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Genetic Proof of Unequal Meiotic Crossovers in Reciprocal Deletion and Duplication of 17p11.2

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A number of common contiguous gene syndromes have been shown to result from nonallelic homologous recombination (NAHR) within region-specific low-copy repeats (LCRs). The reciprocal duplications are predicted to occur at the same frequency; however, probably because of ascertainment bias and milder phenotypes, reciprocal events have been identified in only a few cases to date. We previously described seven patients with dup(17)(p11.2p11.2), the reciprocal of the Smith-Magenis syndrome (SMS) deletion, del(17)(p11.2p11.2). In >90% of patients with SMS, identical ~3.7-Mb deletions in 17p11.2 have been identified. These deletions are flanked by large (~200 kb), highly homologous, directly oriented LCRs (i.e., proximal and distal SMS repeats [SMS-REPs]). The third (middle) SMS-REP is inverted with respect to them and maps inside the commonly deleted genomic region. To investigate the parental origin and to determine whether the common deletion and duplication arise by unequal crossovers mediated through NAHR between the proximal and distal SMS-REPs, we analyzed the haplotypes of 14 families with SMS and six families with dup(17)(p11.2p11.2), using microsatellite markers directly flanking the SMS common deletion breakpoints. Our data indicate that reciprocal deletion and duplication of 17p11.2 result from unequal meiotic crossovers. These rearrangements occur via both interchromosomal and intrachromosomal exchange events between the proximal and distal SMS-REPs, and there appears to be no parental-origin bias associated with common SMS deletions and the reciprocal duplications.

Introduction

Smith-Magenis syndrome (SMS [MIM 182290]) is characterized by multiple congenital anomalies and mental retardation and is associated with an interstitial deletion of chromosome 17p11.2 (Smith et al. 1986; Stratton et al. 1986; Greenberg et al. 1991, 1996; Chen et al. 1996). Features of patients with SMS include neurobehavioral abnormalities, such as aggressive and self-injurious behaviors, sleep disturbances, delayed speech and motor development, midface hypoplasia, short stature, and brachydactyly. The majority (>90%) of patients with SMS have a common ~3.7-Mb deletion, as defined by a unique de novo junction fragment identified by pulsed-field gel electrophoresis (PFGE) (Greenberg et al. 1991; Guzzetta et al. 1992; Juyal et al. 1996; Chen et al. 1997; Bi et al. 2002). Physical mapping studies have shown that the SMS common deletion region is flanked by large (~200 kb), highly homologous, low copy repeats (LCRs) (i.e., proximal and distal SMS repeats [SMS-REPs]) (Chen et al. 1997; Park et al. 2002). A third copy of inverted orientation, middle SMS-REP, has been identified within the SMS common deletion region (Chen et al. 1997; Park et al. 2002). SMS-REPs share ~160 kb of >98% sequence identity (Park et al. 2002). Given the direct orientation and extent of homology between proximal and distal SMS-REPs, we have proposed that SMS-REPs act as substrates for nonallelic homologous recombination (NAHR), or unequal crossing over, resulting in deletions and duplications of the intervening chromosomal region (Chen et al. 1997).

LCRs flanking deletion breakpoints have been identified in other contiguous-gene syndromes, such as Williams-Beuren syndrome (WBS) (Pérez Jurado et al. 1996, 1998; Osborne et al. 1997), Prader-Willi/Angelman syndromes (PWS/AS) (Amos-Landgraf et al. 1999; Christian et al. 1999), DiGeorge/velocardiofacial syndromes (DGS/VCFS) (Edelmann et al. 1999*a*, 1999*b*), and neurofibromatosis type 1 (NF1) (Dorschner et al. 2000). In each case, the microdeletion is proposed to result from NAHR between the flanking LCRs (Urbán et al. 1996; Baumer et al. 1998; Amos-Landgraf et al. 1999; López Correa et al. 2000; Trost et al. 2000; reviewed by Inoue and Lupski [2002] and by Stankiewicz and Lupski [2002*a* and 2002*b*]).

