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Hereditary neuropathy with liability to pressure palsies: two cases with a reciprocal translocation t(16;17)(q12;p11.2) interrupting the *PMP22* gene

EDITOR—Hereditary neuropathy with liability to pressure palsies (HNPP) or tomaculous neuropathy is an autosomal dominant disease.[1] HNPP patients present with acute or recurrent transient muscle palsies and paraesthesias, usually after minor trauma. HNPP is characterised from the pathological point of view by the presence of sausage shaped swelling of the myelin sheath or tomacula[2] in sensory and motor nerves.[3]

A deletion on the proximal short arm of chromosome 17 was detected in affected members of HNPP families.[4 5] The deleted region is the same as that duplicated in Charcot-Marie-Tooth disease type 1 (CMT1A). While the CMT1A phenotype is mostly the result of extra dosage of the genes contained in this duplicated region, the HNPP phenotype results from monosomy of the same region in over 85% of cases.[6] This duplication/deletion event is thought to occur because of the unequal crossing over between two large repeats bordering the CMT1A region,[7] which encompasses 1.5 Mb of 17p11.2.[8]

The association between CMT1A and the peripheral myelin protein 22 (*PMP22*) gene, located within the CMT1A duplicated region, was established by the finding of point mutations in this gene[9 10] in CMT1A patients. The *PMP22* gene spans approximately 40 kb and contains four coding and two 5' untranslated (1A and 1B) exons.[11] In 35 unrelated patients with inherited peripheral neuropathies, 27 mutations in the *PMP22* gene have been described, affecting the different domains of the protein,[12] some of them leading to a truncated protein. The clinical phenotypes of the patients carrying mutations in the *PMP22* gene are variable, giving some clues about correlations between phenotype and genotype. Five mutations in the *PMP22* gene have been described that result in a HNPP phenotype: two frameshift mutations,[13 14] two nonsense mutations,[15 16] and a splice site mutation.[17]

We report here a pedigree with two affected members (mother and son) with HNPP, both of whom carry a reciprocal translocation t(16;17)(q12;p11.2), which we have studied by FISH. The breakpoint on chromosome 17 in both patients lies within exons 1a to 3 of the *PMP22* gene.[11]

Table 1 Electroneurographic findings in two patients with hereditary neuropathy with liability to pressure palsies (HNPP)

	Motor and sensory nerve conduction					
	Ulnar nerve		*Median nerve*		*Peroneal nerve*	
	P	*M*	*P*	*M*	*P*	*M*
MCV (m/sec)						
R	40	40	53	60	—	27
L	39	48	52	44	32	31
N	(>52)		(>52)		(>48)	
DL (m/sec)						
R	3.5	2.8	4.5	4	—	—
L	3.2	3	3.7	3.8	—	—
SCV (m/sec)						
R	35	43	27	33	—	—
L	38	37	37	34	—	—
SAP amplitude (μV)						
R	2	4	2	2	—	—
L	3	2	3	3	—	—

P, proband; M, mother; R, right; L, left; N, normal value; MCV, motor conduction velocity; DL, distal latency; SCV, sensory conduction velocity; SAP, sensory action potential; —, not done.

The proband is a 24 year old male referred to our clinic for molecular analysis to confirm the clinical diagnosis of HNPP. The mother confirmed delayed milestones during infancy, followed by clumsiness and difficulties with running and schooling during childhood and adolescence. At the age of 21, he had two episodes of numbness and muscular weakness of the left arm following compression while sleeping and weight lifting, without full recovery. Clinical examination showed distal muscle atrophy and weakness of the left arm involving the long distal extensors of the upper limb, the abductor of the thumb, and the supinator of the arm. He was able to walk on his toes and heels and had normal reflexes. No other signs of muscle weakness were noted. Nerve conduction studies showed delayed and reduced sensory action potentials with prolonged motor latencies and slow motor conduction velocities (table 1). Clinical and electroneurographic studies were also carried out in the parents and his twin sister. The mother was clinically asymptomatic, although she reported episodes of paraesthesias with complete recovery involving the upper limbs. Electroneurographic findings were consistent with peripheral neuropathy (table 1) and the diagnosis of HNPP was established in the family. No other members were affected.

Chromosome spreads were obtained from peripheral blood of each patient and a G banding karyotype was performed. Conventional cytogenetics showed the presence of a reciprocal translocation between chromosomes 16 and 17 (t(16;17)(q12;p11.2)). FISH analysis was performed as described elsewhere[18] using YAC 181g9 (CEPH) and cosmids c49-E4 (GDB 437232) and c103-B11 (GDB 437233) (both cosmids kindly provided by Dr P I Patel) as probes. FISH analysis showed that YAC 181g9, which encompasses marker D17S122 to marker D17S879 and contains *PMP22*, crossed the translocation breakpoint. FISH with cosmids c49-E4 and c103-B11 showed that the breakpoint was within cosmid c49-E4, which contains the genomic region encoding the first three exons of the *PMP22* gene (fig 1). Therefore, we concluded that the *PMP22* gene[11] is interrupted in these two patients with the HNPP phenotype.

