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DNA Rearrangements on Both Homologues of Chromosome 17 in a Mildly Delayed Individual with a Family History of Autosomal Dominant Carpal Tunnel Syndrome

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Summary

Disorders known to be caused by molecular and cytogenetic abnormalities of the proximal short arm of chromosome 17 include Charcot-Marie-Tooth disease type 1A (CMT1A), hereditary neuropathy with liability to pressure palsies (HNPP), Smith-Magenis syndrome (SMS), and mental retardation and congenital anomalies associated with partial duplication of 17p. We identified a patient with multifocal mononeuropathies and mild distal neuropathy, growth hormone deficiency, and mild mental retardation who was found to have a duplication of the SMS region of 17p11.2 and a deletion of the peripheral myelin protein 22 (*PMP22*) gene within 17p12 on the homologous chromosome. Further molecular analyses reveal that the dup(17)(p11.2p11.2) is a de novo event but that the *PMP22* deletion is familial. The family members with deletions of *PMP22* have abnormalities indicative of carpal tunnel syndrome, documented by electrophysiological studies prior to molecular analysis. The chromosomal duplication was shown by interphase FISH analysis to be a tandem duplication. These data indicate that familial entrapment neuropathies, such as carpal tunnel syndrome and focal ulnar neuropathy syndrome, can occur because of deletions of the *PMP22* gene. The co-occurrence of the 17p11.2 duplication and the *PMP22* deletion in this patient likely reflects the relatively high frequency at which these abnormalities arise and the underlying molecular characteristics of the genome in this region.

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Introduction

Clinically recognized disorders associated with cytogenetic or molecular rearrangements of proximal 17p include Charcot-Marie-Tooth disease type 1A (CMT1A; MIM 118220), caused by a duplication of the peripheral myelin protein 22 gene (*PMP22*) within 17p12 (Lupski 1992; Murakami et al. 1996; Lupski 1998*b*); hereditary neuropathy with liability to pressure palsies (HNPP; MIM 162500), caused by deletion of *PMP22* (Chance et al. 1993; Murakami et al. 1996); and the Smith-Magenis syndrome (SMS; MIM 182290), associated with deletion 17p11.2 (Smith et al. 1986; Chen et al. 1996*a*; Greenberg et al. 1996). Duplication of the SMS region and larger regions of 17p have also been reported, although less frequently (Bartsch-Sandhoff and Hieronimi 1979; Feldman et al. 1982; Mascarello et al. 1983; Magenis et al. 1986; Schrander-Stumpel et al. 1990; Upadhyaya et al. 1993; Brown et al. 1996; Pellegrino et al. 1996; Roa et al. 1996). CMT1A and HNPP are clinically distinct, autosomal dominant peripheral neuropathies that result from an unequal crossing-over event on chromosome 17p, yielding reciprocal products of duplication (CMT1A) and deletion (HNPP) of a DNA segment containing the dosage-sensitive *PMP22* gene (Pentao et al. 1992; Chance et al. 1994; Reiter et al. 1996; Lupski 1997). HNPP is characterized by periodic episodes of numbness after relatively minor compression or trauma to the peripheral nerves, or after muscular weakness or muscular atrophy. Electrophysiological studies sometimes show mildly slowed nerve conduction velocities (NCVs) with conduction blocks in persons with the deletion regardless of the presence or absence of symptoms. Multifocal neuropathy (Tyson et al. 1996) and entrapment neuropathies, such as carpal tunnel syndrome, are frequent manifestations of HNPP.

SMS is a mental retardation, multiple–congenital anomalies syndrome that is clinically distinct from the often nondescript mental retardation phenotype caused by duplication 17p11.2. However, SMS and duplication

17p11.2 are thought to result from DNA rearrangements that are the reciprocal products of an unequal crossing-over event between repeated gene clusters (SMS-REPs) within 17p11.2 (Chen et al. 1997). Clinical characteristics of SMS have been well defined (Greenberg et al. 1991; Finucane et al. 1993; Finucane et al. 1994; Chen et al. 1996*a*, 1996*b*; Greenberg et al. 1996; Dykens et al. 1997) and include dysmorphic craniofacial features; behavioral abnormalities; sleep disturbance; and ophthalmic, otolaryngological, cardiac, and renal anomalies. The clinical phenotype of duplication 17p is less well defined and less frequently reported; however, growth retardation; minor craniofacial anomalies; and cardiac, renal, and musculoskeletal anomalies have been reported (Bartsch-Sandhoff and Hieronimi 1979; Feldman et al. 1982; Mascarello et al. 1983; Magenis et al. 1986; Schrander-Stumpel et al. 1990; Upadhyaya et al. 1993; Brown et al. 1996; Pellegrino et al. 1996; Roa et al. 1996).

