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Mosaicism for the Charcot-Marie-Tooth disease type 1A duplication suggests somatic reversion

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Abstract A female patient with clinical signs and symptoms of a demyelinating neuropathy was shown to have a duplication of the 1.5-Mb region on chromosome 17p11.2, typical of the great majority of cases of Charcot-Marie-Tooth disease type 1A (CMT1A). However, analysis of DNA extracted from peripheral blood revealed a 2:2.4 instead of the usual 2:3 ratio between the 7.8- and 6.0-kb *Eco*RI fragments in the proximal and distal repetitive extragenic palindromic (REP) elements of CMT1A. Detection of a 3.2-kb *Eco*RI/*Sac*I kb junction fragment with probe pLR7.8 confirmed the CMT1A duplication. The dosage of this junction fragment, compared with a 2.8-kb *Eco*RI/*Sac*I fragment of the proximal REP elements of CMT1A, was 2:0.58 instead of the expected 2:1 dosage for heterozygous CMT1A duplications. We hypothesized that the lower dosages of these restriction fragments specific for the CMT1A duplication were due to mosaicism; this was confirmed by fluorescence in situ hybridization analysis with the D17S122-specific probe pVAW409R1. In peripheral blood lymphocytes the percentage of interphase nuclei with a duplication in 17p11.2 was 49%. In interphase nuclei extracted from buccal mucosa, hair-root cells or paraffin-embedded nervous tissue the duplication was detectable in 51%, 66% and 74%, respectively. This is the first report of mosaicism in a patient with a CMT1A duplication identified by three different and independent techniques.

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Introduction

Charcot-Marie-Tooth disease type 1 (CMT1) belongs to the group of hereditary motor and sensory neuropathies (HMSN) that are clinically characterized by progressive weakness of the distal muscles of the limbs and by sensory deficits. CMT1 patients show severely reduced nerve conduction velocities (NCV) and segmental de- and remyelination on sural nerve biopsies, leading to typical onion bulb-like formations (Dyck et al. 1993).

The most frequent autosomal dominantly inherited form is CMT type 1A (CMT1A), which is linked to chromosome 17p11.2, where the gene for the peripheral myelin protein 22 *(PMP22)* gene is located (Raeymakers et al. 1989; Vance et al. 1989; Patel et al. 1992; Matsunami et al. 1992; Timmerman et al. 1992; Valentijn et al. 1992a). CMT type 1B is linked to chromosome 1q21.3–q23 with myelin protein zero *(MPZ, P0)* as a candidate gene (Bird et al. 1982; Lebo et al. 1991; Hayasaka et al. 1993a, b); CMT type 1 C has not been associated with a distinct gene locus (Chance et al. 1992). An X-linked locus was assigned to chromosome Xq13 with the candidate gene connexin 32 (*Cx32*) (Gal et al. 1985; Corcus et al. 1992; Raimondi et al. 1992; Bergoffen et al. 1993; Fairweather et al. 1994; Ionasecu et al. 1994). For further details of the molecular genetics of Charcot-Marie-Tooth disease and related peripheral neuropathies see, e.g., Patel and Lupski (1994), Roa and Lupski (1994), Lupski (1996).

The most frequent mutational event associated with CMT1A is a 1.5-Mb duplication in chromosome 17p11.2 (Lupski et al. 1991; Raeymaekers et al. 1991; Pentao et al. 1992). Only a few CMT1A cases have been shown to be carriers of a point mutation in PMP22 (Valentjin et al. 1992b; Roa et al. 1993a, b; Nelis et al. 1994).

The reciprocal recombination event that leads to the CMT1A duplication is a deletion of 1.5 Mb in chromosome 17p11.2, which results in a different neuropathy called hereditary neuropathy with liability to pressure palsies (HNPP) (Chance et al. 1993).

The duplication/deletion in chromosome 17p11.2 has been hypothesized to result most frequently from an un-

equal nonsister chromatid exchange during male meiosis (Raeymakers et al. 1991; Pentao et al. 1992; Palau et al. 1993). We report a female patient suffering from CMT1A with the diagnosis proven molecularly by identification of the duplication in 17p11.2. However, Southern blot and fluorescence in situ hybridization (FISH) analyses of peripheral blood cells revealed a mosaicism for the CMT1A duplication. Moreover FISH analyses of interphase nuclei derived from buccal mucosa, hair-root cells and nervous tissue of a sural nerve biopsy of the patient uncovered different patterns of mosaicism for the duplication in the four tissues examined.

