A de novo case of hereditary neuropathy with liability to pressure palsies (HNPP) of maternal origin: a new mechanism for deletion in 17p11.2?

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Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant neuropathy, most often associated with a deletion of the 17p11.2 region, which is duplicated in 70% of patients with Charcot–Marie–Tooth type 1 (CMT1A). Most de novo CMT1A and HNPP cases have been of paternal origin. A rare case of de novo HNPP of maternal origin was analysed to determine the underlying mechanism. Affected individuals in the family carried a deletion corresponding to the CMT1A/HNPP monomer unit associated with a rearrangement of the CMT1A–REP sequences. Segregation analysis of 17p11-p12 markers in the family indicated that the deletion was not generated by unequal crossing over between homologous 17 chromosomes, as in de novo cases from paternal origin, but rather by an intrachromosomal rearrangement. Two distinct mechanisms can therefore lead to the same 17p11.2 deletion. This result suggests that intrachromosomal rearrangement may be specific to maternal transmissions.

INTRODUCTION

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant peripheral neuropathy (1). HNPP patients present variously located recurrent truncular palsies or sensory loss, precipitated by minor trauma. In most cases, patients recover within days or weeks, but relapses may be frequent, and paresis may last for long periods. Nerve conduction studies reveal a characteristic pattern of decreased motor velocities, prolonged distal latencies and altered sensory nerve action potentials, even in clinically non affected areas or in asymptomatic at risk individuals (2). Peripheral nerve biopsies show a characteristic focal sausage-shaped thickening of the myelin sheath (tomacula) in numerous internodes.

The presence of an interstitial deletion of the 17p11.2 region associated with this disorder was demonstrated in most of the HNPP families (3,4). The same region, designated the CMT1A/HNPP monomer unit, is duplicated in a more frequently diagnosed neuropathy, Charcot-Marie-Tooth type 1A disease (CMT1A) (5–8). Thus, it was hypothesized that an unequal crossing-over would generate both a duplication that could lead to CMT1A or a deletion that could result in HNPP. The identification of two homologous sequences flanking the CMT1A/HNPP monomer unit, the CMT1A-REPs, supported this hypothesis (9). Recently, Chance et al. (10) proposed that the CMT1A duplication and the HNPP deletion could both arise from recombination events that occur within a limited region of the CMT1A-REP.

De novo deletions have been reported in five HNPP patients, four of paternal origin (3,11,12) and one of possible maternal origin (13). In CMT1A, however, the de novo duplications, where the parental origin could be determined, were paternal (5,14,15).

In order to analyse the mechanism underlying maternal de novo deletions in HNPP, we performed a molecular study of a family with a HNPP patient presenting a de novo deletion from maternal origin using 17p11-p12 markers and the CMT1A-REP probe pNEA102. The deletion was found to be associated with a rearrangement of the CMT1A-REPs but, unlike previous reports, haplotype reconstruction strongly supported the hypothesis that an intrachromosomal rearrangement generated the deletion.

RESULTS

Eight members of the family SAL-902 were genotyped for eight microsatellites and two RFLP markers from 17p11-12. Segregation analysis with the RM11GT microsatellite at D17S122 locus demonstrated the presence of a 17p11.2 deletion in patient 15 who carried allele 5, but received no allele from his mother (2/3) at this locus, showing that, in this family, the phenotype was associated with a deletion within 17p11.2 as described previously (2–4,11–13). The absence of maternal contribution to the patient 15 at the D17S122 locus, demonstrated the maternal origin of this de novo case of HNPP. All tested at risk individuals (7,17,20)

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shown to be unaffected by clinical and electrophysiological examination were heterozygous for at least one of the markers within the CMT1A/HNPP monomer unit (Fig. 1).