Here we describe the clinical features and molecular analysis of a patient with a duplication of the SMS region of 17p11.2 on one chromosome 17 and a deletion of the *PMP22* gene within 17p12 on the other homologue. Analysis of her family reveals that the *PMP22* deletion segregates as an autosomal dominant trait on the maternal side of the family and is associated with signs and symptoms of carpal tunnel syndrome. The dup(17)(p11.2p11.2) is de novo from the paternally derived chromosome 17, tandem in nature, and associated with a unique junction fragment detected by pulsed field-gel electrophoresis (PFGE). This suggests that this duplication event may be the reciprocal product of the SMS deletion because of unequal crossing over and homologous recombination involving the SMS-REP flanking the rearranged region.

Patients and Methods

Clinical Reports

The patient (1006) was initially referred for a genetics consultation at age 12 years when a chromosome analysis (performed because of short stature and growth hormone deficiency) revealed an apparent duplication of bands p11.2p12 in one chromosome 17. Reevaluation at age 14 years was prompted by the patient's worsening clinical status, characterized by increasing hand and lower-leg fatigue; muscle weakness of the hands, lower legs, and feet; and progressive pes cavus deformity of the left foot.

The patient, weighing 6 pounds, 2 ounces at birth, was delivered vaginally to a 27-year-old primigravida whose pregnancy was normal and full term. The neonatal period was complicated by a spontaneous pneumothorax, which necessitated mechanical ventilation, and a left club-foot deformity, which required casting until age 13 mo and corrective surgery at age 14 mo. A right metatarsus adductus was noted in infancy and required splinting. Developmentally, the patient sat independently at 6 1/2 mo, crawled at 9 mo, walked with assistance at 14 mo, and walked independently at 19 mo. Delayed speech and poor articulation necessitated speech therapy, which was instituted by age 3 years. Attention deficit was diagnosed at age 7 years and Ritalin was prescribed. Formal developmental testing at age 12 years revealed a full-scale IQ of 62, verbal scale IQ of 75, and performance scale of 53 (Wechsler Intelligence Scale for Children). Short stature was noted at age 10–11 years. Evaluation revealed growth hormone deficiency with a normal pituitary gland. The patient currently receives daily growth hormone injections. Other medical history includes episodic microscopic hematuria, hyperopia, and dental malocclusion.

Significant findings on physical examination at age 14 years include height at the 7th percentile; occipital-frontal circumference at the 50th percentile; triangular facies; micrognathia; dental malocclusion; small, tapered teeth; mild thoracolumbar scoliosis; atrophy of interosseous, thenar, and hypothenar hand muscles; atrophy of calf muscles (left greater than right); left club-foot deformity with hammer toes; and right pes cavus with metatarsus adductus. The patient's deep-tendon reflexes were 1+ and symmetric at the triceps, biceps, brachioradialis, and quadriceps, with absent ankle reflexes. Her strength was 4/5 in the distal upper and 3/5 in the distal lower extremities bilaterally, and there were equivocal bilateral Babinski responses. Pain and position sense were reduced in her toes and normal in her legs and arms. NCVs revealed multifocal abnormalities of both median nerves at the wrist and ulnar nerves at the elbow, with no generalized motor slowing in the arms. Atrophy of her distal left leg and both feet limited motor conduction studies, but proximal velocities of her right peroneal nerve were normal with low amplitude, suggesting an axonal-type neuropathy.

Family history revealed carpal tunnel syndrome in the patient's mother (1005), maternal aunt (1187), maternal uncle (1188), and maternal grandfather (1160). The patient's mother was 41 years old at evaluation. For several years she had had recurrent numbness in her hands and feet, which was sometimes precipitated by stretching, trauma, or overuse. The duration of these symptoms was variable, but they usually persisted for 3–8 weeks and required treatment with physical therapy and splinting. On neurological examination her strength was 4/5 in the ulnar arm and hand muscles, and 5/5 in the lower extremities. Her deep-tendon reflexes were 2+ in the biceps, triceps, and supinators, and 1+ at the quadriceps; trace ankle jerks were present bilaterally. There was normal sensation in the hands and feet, and tenderness over

Figure 1 Chromosome analysis of patient 1006. Ideogram of chromosome 17 is shown on the left. The left chromosome 17 of each pair is the dup(17)(p11.2p11.2) chromosome. The right one is the submicroscopic HNPP deletion chromosome.

the ulnar nerves at the elbows. NCVs showed abnormalities of the right median motor and bilateral sensory median nerves at the wrists.

The patient's maternal grandfather (1160) was 68 years at evaluation. He had had episodic numbness in the hands and feet for >20 years and adult-onset diabetes for 4 years. Significant surgical history included a right ulnar nerve transfer because of nerve compression and numbness, and a removal of a "neuroma" of his foot. On neurological examination he had normal strength in the lower extremities and minimal weakness in the thenar hand muscles. Deep-tendon reflexes were absent in his arms and legs, and sensation to pinprick in the feet was decreased. Other modalities were normal. He had no sensory abnormalities in the hands and his nerves were not enlarged. NCVs revealed a mild sensorimotor polyneuropathy. He also had bilateral median nerve lesions at the wrist and a right ulnar nerve lesion at the elbow.

The patient's maternal aunt (1187) has a diagnosis of carpal tunnel syndrome by NCVs and has had surgery for carpal tunnel syndrome. The patient's maternal uncle (1188) has a diagnosis of carpal tunnel syndrome by NCVs. The patient's sister (1186), at age 7, has not been evaluated for a formal diagnosis of peripheral neuropathy.