Materials and methods

Molecular analysis

Southern analysis of the duplicated region in CMT1A patients was performed using *Eco*RI- and *Eco*RI/*Sac*I-digested genomic DNA from affected and healthy individuals probed with pNEA102 and pLR7.8. The probe pNEA102 maps to the distal repetitive CMT1A-REP element (Pentao et al. 1992; Lorenzetti et al. 1995) and recognizes two *Eco*RI fragments of 7.8 and 6.0 kb in the proximal and distal REP elements, respectively, of CMT1A. In healthy individuals and patients without a duplication in 17p11.2 the two resulting bands show a ratio of approximately 1:1, reflecting two copies of each band one on each chromosomal homolog (see Fig. 2, lanes 2 and 3). The duplication usually leads to three copies of the 6.0-kb *Eco*RI fragment (ratio of 2:3) (see Fig. 2, lane 1). The reciprocal deletion leads to loss of a single 6.0-kb *Eco*RI fragment (ratio of 2:1) (not shown). The probe pLR7.8 maps to the proximal CMT1A-REP element and is identical to the 7.8-kb fragment recognized by probe pNEA102. It recognizes the 7.8-kb *Eco*RI fragment within the proximal CMT1A-REP element and the 6.0-kb *Eco*RI fragment of the distal CMT1A-REP element. The proximal 7.8-kb *Eco*RI fragment comprises a *Sac*I recognition site producing *Eco*RI/*Sac*I fragments of 5 and 2.8 kb (Fig. 3, lane 1). In CMT1A duplications an additional *Eco*RI/*Sac*I junction fragment of 3.2 kb resulting from a recombination mutation is recognized (Fig. 3, lanes 3, 4) (Reiter et al. 1996). For heterozygous CMT1A duplications the dosage of this junction fragment compared with the 2.8-kb *Eco*RI/*Sac*I restriction fragments of both proximal CMT1A-REP alleles of chromosome 17p11.2 is usually 1:2 (for further details see Reiter et al. 1996). Densitometric analysis on autoradiographs was performed using an Ultroscan XL laser densitometer.

Molecular cytogenetics

Two-color FISH was performed according to standard protocols (Liehr and Rautenstrauss 1995; Liehr et al. 1995). As probes we used the 10-kb plasmid pVAW409R1 (specific for chromosome 17p11.2; Barker et al. 1978) and as an internal standard, to obtain information about the stage of the cell cycle of the examined nucleus, the 30-kb cosmid cRCNeu1 (located on chromosome 17q11.12) (Kallioniemi et al. 1992). Plasmid pVAW409R1 was labeled with biotin and detected by an avidin-FITC (fluorescein isothiocyanate) system (green spots on Figs. 4, 5), cRCNeu1 was digoxigenated and detected by anti-digoxigenin-rhodamine (red spots on Figs. 4, 5). Probes were labeled with the two respective ligands by nick-translation.

Fifty to 100 nonoverlapping nuclei per tissue were analyzed. A patient was estimated to be a carrier of a duplication or to have a normal dosage of the 1.5-Mb region of chromosome 17p11.2, if more than 80% of the evaluable nuclei showed three or two specific (green) signals, respectively.

The FISH procedure was performed on interphase nuclei derived from four different kinds of tissue. Interphase nuclei from heparinized peripheral lymphocytes were prepared according to Verma and Babu (1989) or extracted from the three tissues mentioned above. Nuclei from buccal mucosa were prepared according to Pfeiffer and Schulze (1994) except that, for hypotonic treatment, the 0.4% KCl was replaced by Otto's solution (100 ml 10 mmol TRIS-HCl, pH 7.5, 220 mg KCl, 100 mg $MgCl_2$, 46 mg dithioerythritol) and incubation at 37°C was prolonged to 90 min. Hair-root cells were treated according to Lampel et al. (1993) and paraffin-embedded nervous tissue as described before by Liehr et al. (1995).

