed Transient (22,5')	124*	122*	2	2
	Pattern-reversed steady state	118	111	3	3
III–3	Foveal	Nr*	Nr*	—	—
	Pattern-reversed transient (22.5')	Nr*	146*	—	2
	Pattern-reversed steady state	160*	169*	8	5
III–4	Foveal	158*	164*	5	4
	Pattern-reversed transient (22.5')	131*	131*	6	5
	Pattern-reversed steady state	131*	125*	3	4
Normal controls (mean+3SD)	Foveal	124	124		
	Pattern-reversed transient (22.5')	119	119		
	Pattern-reversed steady state	123	123		

The transmitting mother (II-2) had a completely normal VEP; the VEP latencies of the unaffected daughter (III-1) were also normal except that no potential could be recorded under foveal stimulation on one eye, which seems to be unrelated to the disease, since no CMT1X mutation was found in this patient. The affected brothers/half-brothers all show pathological slowing (indicated by asterisks) of the P100 potential indicating demyelination of the visual pathways.

Table 3 Brainstem auditory evoked potentials

Patient		Latencies (ms)					Interpeak latencies (ms)	
		W I	II	III	IV	V	W I–III	W III–V
II–2	L	1.5	2.7	3.7	—	5.1	2.2	1.4
	R	1.6	2.7	3.6	4.9	5.4	2.0	1.8
III–1	L	1.7	3.0	3.8	4.7	5.6	2.1	1.8
	R	1.7	2.8	3.7	4.6	5.5	2.0	1.8
III–2	L	1.5	—	4.2*	—	6.2*	2.7*	2.0
	R	—*	—*	—*	—*	—*	—	—
III–3	L	1.8	2.6	4.2*	6.1*	7.1*	2.4	2.9*
	R	1.7	2.9	4.3*	5.9*	6.9*	2.6*	2.6*
III–4	L	2.0	3.2	4.4*	6.0*	6.4*	2.4	2.0
	R	2.3*	3.2	4.4*	—	7.4*	2.1	3.0*
Normal control (mean+3 SD)		2.0	3.1	4.0	5.3	6.1	2.4	2.3

In the unaffected mother (II-2) and her daughter (III-1) no abnormalities were found. The measurements in patient III-2. who was clinically only slightly affected but carries the same mutation as his more severely affected younger half brothers (III-3 and III 4) does not show clear indication of a central auditory pathway involvement. since the peak II was not evoked at all and the peak III was already delayed suggesting a peripheral auditory nerve pathology rather than a central pathology. The clinically affected brothers III-3 and III 4 both show abnormalities compatible with central auditory pathway involvement as demonstrated by pathological slowings (indicated by asterisks) of the IPL III-V.

density of myelinated fibres and loss of myelin on light and electron microscopy. Endoneural fibrosis with endoneural collagenisation and signs of demyelinisation and remyelinisation with onion bulb formation were also present (data not shown). Brain MRI measurements in patient III-3 showed no white matter lesions and were normal before and after contrast with gadolinium (data not shown).

Interestingly, the older half brother III-2 (age 21 years) showed only signs of a peripheral neuropathy without evidence of central nervous system involvement. Foot drop, steppage gait, and pes cavus were absent. The triceps surae reflex was hypoactive. The motor median and tibial NCVs were reduced (table 1). All other tests (VEP, BAEP, and transcortical magnetic stimulation) were normal in this male patient (tables 2–4).

The sister III-1 (age 25 years) of male patient III-2 had a normal clinical examination but showed slight abnormalities of the motor median nerve distal latency, compatible with a subclinical carpal tunnel syndrome (table 1). Her VEPs were completely normal except that no potential was evoked after foveal stimulation (table 2). Because all other recordings, such as BAEPs and transcortical magnetic stimulation (tables 3 and 4), were normal, this abnormality cannot be attributed to demyelination but is rather due to incorrect fixation or myopia.

Finally, the transmitting mother II-2 was asymptomatic on clinical examination. Nevertheless, she had slightly reduced sensory NCVs, the evoked responses had reduced amplitudes and we found pathological central latencies after transcortical magnetic stimulation (table 1 and 4).

Discussion

At least 65 different mutations in all domains of the Cx32 gene have been found in unrelated patients with CMT1X.[6] All these patients had a peripheral nerve pathology documented by slowed NCVs. We identified a novel mutation in the Cx32 gene (Asn205Ser) in a CMT1X family. In this family we found, besides a peripheral neuropathy, abnormalities in motor and sensory central nervous system pathways on VEP, BAEP, and central motor nerve conduction testing.