Sample Analysis

Informed consent for these studies was obtained from the patient's parents and the participating family members under a protocol approved by the Baylor College of Medicine Institutional Review Board. Chromosome analysis by Giemsa Trypsin banding (G banding) was performed on peripheral blood lymphocytes from patient 1006, her parents (1005 and 1157), and her maternal grandfather (1160). FISH was performed on samples from the patient and her siblings, parents, maternal grandparents (1160 and 1180), maternal uncle (1188), and maternal aunt (1187). We performed two-color FISH as described (Shaffer et al. 1997), using cosmid probes for the *PMP22* gene located in 17p12 and the *FLI* locus in 17p11.2 (Chen et al. 1995). Alternatively, we performed two-color FISH using *FLI* and cosmid probe c86e11 for the *MFAP* (Zhao et al. 1995) gene that maps centromeric to *FLI* within the SMS critical region in 17p11.2, to determine the orientation of the duplicated region. We assigned parental origin of the duplicated chromosome by means of PCR-based microsatellite markers mapping to the SMS and CMT1A/HNPP regions, using methods described elsewhere (Greenberg et al. 1991; Shaffer et al. 1993). We identified the diagnostic HNPP junction fragment in this family by Southern analysis, using a CMT1A-REP probe on DNA extracted from peripheral lymphocytes (Reiter et al. 1996). PFGE of cells obtained from lymphoblast cultures was followed by Southern analysis with an SMS-REP probe (*CLP*) to identify a novel dup17p11.2 junction fragment (Chen et al. 1997).

Results

Chromosome Analyses

Our laboratory's previous (1994) G-band analysis of patient 1006 showed an apparent chromosome pattern of 46,XX,dup(17)(p11.2p12). Recent analysis of 30 G-banded cells and in situ hybridization analysis of 50 cells demonstrated a revised karyotype: 46,XX,dup(17)(p11.2p11.2).nuc ish dup(17)(p11.2p11.2)(FLIx3),del(17)(p12p12)(PMP22x1) chromosome pattern (fig. 1 and fig. 2). Two-color FISH with two probes from the SMS common deletion region (c86e11 and FLI) revealed a pattern consistent with a tandem duplication of 17p11.2 and inconsistent with an inverted duplication (fig. 2*B*). The patient therefore has no normal copies of chromosome 17, since there is a tandem duplication in