Results

Clinical report

The 25-year-old female patient reported painful sensations in the shoulders, which increased after exercise. Earlier examinations had revealed markedly reduced motor and sensory NCVs. The patient shows a bilateral pes cavus, which has also been observed in the mother and a younger brother (see pedigree, Fig. 1). Neither of them, however, suffered from pain or motor sensory deficits; unfortunately no blood was available from these two relatives. On examination the patient showed a mild distally pronounced muscular weakness of the arms and legs. Muscle stretch reflexes were absent. Sensory disturbances of the limbs were located distal to the elbow or knee, respectively. Vibration sense was reduced at the malleolus internus. Motor NCVs from the median, ulnar and tibial nerves were reduced to 18–20 m/s. No sensory action potentials could be recorded from the sural, radial or median nerves. Sensory evoked potentials from the median nerve were absent, as well. Sural nerve biopsy showed a marked reduction of myelinated fibers with signs of demyelination and onion bulb formation.

Molecular and molecular cytogenetic results

Densitometric analysis of the autoradiograph resulting from Southern blot analysis of *Eco*RI-digested DNA samples from the patient with mosaicism using the probe pNEA102 (Lorenzetti et al. 1995) revealed a dosage difference of 2:2.4 between the two detectable *Eco*RI fragments of 7.8 and 6.0 kb (see Fig. 2, lane 4), not 2:3 as expected for a nonmosaic duplication (see Fig. 2, lane 1).

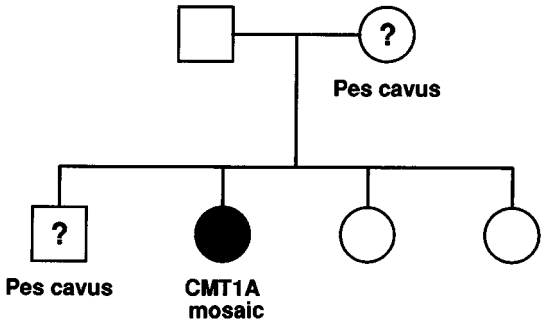

Fig. 1 Patient's pedigree

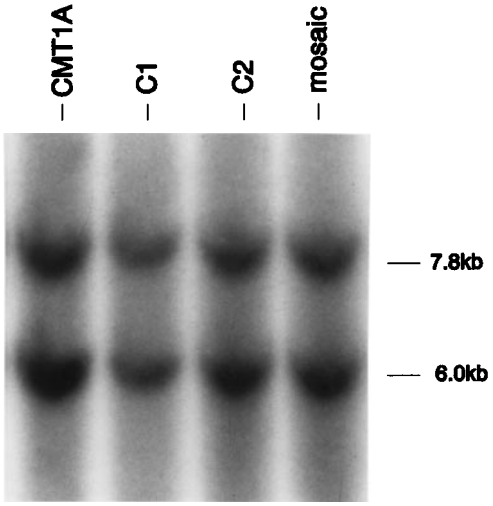

Fig. 2 Dosage of the repetitive CMT1A-REP sequences detected with the probe pNEA102 on a Southern blot of *Eco*RI-digested DNA. The 7.8- and 6.0-kb *Eco*RI fragments correspond to the proximal and distal CMT1A-REP units. A 1:1 ratio was detected for the two healthy controls (*C1, C2*). A CMT1A patient with a duplication in 17p11.2 showed the typical 2:3 ratio and no mosaicism in fluorescence in situ hybridization (FISH) analyses (see Table 1). For the mosaic patient a 2:2.4 ratio was estimated densitometrically