Although it is anticipated that the reciprocal duplications may occur at the same frequency as deletions,

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only a few such reciprocal deletion/duplication syndromes have been reported. The best-characterized example is that of hereditary neuropathy with liability to pressure palsies (HNPP) and Charcot-Marie-Tooth disease type 1A (CMT1A). CMT1A is associated with a 1.4-Mb duplication that results from NAHR between highly homologous 24-kb LCRs in 17p12, termed "CMT1A-REPs," whereas HNPP results from the reciprocal deletion (Pentao et al. 1992; Chance et al. 1994; Reiter et al. 1996; Inoue et al. 2001). PWS/AS commonly result from a 4-Mb deletion, with breakpoints mapping within LCRs on chromosome 15 (Christian et al. 1995; Amos-Landgraf et al. 1999). An apparent reciprocal duplication of 15q11-q13, between the common PWS/AS deletion breakpoints, has been identified in at least 13 patients to date (Browne et al. 1997; Repetto et al. 1998; Thomas et al. 1999; Roberts et al. 2002), although, as is the case with WBS, DGS/VCFS, or NF1, physical evidence of a predicted specific and recurrent junction fragment for a reciprocal duplication remains to be demonstrated.

Only a few patients with dup(17)(p11.2p11.2) have been ascertained. It is predicted that the incidence of dup(17)(p11.2p11.2) is equal to that of SMS (1:20,000), but duplications remain underdetected. This may result from an ascertainment bias, because patients with duplications usually exhibit a significantly milder phenotype than do patients with deletions, and G-banded duplications can be more difficult to identify than deletions. Alternatively, duplication gametes may be at a selective disadvantage. This discrepancy in ascertainment for predicted reciprocal duplications may be common to other contiguous gene deletion syndromes with breakpoints flanked by LCRs. Individuals with reciprocal duplications may not be ascertained, because they exhibit a relatively milder phenotype or are unaffected.

Elsewhere, we reported seven individuals with the duplication dup(17)(p11.2p11.2), the predicted reciprocal homologous recombination product of the common SMS deletion (Potocki et al. 2000). A unique junction fragment of the same apparent size was identified in all seven patients by use of PFGE, indicating a precise and recurrent recombination and further suggesting that the seven duplications were of the same size. Microsatellite analysis of one pedigree with dup(17)(p11.2p11.2) revealed that the SMS reciprocal duplication was due to unequal meiotic crossing over between the proximal and distal SMS-REPs. This led us to analyze additional pedigrees with dup(17)(p11.2p11.2) and to further investigate, by segregation of genetic markers, the hypothesis that unequal meiotic crossing over between proximal and distal SMS-REPs results in both dup(17)(p11.2p11.2) and the SMS microdeletion.

Subjects and Methods

Subjects

For our DNA analysis we collected 14 families of patients with SMS and six families of patients with dup(17)(p11.2p11.2). All patients with SMS met diagnostic criteria for SMS (Chen et al. 1996). Peripheral blood samples from patients and family members were obtained after informed consent. The presence of a deletion in patients with SMS was confirmed by FISH analysis, using probes specific for *FLII* (the human ortholog of *Drosophila melanogaster flightless–I* [*fliI*]) (Chen et al. 1995) and *ZNF179* (Zhao et al. 1998)—both mapping within the SMS common deletion region—and using the peripheral myelin protein 22 gene, *PMP22*, mapping within the commonly duplicated CMT1A region (Patel et al. 1992), as a control.

PFGE was performed on the patient samples, as described elsewhere (Chen et al. 1997; Potocki et al. 2000), to determine whether their deletions and duplications represent the repeat-mediated common rearrangements. A deletion or duplication is considered common if the breakpoints map within the proximal and distal SMS-REPs. Coincidentally, common deletions and duplications are each distinguished by a unique de novo ~1.1-Mb band corresponding to the SMS rearrangement-specific common junction fragment.