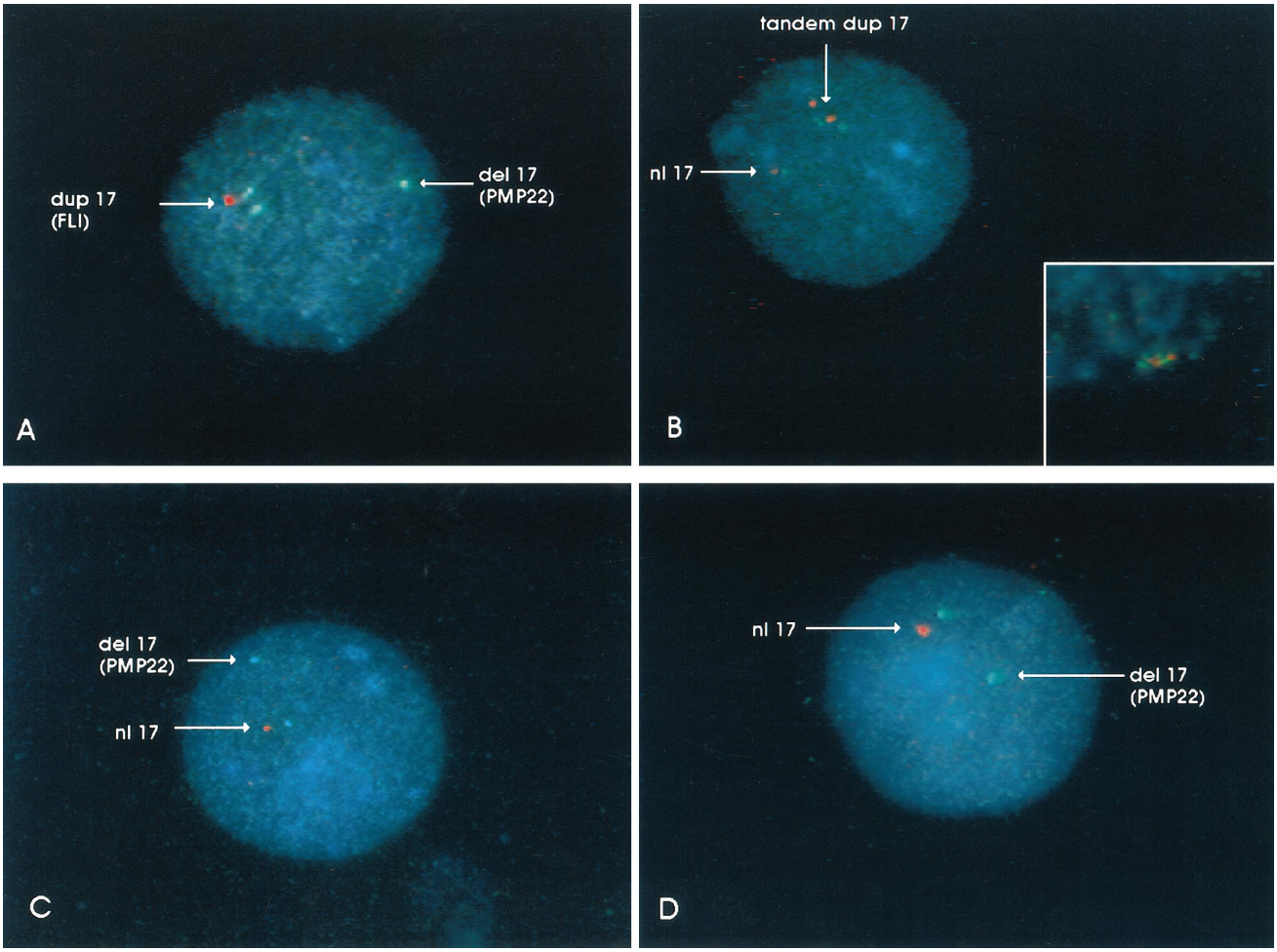

Figure 2 Representative results of the FISH analyses. *A*, Patient 1006. The *FLI* locus (green) is duplicated on one chromosome 17. The *PMP22* locus (red) is deleted on the other homologue. *B*, Patient 1006. The tandem nature of the duplication is shown for two cells (see inset); probes for the *FLI* locus (red) and cosmid c86e11 (green) were used. *C*, The proband's mother, 1005. *D*, The proband's maternal grandfather, 1160. The other homologue is normal (nl). The *PMP22* locus (red) is deleted on one chromosome 17. For *A*, *C*, and *D*, the *PMP22* cosmids were labeled with digoxigenin and detected with antidigoxigenin conjugated to rhodamine, which fluoresced red. In *B*, the *FLI* contig was labeled with digoxigenin and detected with antidigoxigenin conjugated to rhodamine, which fluoresced red. The *FLI* contig (in *A*, *C*, and *D*) and the c86e11 probe (in *B*) were labeled with biotin and detected with avidin conjugated to FITC, which fluoresced green.

the proximal band p11.2 on one chromosome 17 and a deletion in band p12 on the other chromosome 17.

Analysis of the patient's mother (1005) showed a chromosome pattern of 46,XX,nuc. ish del(17)(p12p12)(PMP22x1) (fig. 2*C*). FISH analysis of the patient's father (1157) showed a normal 46,XY pattern with no deletion of *PMP22*. Analysis of the patient's maternal grandfather (1160) (fig. 2*D*), maternal aunt (1187), maternal uncle (1188), and sister (1186) revealed the *PMP22* deletion. FISH analysis of the patient's brother (1185) and other sister (1184) revealed two copies of the *PMP22* gene (data not shown).

DNA Analyses

Molecular analysis of DNA samples from the patient and her family confirmed that the HNPP deletion segregates in an autosomal dominant manner and that the 17p11.2 duplication was de novo in the patient. Comparison with parental genotypes, using polymorphic dinucleotide repeats, indicates that the de novo duplication arose from the paternal chromosome 17 (data not shown). A unique junction fragment generated by the recombination event of the CMT1A-REPs (7.8-kb *Eco*RI HNPP junction fragment [Reiter et al. 1996]) was identified by Southern analysis in the patient, her younger sister, mother, maternal aunt and uncle, and maternal grandfather, all carrying the *PMP22* deletion (fig. 3). This 7.8-kb junction fragment was not detected in unaffected family members or controls.

PFGE was used to separate high–molecular weight DNA in the patient and relevant family members. A unique junction fragment, presumably generated by the