Patient 15 did not transmit any alleles of D17S955 and D17S921 to his affected son 32. The deletion encompassed the D17S122 locus, which was mapped within the first 500 kb of the 1.5 Mb CMT1A/HNPP monomer unit at its centromeric extremity (9) and the D17S921 locus, which was physically and genetically shown to be the most telomeric marker of the CMT1A monomer unit (16,17). Patients 15 and 32 were heterozygous for at least one of the markers which are not informative of transmission. (b) Schematic map of the 17p11-p12 Généthon markers. The clear box indicates the CMT1A/HNPP monomer unit. The genetic distances are given in cM. D17S122 was physically mapped between D17S953 and D17S839 (15,16) but their relative genetic distances are not known.

Figure 1. (A) Haplotype reconstruction for 10 17p11-12 markers in family SAL-902. Genotypes are indicated below individuals. Affected subjects are represented in black. *, clinically and electrophysiologically examined subjects from whom blood samples were obtained. The solid line to the left to the loci designation indicates the groups of markers for which the order cannot be resolved with odds >1000:1 (23). Clear boxes correspond to the deleted region deduced by allele segregation of the markers; hatched boxes represent the loci which are not informative of transmission. (B) Schematic map of the 17p11-p12 Généthon markers. The clear box indicates the CMT1A/HNPP monomer unit. The genetic distances are given in cM. D17S122 was physically mapped between D17S953 and D17S839 (15,16) but their relative genetic distances are not known.

In addition, the two affected individuals 15 and 32 were tested with probe pNEA102 which detects, on EcoRI digested Southern blots, two fragments of 6.0 and 7.8 kb corresponding to the distal and proximal CMT1A-REP respectively (10). The hybridization signal for the 7.8 kb fragment was stronger than for the 6.0 kb fragment, suggesting that a part of a distal CMT1A-REP was deleted (Fig. 2). It can be concluded that the deletion is associated with a rearrangement of the CMT1A-REP sequences and confirms that the CMT1A/HNPP monomer unit is involved (10,18,19).

Using the microsatellites D17S842 (afm240xe5), D17S783 (afm026vh7) and D17S953 (afm304xh5) which are centromeric to the CMT1A/HNPP monomer unit and the telomeric marker D17S922 (afm197xh6)(16,17), the most probable haplotypes for the 17p11-p12 region were reconstructed, as shown in Figure 1. The flanking markers on each side of the deletion were inherited intact from the mother and showed no crossing-over. Considering the genetic distances between the tested markers (see Materials and Methods), the probability of a double recombination in patient 15 is very low. Therefore, an unequal crossing-over between the chromosome 17 homologues, as in de novo deletions and duplications of paternal origin associated with HNPP and CMT1A (3,5,11,12,14,15), is very unlikely in this family.

DISCUSSION

We report a de novo case of HNPP of maternal origin. The deletion detected in affected members is associated with a rearrangement of CMT1A-REP sequences and corresponds to the CMT1A/HNPP monomer unit. However, haplotype reconstruction highly suggests that this deletion was not caused by an unequal crossing-over as described previously (3,11,12). It is highly probable that the de novo deletion observed in family SAL-902 results from an intrachromosomal rearrangement.

Our observation provides the first evidence that rearrangements involving identical autosomal sequences can occur either by unequal crossing-over between homologues or by intra-homologue rearrangement. Interestingly, all documented de novo duplications of paternal origin resulting in CMT1A, have been shown by haplotype reconstruction to result from an unequal recombination between homologue chromosomes 17 (5,14,15). In HNPP, both paternal de novo deletions (3,11,12) but also a possible maternal deletion (13) have been reported. The latter received no allele of the pEW401HE 17p11.2 marker (D17S61) from his mother who was shown to be unaffected by clinical and electrophysiological examination. The molecular mechanism underlying this deletion was not analyzed, however.