All male patients (III-2, III-3, and III-4) had prolonged VEP latencies. In patients III-3 and III-4, BAEPs showed a peripheral (prolonged I-III interpeak latency) (IPL)) and central auditory pathway pathology (abnormal III-V IPL). A predominantly peripheral neuropathy of the auditory nerve (abnormal I-III IPL, loss of peak II, and delayed peak III) was found in the half brother III-2. Both the transmitting mother (II-2) and her unaffected daughter (III-1) showed no abnormalities on VEP and BAEP examination.

Involvement of CNS sensory pathways in hereditary motor and sensory neuropathies has been reported by Carroll *et al* and Jones *et al*.[14 15] However, at that time molecular genetic diagnosis was not yet available and their finding could not be linked to a particular gene defect. Jones *et al*[15] speculated that the abnormalities might be due to a dying back phenomenon of the affected peripheral nerves. On the other hand, Scaioli *et al*[16] failed to show central nervous system involvement in patients with CMT. Recently, evidence for involvement of the central acoustic pathway was obtained by measuring BAEPs in patients with CMT1X with Cx32 mutations.[17] However, no other CNS pathways were examined in this study (for example, VEPs or transcortical magnetic stimulation measurements) and it remained unclear whether the disorder would also affect structures other than the acoustic pathway.

In our CMT1X family, not only acoustic but also visual and central motor pathways are affected, suggesting a much larger central nervous system involvement than has been

Table 4 Transcortical magnetic stimulation

Patient	Latency to M tibialis anterior (ms) R/L	C(MEP) amplitude (mV)	Central latency (ms)
II–2	42.9*/42.7*	2.0/3.5	16.6*/15.0
III–1	36.0/36.2	2/1	13.7/13.5
III–2	41.1*/40.9*	2.3/2.9	NC/NC
III–3	39.6*/40.4*	1.6/2.7	13.7/17.4*
III–4	38.0*/36.8*	4.8/4.0	NC/NC

*Pathological values. NC=could not be calculated because the F-wave latency could not be measured.
Since neither F-wave latencies nor lumbar potentials could be determined in III-2 and III-4, no central latency could be calculated in these patients. However, the abnormal long latency to the M. tibialis anterior in these patients with only moderate peripheral motor NCV slowing suggests strongly a central involvement. Most interestingly, although severely affected, a pathological central latency could be determined in index patient III-3, which clearly demonstrates central motor involvement in this patient.

presumed from clinical examinations, in which such widespread central nervous system abnormalities have not been reported to date. Thus, screening for Cx32 mutations seems to be important in patients with a peripheral neuropathy and abnormalities in motor and sensory central nervous system pathways. Abnormalities on MRI in patients with CMT1X have also recently been reported by Bell *et al*[18] In the present study, an MRI examination was only performed in the index patient III-3 and we could not find any abnormalities indicative of white matter lesions. The histopathological examination of his sural nerve showed signs of a demyelinating peripheral neuropathy with degeneration and regeneration and onion bulbs. This is interesting as former studies have pointed out that features of an axonopathy are found in patients with an X linked dominant neuropathy. Furthermore, no real onion bulb formations were noted in these patients.[19] Detailed histopathological studies of patients genetically diagnosed with CMT1X are, however, lacking and further studies are necessary to clarify this issue.

The exact molecular mechanisms that lead to the pathology with predominant disturbance of the peripheral myelin and to a lesser extent the central myelin integrity in CMT1X are unknown. The expression pattern of Cx32 in Schwann cells, where connexons are found in the paranodal region, differs from the the central nervous system where Cx32 is expressed throughout the internodal region and in oligodendrocytes. The reason for this different expression pattern is not known yet, but it might explain the differences in severity of peripheral nervous system versus central nervous system involvement. Because several other connexins are expressed in the central nervous system and the expression patterns differ in the central nervous system and the peripheral nervous system, substitution of the Cx32 function by another connexin gene could be responsible for these differences.[20] As the number of patients that share the same mutation is limited, it is difficult to compare the molecular genetic findings with the resulting disease phenotypes—for example, mutations in the third transmembrane domain of Cx32, which lines the pore, possibly lead to an incorrect alignment of two connexons or an inability to form a proper functional gap junction.[21] A Gly199Arg mutation in the fourth transmembrane region has been described recently and introduces a positive charge which may reduce the membrane stability or modify channel formation.[22] In our CMT1X family, the Asn205Ser mutation creates a hydroxyl containing side change in the fourth transmembrane domain which also might influence the channel formation. Further cellular and molecular biology studies are essential to determine the changes in structure and metabolism of central nervous system and peripheral nervous system myelin sheaths that cause the demyelination in patients with CMT with Cx32 mutations and to examine the influence of the genetic background on the variation of the CMT1X phenotype.

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