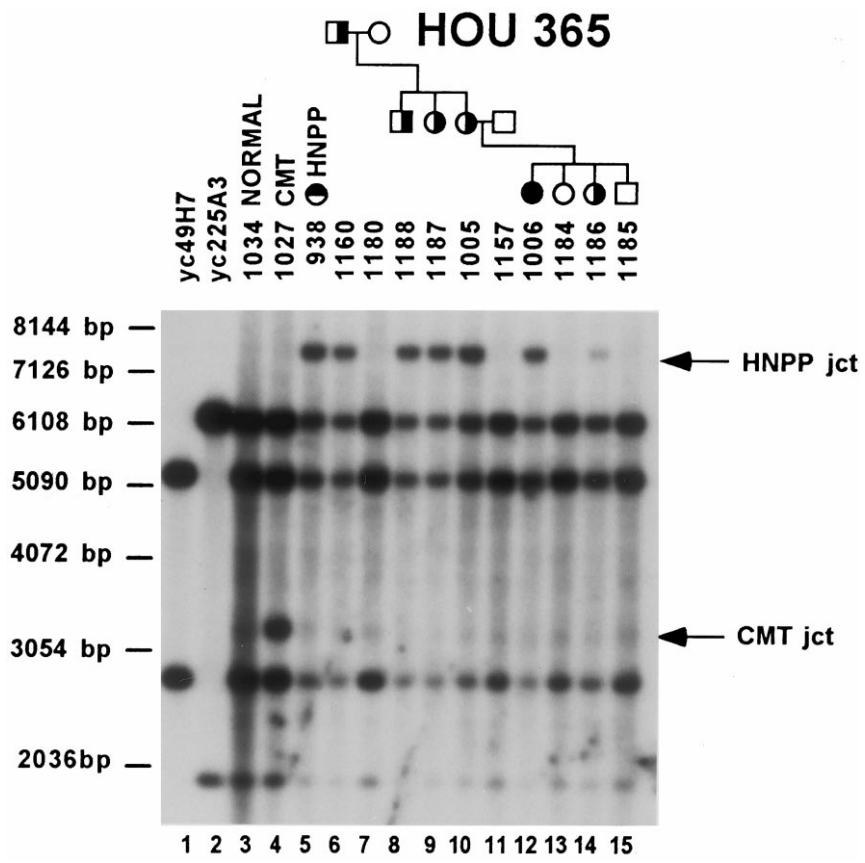

Figure 3 Southern blot analysis revealing the identification of the 7.8-kb HNPP-specific junction fragment in patient 1006 and family members (1160, 1188, 1187, 1005, and 1186) affected with peripheral neuropathy. Lanes 1 and 2 are control YAC clones containing proximal and distal CMT1A-REP, respectively. Lanes 3, 4, and 5 are control genomic DNA from an unaffected individual, a CMT1A duplication patient with the common crossover, and an HNPP patient with the common crossover. Note the 7.8-kb HNPP-specific junction fragment identified by means of a CMT1A-REP probe and not observed in the genomic YACs or in unaffected and CMT1A duplication controls. This HNPP junction fragment cosegregates with carpal tunnel syndrome in this family (lanes 6–15).

recombination event involving flanking SMS-REPs (1.2-Mb dup17p11.2 junction [Chen et al. 1997]), was identified by Southern analysis by means of an SMS-REP specific probe in the patient, but not in either of her parents (fig. 4). Similarly, a 17p11.2 duplication–specific junction fragment was identified in an unrelated individual (patient 990 in Chen et al. 1997) with a chromosomal duplication of 17p11.2, documented by FISH and G-band analysis.

Discussion

The proband in this family is affected with mild mental retardation, growth hormone deficiency, and peripheral neuropathy. Both of her chromosome 17 homologues are abnormal; one has a deletion of the *PMP22* gene inherited from her mother, and the other has a de novo tandem duplication of the SMS critical region. G-banded chromosome analysis, FISH, and PFGE/Southern analyses were consistent with the proband having a de novo, tandem dup(17)(p11.2p11.2). By means of polymorphic dinucleotide repeats, it was shown that the duplication was derived from the paternal chromosome 17. These results are consistent with a sister chromatid exchange of paternal origin likely arising during meiosis. Southern and FISH analyses showed that the *PMP22* deletion segregated in an autosomal dominant manner in this family and was found in all family members with a medical history of carpal tunnel syndrome. The peripheral neuropathy in the proband is much more severe than that of other members of her family. There may be dosage-sensitive genes within 17p11.2 that are duplicated and contribute to the more significant neurological findings in this patient, as opposed to her mother and other affected family members who only have deletions of *PMP22*.

Primary (i.e., not associated with other systemic disorders) familial autosomal dominant carpal tunnel syndrome (MIM 115430), although uncommon, has been reported and can present with bilateral neurological