Terminal or interstitial deletions detected by classical cytogenetic techniques are generally caused by the occurrence of one or two breaks respectively, within a chromosome with the loss of theacentric fragment. An intrachromosomal mechanism was also postulated to cause the de novo deletions occurring in males in Duchenne muscular dystrophy or haemophilia A (20). It was demonstrated that some deletions in these genes, which are located on the X chromosome can occur in male gametes. Since male gametes bear only one X chromosome, the origin of these
rearrangements is mitotic and the corresponding process is certainly intrachromosomal. Intrachromosomal rearrangement has also been invoked for deletions of several Mb on autosomes, in particular in the Angelman/Prader–Willi syndrome (21,22). For de novo deletions occurring in males in Duchenne muscular dystrophy or in haemophilia A, the excision of a chromatidal loop during replication was proposed (20). This mechanism was also postulated for the deletions within the beta-globin gene domain resulting in the hereditary persistence of fetal hemoglobin (HPFH) (23). In Angelman/Prader–Willi syndrome, unequal sister chromatid exchange was thought as an alternative to explain the deletion (21,22). Unfortunately, the molecular tools which would distinguish between these two intrachromosomal mechanisms in our family are not yet available.

Since deletions in HNPP can result both from crossing-over between homologues and intra-chromosomal rearrangement but duplications only by crossing over, HNPP should be more frequent than CMT1A with duplication. HNPP is apparently less prevalent, however, than CMT1A but this is probably because of underdiagnosis (2). Since unequal crossing-overs resulting in deletion or duplication were observed during male meioses, the intrachromosomal deletion of this region detected in this study may preferentially occur in females, although additional cases must be analyzed before a generalization can be made.

MATERIALS AND METHODS

Clinical data

Index case 15 from family SAL-902, examined at age 41, described three episodes of acute sensory–motor truncular deficits without obvious precipitating factors. Several nerves were affected simultaneously during the third episode. Motor nerve conduction (MNCV) and sensory nerve conduction velocities (SNVC) were abnormal bilaterally in the median, ulnar and peroneal nerves. Tomaculous changes involving 36% of inter-nodes were found in superficial peroneal nerve biopsies. Clinical and electrophysiological examinations were performed in all first degree relatives. Individual 32, the son of the index case, presented three episodes of truncular sensory-motor palsies and his brother, 31, described paresthesias with a right ulnar distribution lasting a few hours. Patients 31 and 32 both presented diffuse MNCV and SNVC abnormalities. Parents and siblings never complained of motor or sensory abnormalities. The mother (6) of index case 15 was a 73 year old farmer, who presented with unilateral electrophysiological carpal tunnel syndrome but had no other abnormal electrophysiological features. The father of the index case was not available for examination. All siblings had normal MCV and SCV. Individuals 6 and 15 were genotyped twice with different blood samples in order to eliminate sampling or typing errors.

RIFLP markers

The genomic probes EW401 (D17S61) detects two MspI alleles with sizes of 5.5 and 4.4 kb, and VAW409R3a (D17S122) three MspI alleles with sizes of 2.8, 2.7 and 1.9 kb. Probe pNEA102, which detects two EcoRI fragments of 6.0 and 7.8 kb corresponding respectively, to the proximal and distal CMT1A-REP which flank the CMT1A/HNPP monomer unit, was also used. The probes were hybridized to Southern blots after preannealing with placental DNA. The CMT1A-REP deletion was assessed by visual comparison of the hybridization signals of the two EcoRI fragments hybridized with probe pNEA102.

Microsatellite markers

The following (Ca)n microsatellites, which span 13 cM on chromosome 17p11-p12, were used: D17S122 (RM11GT) (6), D17S842 (afm240x65), D17S783 (afm026xh7), D17S593 (afm304xh5), D17S839 (afm200yh12), D17S595 (afm317ygl), D17S592 (afm191xh12) and D17S922 (afm197xh6). Genetic distances between the Génétou markere markers were as follows: (D17S842–D17S783), 6 cM, D17S593, 5 cM, (D17S839–D17S955), 1 cM, D17S921, 1 cM, D17S922 (24). Genotypes were determined with the PCR/blotting technique (25).

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