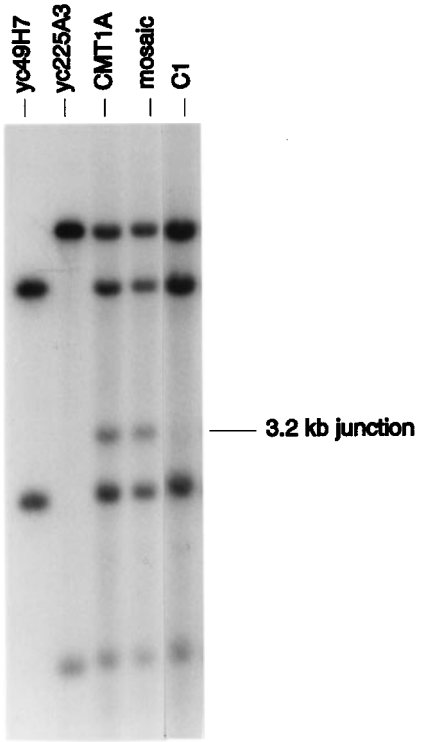

Fig. 3 Reduced dosage of a 3.2-kb *Eco*RI/*Sac*I junction fragment of the mosaic patient (*lane 4 mosaic*) compared with a typical CMT1A duplication (*lane 3 CMT1A*) and a healthy control (*lane 5 C1*) detected with probe pLR7.8. The yeast artificial chromosomes yc49H7 (proximal CMT1A-REP element) and yc225A3 (distal CMT1A-REP element) reveal the wild-type *Eco*RI/*Sac*I restriction fragments derived from the corresponding CMT1A-REP elements

Table 1 Summary of the FISH evaluation of a CMT1A case with duplication in chromosome 17p11.2 *(CMT1A)*, a healthy control *(C1)* and the CMT1A patient with mosaicism *(mosaic)*

Individual and examined tissue	Signals (%)			Evaluated nuclei
	1	2	3	
Mosaic				
Blood	3.0	48.0	49.0	100
Buccal mucosa	5.0	44.0	51.0	100
Hair-root cells	6.0	28.0	66.0	50
Nerve	4.0	22.0	74.0	50
CMT1A				
Blood	3.0	12.0	85.0	100
C1				
Blood	6.0	91.0	3.0	100

Further examination of the recombination site by Southern hybridization of *Eco*RI/*Sac*I-digested DNA with the 7.8-kb *Eco*RI fragment derived from the proximal CMT1A-REP element as ^{32}P-labeled probe revealed a 3.2-kb junction fragment (Fig. 3, lane 4) as observed in at least 80% of CMT1A duplication carriers (Reiter et al. 1996). The predicted dosage of 2:1 compared with restriction fragments of 5.0 or 2.8 kb derived from the proximal CMT1A-REP elements for nonmosaic CMT1A duplications is visible in Fig. 3, lane 3. However, the junction fragment of the mosaic patient revealed a reduced dosage of 2:0.58 (Fig. 3, lane 4). This indicates clearly that only about 40–58% of the analyzed blood cells carry the CMT1A duplication.

A duplication within the CMT1A region could also be detected by means of two-colour FISH. This revealed different patterns of mosaicism in the four different tissues examined (see Table 1). A higher percentage of nuclei showing three specific signals (representing the duplication) was detected in hair-root cells (66%) and nervous tissue (74%), whereas only 49% of the evaluated nuclei in peripheral blood and 51% of those in buccal mucosa showed three specific signals. FISH analysis was performed on two different blood samples and yielded the same result. Examples of typical nuclei are shown in Figs. 4, 5.

Discussion

In the presented case the duplication in chromosome 17p11.2 typical for CMT1A could be demonstrated by three different, well-established methods. About 200 patients have been examined to date by these techniques in Erlangen (unpublished data). The presence or absence of the duplication or the reciprocal deletion was successfully diagnosed in all of them. Furthermore, we found different patterns of mosaicism in different tissues for the patient reported here that could not be demonstrated in any other patient from this group. The percentage of cells with the duplication tended to be lower in rapidly proliferating tis-

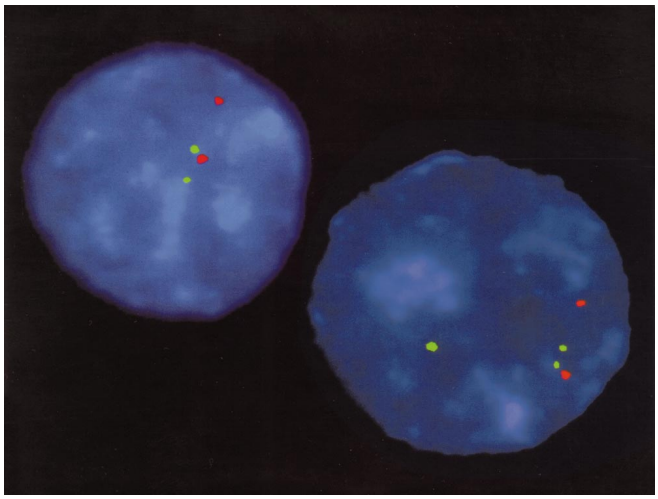

Fig. 4 Two interphase nuclei prepared from peripheral blood of the mosaic patient after FISH are shown. The nuclei were counterstained with 4′6-diamidino-2-phenylindole and hybridized with the probes pVAW409R1, located on chromosome 17p11.2 (*green spots*), and cRCNeu1, mapping to chromosome 17q11.12 (*red spots*). One nucleus shows only two specific green signals (no duplication), whereas the other has three specific green spots (duplication). The picture was taken on a Zeiss Axiophat microscope equipped with a CCD camera using Metasystems software

sues (blood, buccal mucosa) than in those not proliferating so rapidly (hair-root cells, nervous tissue).