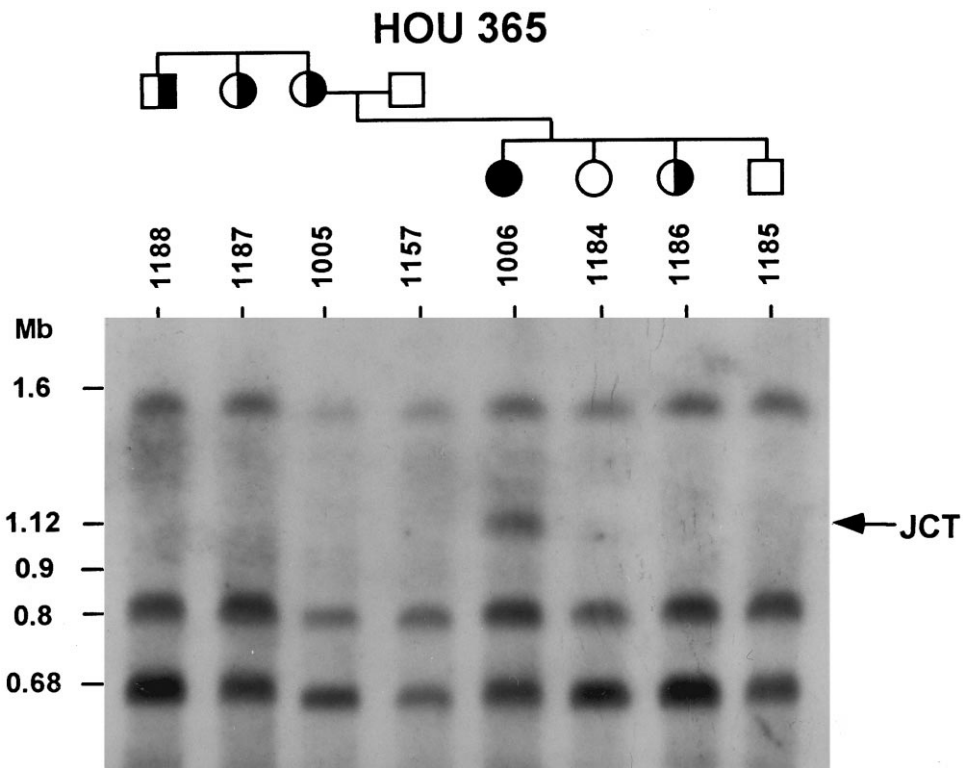

Figure 4 A 1.2-Mb junction fragment identified by PFGE. *Not*I-digested PFGE-separated genomic DNA from family HOU365 was probed with a *CLP* gene fragment from the SMS-REP. A unique apparent junction fragment (JCT) of ~1.2 Mb was identified in patient 1006. This junction fragment is present in patient 1006 but not in her parents or other family members.

symptoms, such as numbness and paresthesias in children or young adults (Danta 1975; Gray et al. 1979; Mochizuki et al. 1981; McDonnell et al. 1987; Leifer et al. 1992; Vadasz et al. 1997). The possibility of a *PMP22* deletion has been investigated in only one family segregating autosomal dominant carpal tunnel syndrome (Vadasz et al. 1997), in which there was found to be no evidence for the CMT1A duplication or HNPP deletion by molecular testing of selected family members. The diagnosis of familial carpal tunnel syndrome—in particular, those pedigrees with male-to-male transmission of the phenotype—should warrant specific molecular analysis for the HNPP deletion, either by FISH with the *PMP22* gene probe (Shaffer et al. 1997) or by other analyses. If a deletion is found, other family members should be counseled and tested as appropriate. A detailed family history in seemingly "sporadic" cases of carpal tunnel syndrome may yield valuable information, since clinical signs and symptoms of HNPP may go unrecognized and unreported in an individual for decades, as was the case for this patient's mother, maternal grandfather, and others in her family.

The fact that this patient has rearrangements of both of her chromosome 17 homologues suggests that rearrangements of this region may be relatively frequent events. The frequency of rearrangements in proximal 17p likely reflects the molecular characteristics of the human genome in this region. Theoretically, the 17p11.2 duplication could have resulted from unequal crossover between paternal homologues, maternal homologues, or sister chromatids of either paternal or maternal origin. On the basis of the analysis of DNA markers, the duplication in patient 1006 appears to have arisen from unequal crossover of sister chromatids of a paternal chromosome 17. Furthermore, FISH experiments in patient 1006 showed that the 17p11.2 duplication is tandem in nature, and data derived from PFGE reveal a de novo junction fragment. These findings are consistent with this duplication's representing the reciprocal product of the SMS deletion.

The mechanism of homologous recombination and unequal crossing over yielding reciprocal duplication and deletion products has been well documented in CMT1A and HNPP (Pentao et al. 1992; Reiter et al. 1996, 1997, 1998). There are two large 24,011-bp region-specific low–copy-number repeats (CMT1A-REPs) that flank the CMT1A/HNPP region (Pentao et al. 1992; Reiter et al. 1997). Within the CMT1A-REPs there is a 1.7-kb homologous recombination hotspot (Reiter et al. 1996). Furthermore, there is a *mariner* transposon-like

element located near the hotspot for homologous recombination that may mediate the double strand breaks that initiate homologous recombination, leading to duplication associated with CMT1A and the reciprocal deletion causing HNPP (Reiter et al. 1996, 1998). Similarly, SMS-REPs have been shown to be the substrate for homologous recombination and unequal crossing over, yielding deletion and apparent reciprocal duplication products in 17p11.2 (Chen et al. 1997). The 17p11.2 SMS deletion generates a novel junction fragment of 1.2 Mb (within the limits of resolution of PFGE), which is identified by Southern analysis of *Not*I digested DNA samples subjected to PFGE, by means of the SMS-REP specific *CLP* gene probe (Chen et al. 1997). The *CLP* probe also identifies a junction fragment in a 17p11.2 duplication patient (Chen et al. 1997) and is seen in patient 1006 reported here. Few patients with duplication of 17p11.2 have been reported (Brown et al. 1996; Roa et al. 1996). This likely reflects difficulties in ascertainment, since the clinical phenotype of these patients is neither striking nor distinct, and the duplication of the gene-rich, light–Giemsa-staining p11.2 band is a subtle cytogenetic finding.