This is the first case of HNPP being caused by a reciprocal translocation that interrupts the *PMP22* gene. Cytogenetic studies and FISH confirmed the diagnosis in the patient. The two cases presented here not only confirm that the HNPP phenotype was the result of the interruption of the *PMP22* gene, but also show the variable penetrance of the phenotype in two related patients carrying the same mutation. It is therefore unlikely that other genes within the commonly deleted region have contributed to the phenotype. This suggests that modifiers in other genomic regions are involved in the clinical variability of peripheral neuropathies.

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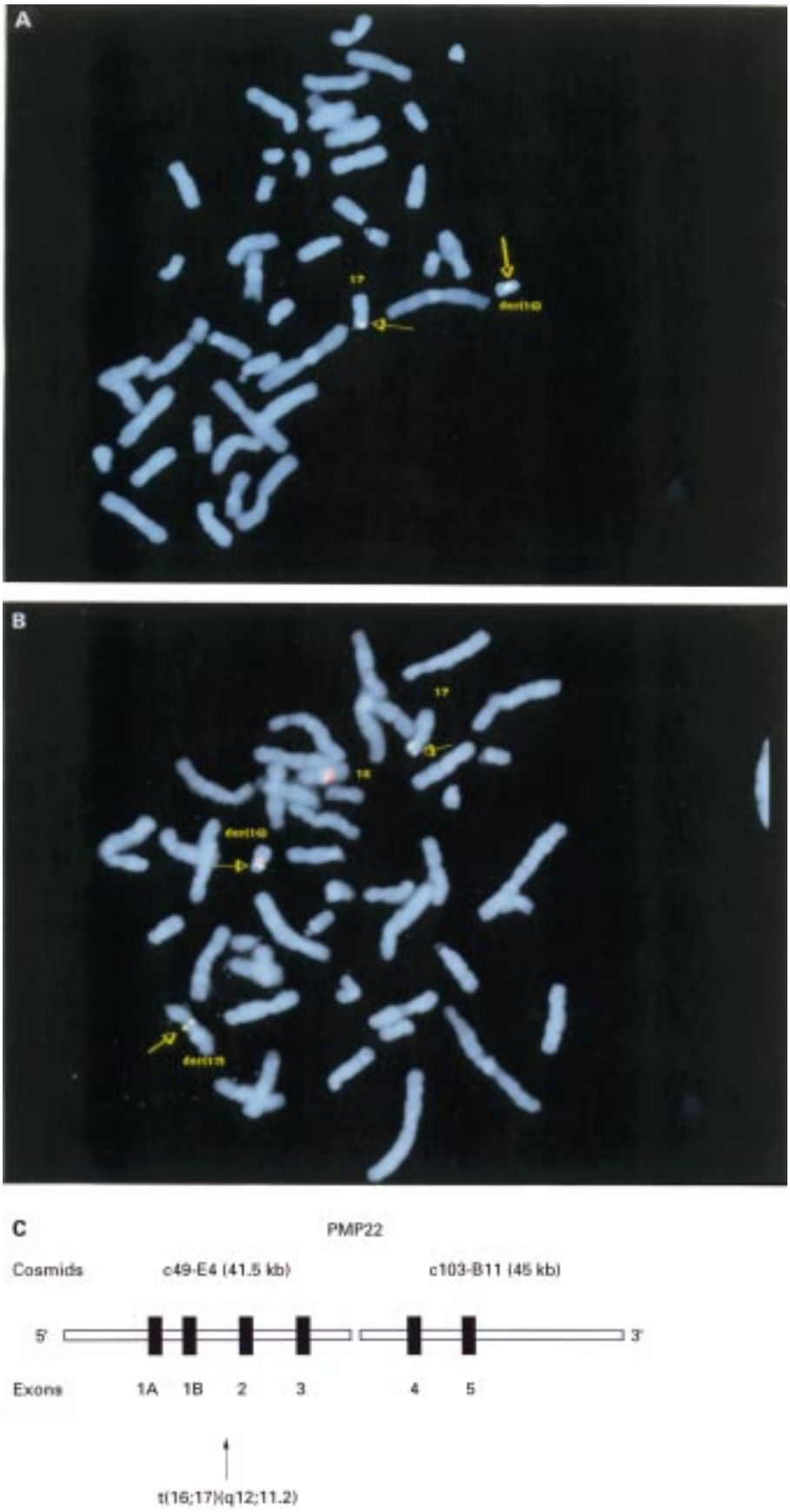

Figure 1 Hereditary neuropathy with liability to pressure palsies (HNPP) resulting from a t(16;17)(q12;p11.2) reciprocal translocation. (A) FISH with cosmid c103-B11 shows signals on chromosomes 17p11.2 and der(16) and does not cross the breakpoint. (B) FISH with cosmid c49-E4 (green) shows signals on chromosomes 17p11.2, der(16), and der(17), indicating that this cosmid crosses the breakpoint and that the PMP22 gene is interrupted by the reciprocal translocation. Probe D16Z1 (red) hybridises to the centromeric region of both chromosome 16 and der(16) (C) Schematic representation of the genomic region encompassing the PMP22 gene, indicating the t(16;17)(q12;p11.2) breakpoint (arrow).

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