On the one hand this finding could be explained by a growth advantage of those cells without the duplication. Cells without a duplication in chromosome 17p11.2 have to replicate 1.5 Mb of DNA less than the others and might be slightly faster growing. Similar events have been described for the Pallister-Kilian syndrome, where the marker chromosome + 12p is detectable in nearly 100% of bone marrow cells but only in a very low percentage of peripheral blood cells (Schinzel 1991).

On the other hand, it is also possible that cells with and without the duplication are distributed more or less by chance in each tissue, similar to, e.g., cases of mosaicism with supernumerary (marker) chromosomes (see, e.g., Pfeiffer and Schulze 1994).

In the patient of the present report we found an atypical 2:2.4 ratio with the probe pNEA102 on DNA extracted from blood (Fig. 2). Also, the 3.2-kb *Eco*RI/*Sac*I junction fragment most frequently observed for the CMT1A duplication was present in reduced dosage (2:0.58). Using FISH analysis with the specific probe pVAW409R1 (Table 1), we were able to confirm our assumption that this effect was due to mosaicism of the duplicated region in a case of

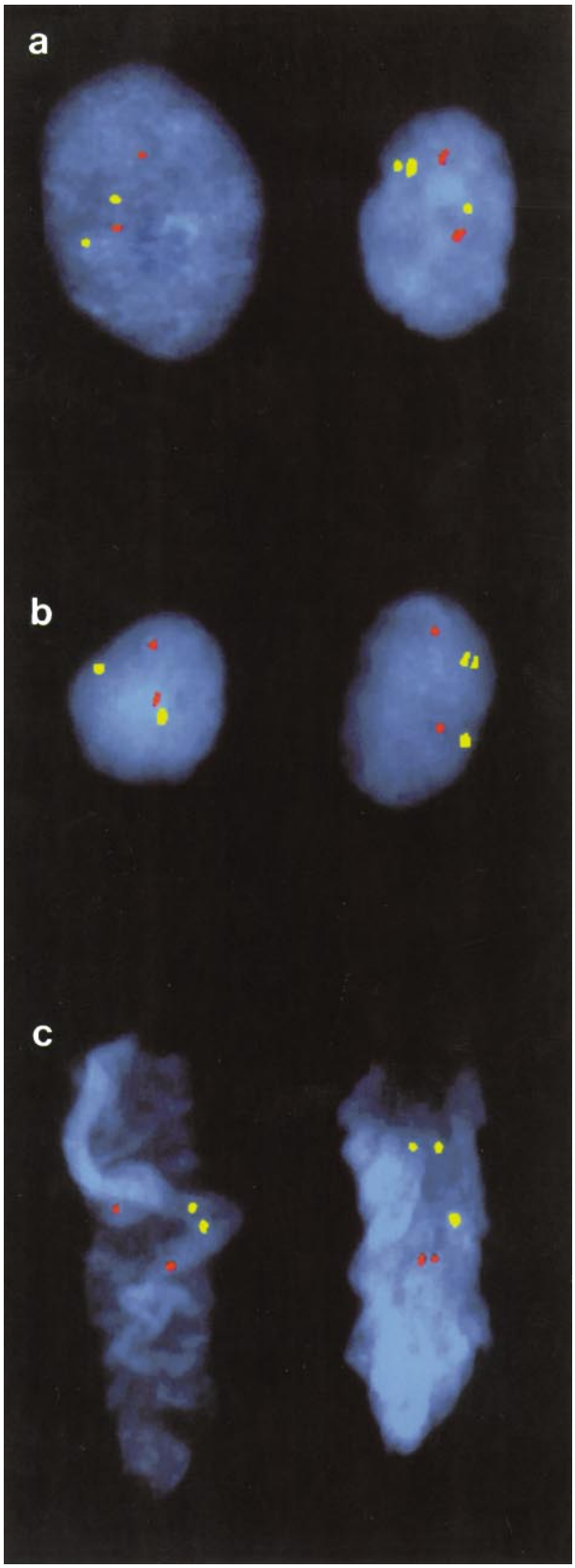

Fig. 5a–c Six interphase nuclei prepared from three different tissues of the mosaic CMT1A patient are shown: buccal mucosa (**a**), hair-root cells (**b**) and nervous tissue (**c**). On the *left* are presented nuclei of the mosaic with two specific green spots (no duplication) and on the *right* nuclei with three specific green signals (duplication). Hybridization, counterstaining and documentation were as for Fig. 4

CMT1A. Nevertheless this mosaicism may explain the mild clinical features observed in this patient.

According to the current theory that unequal crossing over during meiosis leads to duplication or reciprocal deletion in 17p11.2 (Raeymaekers et al. 1991; Pentao et al. 1992), mosaicism should be excluded. Sorour et al. (1995), however, have also described a case with the typical CMT1A duplication detectable in only 47.6% of peripheral blood cells. They were able to substantiate their findings by means of FISH, but their Southern blot experiments did not lead to informative results. Moreover Ionasecu et al. (1993) suggested mosaicism in a further CMT1A family, but this could not be proved for technical reasons. A somatic mosaicism has also been described for a cytogenetically visible deletion of this region in chromosome 17 (Zori et al. 1993). In all three cases de novo development during embryogenesis of the proband was assumed.