In summary, the clinical and molecular findings in this patient and her family illustrate three general principles. First, cytologically visible duplications of the human genome, as opposed to deletions of the same regions, may be associated with relatively minor phenotypes. Other than the patient's progressive peripheral neuropathy (owing, at least in part, to the *PMP22* deletion), her phenotype is relatively minor even though she has a large DNA duplication for the ~5-Mb SMS region in 17p11.2. Individuals with similar neurological symptoms would likely be ascertained through neurological assessment, and interphase FISH for the *PMP22* deletion should be considered in those patients. Chromosome analysis should also be considered if there is a component of developmental delay or other congenital anomalies complicating the peripheral neuropathy. Second, the family history is an integral aspect of any clinical evaluation, even where the disorder is not an obviously inherited one. Although several members in three generations of this family had neurological findings of carpal tunnel syndrome, often requiring surgical intervention, the etiology of carpal tunnel syndrome was not investigated until the proband was found, by FISH, to have a deletion of *PMP22*. Subsequent analysis revealed the *PMP22* deletion in all affected family members, thus providing an explanation for the familial carpal tunnel syndrome in this family. And third, this case illustrates yet another example of a genomic disorder in which no mutation or alteration of the genes is involved, yet an abnormal phenotype results when there is deletion and/or duplication of a region of the genome that harbors dosage-sensitive genes (Lupski 1998*a*).

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Electronic-Database Information

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for CMT1A [MIM 118220], HNPP [MIM 162500], SMS [MIM 182290], and carpal tunnel syndrome [MIM 115430])

References

Bartsch-Sandhoff M, Hieronimi G (1979) Partial duplication of 17p: a new chromosomal syndrome. Hum Genet 49: 123–127

Brown A, Phelan MC, Patil S, Crawford E, Rogers RC, Schwartz C (1996) Two patients with duplication of 17p11.2: the reciprocal of the Smith-Magenis syndrome deletion? Am J Med Genet 63:373–377

Chance PF, Abbas N, Lensch MW, Pentao L, Roa BB, Patel PI, Lupski JR (1994) Two autosomal dominant neuropathies result from reciprocal DNA duplication/deletion of a region on chromosome 17. Hum Mol Genet 3:223–228

Chance PF, Alderson MK, Leppig KA, Lensch MW, Matsunami N, Smith B, Swanson PD, et al (1993) DNA deletion associated with hereditary neuropathy with liability to pressure palsies. Cell 72:143–151

Chen K-S, Gunaratne PH, Hoheisel JD, Young IG, Gabor Miklos GL, Greenberg F, Shaffer LG, et al (1995) The human homologue of the *Drosophila melanogaster* flightless-I gene (*fliI*) maps within the Smith-Magenis microdeletion critical region in 17p11.2. Am J Hum Genet 56:175–182

Chen K-S, Manian P, Koeuth T, Potocki L, Zhao Q, Chinault AC, Lee C-C, et al (1997) Homologous recombination of a flanking repeat gene cluster is a mechanism for a common contiguous gene deletion syndrome. Nat Genet 17:154–163

Chen K-S, Potocki L, Lupski JR (1996*a*) The Smith-Magenis syndrome [del(17)p11.2]: clinical review and molecular advances. Ment Retard Dev Disabil Res Rev 2:122–129

Chen RM, Lupski JR, Greenberg F, Lewis RA (1996*b*) Ophthalmic manifestations of Smith-Magenis syndrome. Ophthalmology 103:1084–1091

Danta G (1975) Familial carpal tunnel syndrome with onset in childhood. J Neurol Neurosurg Psychiatry 38:350–355

Dykens EM, Finucane BM, Gayley C (1997) Brief report: cognitive and behavioral profiles in persons with Smith-Magenis syndrome. J Autism Dev Disord 27:203–211

Feldman GM, Baumer JG, Sparkes RS (1982) Brief clinical

report: the dup(17p) syndrome. Am J Med Genet 11: 299–304

Finucane BM, Jaeger ER, Kurtz MB, Weinstein M, Scott CI Jr. (1993) Eye abnormalities in the Smith-Magenis contiguous gene deletion syndrome. Am J Med Genet 45:443–446

Finucane BM, Konar D, Haas-Givler B, Kurtz MB, Scott CI Jr. (1994) The spasmodic upper-body squeeze: a characteristic behavior in Smith-Magenis syndrome. Dev Med Child Neurol 36:78–83

Gray RG, Poppo MJ, Gottlieb NL (1979) Primary familial bilateral carpal tunnel syndrome. Ann Intern Med 91:37–40

Greenberg F, Guzzetta V, Montes de Oca-Luna R, Magenis RE, Smith ACM, Richter SF, Kondo I, et al (1991) Molecular analysis of the Smith-Magenis syndrome: a possible contiguous-gene syndrome associated with del(17)(p11.2). Am J Hum Genet 49:1207–1218

Greenberg F, Lewis RA, Potocki L, Glaze D, Parke J, Killian J, Murphy MA, et al (1996) Multi-disciplinary clinical study of Smith-Magenis syndrome (deletion 17p11.2). Am J Med Genet 62:247–254

Leifer D, Cros D, Halperin JJ, Gallico GG, Pierce DS, Shahani BT (1992) Familial bilateral carpal tunnel syndrome: report of two families. Arch Phys Med Rehabil 73:393–397

Lupski JR (1992) An inherited DNA rearrangement and gene dosage effect are responsible for the most common autosomal dominant peripheral neuropathy: Charcot-Marie-Tooth disease type 1A. Clin Res 40:645–652

Lupski JR (1997) Charcot-Marie-Tooth disease: a gene-dosage effect. Hosp Pract 32:83–122

Lupski JR (1998*a*) Genomic disorders: structural features of the genome can lead to DNA rearrangements and human genetic disease traits. Trends Genet 14:417–422

Lupski JR (1998*b*) Molecular genetics of peripheral neuropathies. In: Martin JB (ed) Scientific American molecular neurology. Scientific American, New York, pp 239–256

Magenis RE, Brown MG, Allen L, Reiss J (1986) De novo partial duplication of 17p [dup(17)(p12→p11.2)]: clinical report. Am J Med Genet 24:415–420

Mascarello JT, Jones MC, Hoyme HE, Freebury MM (1983) Duplication (17p) in a child with an isodicentric (17p) chromosome. Am J Med Genet 14:67–72

McDonnell JM, Makley JT, Horwitz SJ (1987) Familial carpal-tunnel syndrome presenting in childhood. Report of two cases. J Bone Joint Surg Am 69:928–930

Mochizuki Y, Ohkubo H, Motomura T (1981) Familial bilateral carpal tunnel syndrome. J Neurol Neurosurg Psychiatry 44:367

Murakami T, Garcia CA, Reiter LT, Lupski JR (1996) Charcot-Marie-Tooth disease and related inherited neuropathies. Medicine 75:233–250

Pellegrino JE, Pellegrino L, Spinner NB, Sladky J, Chance PF, Zackai EH (1996) Developmental profile in a patient with monosomy 10q and dup(17p) associated with a peripheral neuropathy. Am J Med Genet 61:377–381

Pentao L, Wise CA, Chinault AC, Patel PI, Lupski JR (1992) Charcot-Marie-Tooth type 1A duplication appears to arise from recombination at repeat sequences flanking the 1.5 Mb monomer unit. Nat Genet 2:292–300

Reiter LT, Hastings PJ, Nelis E, De Jonghe P, Van Broeckhoven C, Lupski JR (1998) Human meiotic recombination products revealed by sequencing a hotspot for homologous strand exchange in multiple HNPP deletion patients. Am J Hum Genet 62:1023–1033

Reiter LT, Murakami T, Koeuth T, Gibbs RA, Lupski JR (1997) The human *COX10* gene is disrupted during homologous recombination between the 24 kb proximal and distal CMT1A-REPs. Hum Mol Genet 6:1595–1603

Reiter LT, Murakami T, Koeuth T, Pentao L, Muzny DM, Gibbs RA, Lupski JR (1996) A recombination hotspot responsible for two inherited peripheral neuropathies is located near a *mariner* transposon-like element. Nat Genet 12:288–297

Roa BB, Greenberg F, Gunaratne P, Sauer CM, Lubinsky MS, Kozma C, Meck JM, et al (1996) Duplication of the *PMP22* gene in 17p partial trisomy patients with Charcot-Marie-Tooth type-1A neuropathy. Hum Genet 97:642–649

Schrander-Stumpel C, Schrander J, Fryns JP, Hamers G (1990) Trisomy 17p due to a t(8;17) (p23;p11.2)pat translocation: case report and review of the literature. Clin Genet 37: 148–152

Shaffer LG, Overhauser J, Jackson LG, Ledbetter DH (1993) Genetic syndromes and uniparental disomy: a study of 16 cases of Brachmann-de Lange syndrome. Am J Med Genet 47:383–386

Shaffer LG, Kennedy GM, Spikes AS, Lupski JR (1997) Diagnosis of CMT1A duplications and HNPP deletions by interphase FISH: implications for testing in the cytogenetics laboratory. Am J Med Genet 69:325–331

Smith ACM, McGavran L, Robinson J, Waldstein G, Macfarlane J, Zonona J, Reiss J, et al (1986) Interstitial deletion of (17)(p11.2p11.2) in nine patients. Am J Med Genet 24: 393–414

Tyson J, Malcolm S, Thomas PK, Harding AE (1996) Deletions of chromosome 17p11.2 in multifocal neuropathies. Ann Neurol 39:180–186

Upadhyaya M, Roberts SH, Farnham J, MacMillan JC, Clarke A, Heath JP, Hodges ICG, et al (1993) Charcot-Marie-Tooth disease 1A (CMT1A) associated with a maternal duplication of chromosome 17p11.2→12. Hum Genet 91:392–394

Vadasz AG, Chance PF, Epstein LG, Lou J-S (1997) Familial autosomal-dominant carpal tunnel syndrome presenting in a 5-year-old—case report and review of the literature. Muscle Nerve 20:376–378

Zhao Z, Lee C-C, Jiralerspong S, Juyal RC, Lu F, Baldini A, Greenberg F, et al (1995) The gene for a human microfibril-associated glycoprotein is commonly deleted in Smith-Magenis syndrome patients. Hum Mol Genet 4:589–597