There are at least three possible explanations of these unusual findings: chimerism, somatic unequal crossing over or homologous recombination of the distal CMT1A-REP elements within the duplicated region followed by interstitial deletion of the 1.5 Mb. Chimerism is the formation of one individual from cells of two fertilized eggs – an extremely rare event (Thompson and Thompson 1986). This mechanism seems unlikely in at least three reported cases without additional hermaphroditism, which has been excluded by FISH for our case using centromeric probes specific for chromosomes X and Y (data not shown). Chimerism in man may also occur if, in a dizygotic twin pregnancy, cells of one fetus are transfused to the other (Thompson and Thompson 1986). This explanation could also be excluded in the reported case (see Fig. 1, pedigree).

It could be postulated that somatic unequal crossing over could lead either to induction of the duplication and deletion in some somatic cells or to a back mutation or reversion to normal of cells derived from a primarily duplicated zygote. In our case, the first can be excluded by our FISH results, as an elevated number of nuclei with only one specific signal was not detected (Table 1). The second possibility could only hold true if it were postulated that the additional resulting cell population with four copies of the 1.5-Mb region would not survive. Somatic crossing over is, however, not definitively proven. There are some observations in plants and *Drosophila* that suggest that it occurs (Stern 1936; Harrison et al. 1977). In man, twin nevi are suggested to be caused by somatic recombination (Happle et al. 1990; Happle 1991). Although apparently existing, this phenomenon has been believed to be very rare.

Homologous recombination followed by interstitial deletion of the 1.5-Mb region is a third possibility (Bahr 1977). If recombination between the two distal REP elements of the duplicated region of CMT1A takes place, the supernumerary 1.5 Mb in one chromosome 17 could be excised and would be lost throughout further cell cycles. Chromosomal duplications in bacteria and fruit fly are well known to revert at a high frequency (Lupski et al. 1996).

In conclusion, at least three CMT1A cases with a duplication in 17p11.2 plus mosaicism have been reported. Their origin, whether bychimerism, somatic unequal crossing over, homologous recombination followed by deletion, or another mechanism, will have to be studied in future. However, given the mechanism of formation of duplications, and the observed reversion frequencies of chromosomal duplications in bacteria and fruit fly (Lupski et al. 1996), homologous recombination followed by deletion (somatic reversion) is the most likely cause.

In summary, this is the first report proving mosaicism in CMT1A disease by means of three different techniques (FISH and two distinct Southern blots), which is moreover supported by the clinical features of the patient. It is also the first time that four different tissues have been investigated successfully, yielding different patterns of mosaicism. Although mosaicism in CMT1A patients seems to be a rare event, it should always be tested when an unusual Southern blot pattern occurs. To confirm mosaicism, FISH is the most reliable technique.

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