Two of the patients with dup(17)(p11.2p11.2) reported here (patients 1006 and 1364) were reported elsewhere (Potocki et al. 2000). However, at the time of that report, siblings were not available for allele phasing for either patient. In addition, the father of patient 1364 is deceased, and microsatellite analysis was previously uninformative.

Genotyping

We determined both the parental origin of the rearranged chromosomes and the recombination mechanism resulting in the deletion or duplication by microsatellite haplotype reconstruction and the segregation of marker genotypes, using genomic DNA purified from peripheral blood. Nine microsatellite markers were used to reconstruct haplotypes, including three within the common SMS region (D17S2256, D17S2257, and D17S805), three centromeric to the proximal SMS-REP (D17S842, D17S841, and D17S1871) and three telomeric to the distal SMS-REP (D17S955, D17S122, and D17S1857). Two novel microsatellite markers (D17S2256 and D17S2257) were developed on the basis of BAC genomic sequence available from the National Center for Biotechnology Information. D17S2256 represents a $(TG)_{20}$ direct repeat within RP11-1084K4; D17S2257 represents a $(CA)_{29}$ direct repeat within

RP11-189D22. Oligonucleotide primer sequences flanking each microsatellite were designed using Primer3 (Whitehead Institute; sequences available at the Lupski Lab Web site) or obtained from the Genome Database. The 5′ ends of forward primers were end-labeled with fluorescent dyes of 6-FAM, TET, or HEX (Applied Biosystems). PCR was performed in a final volume of 20 μl containing genomic DNA (100 ng), 10 × buffer (Qiagen), dNTPs (2.5 mM each; Invitrogen), primers (15 pmol each) and HotStar*Taq* (0.75 U; Qiagen). Initial denaturation was at 95°C for 15 min, followed by 40 cycles of denaturation at 94°C for 1 min, annealing at 55°–67°C for 1 min, extension at 72°C for 1 min, and a final extension at 72°C for 10 min. PCR products were visualized by 2% agarose gel electrophoresis and were diluted 2–15 times, according to the band intensity. We mixed diluted PCR products (1.5 μl) with 3.5 μl formamide loading dye and TAMRA 500 standard (Applied Biosystems), and we performed electrophoresis on 5% denaturing polyacrylamide gel in the 377-96 DNA sequencer (Applied Biosystems). Sizes and relative intensities of the peaks were calculated by use of GENESCAN (v. 2.1) and GENOTYPER (v. 2.5) software (Applied Biosystems). Genotypes were analyzed according to the Manual of Linkage Mapping Set (Applied Biosystems). Phases of parental haplotypes were defined on the basis of the most parsimonious explanation for observed genotypes in the siblings and under the assumption of no recombination.

Results

Molecular Evidence for the Common-Size Deletion/Duplication of 17p11.2

To confirm the presence of a deletion or duplication, FISH analysis, using probes specific to the SMS common-deletion region, was performed on patient samples. Both *FLII* and *ZNF179* map within the SMS common-deletion region and are deleted in all 14 patients with SMS, while all patients are not deleted for *PMP22,* suggesting the common deletion. The duplication in the six patients with dup(17)(p11.2p11.2) was determined, using FISH, to be tandem in orientation, as described elsewhere (Potocki et al. 2000). The majority of SMS deletions and reciprocal duplications have common breakpoints, although deletions and duplications of different sizes have been identified. PFGE was performed on patient samples to determine whether the deletion/duplication breakpoints were common. The ~1.1-Mb SMS rearrangement-specific common junction fragment was identified in all patients with SMS and dup(17)(p11.2p11.2), indicating that all deletions/duplications were the common or predominant rearrangements.

Further Genetic Confirmation That dup(17)(p11.2p11.2) Occurs via Unequal Crossovers

We have previously reported seven patients with dup(17)(p11.2p11.2), five of which were paternal in origin, suggesting a potential parent-of-origin bias with the duplication (Potocki et al. 2000). To further investigate a potential bias, we determined the parent of origin in one uninformative patient included in the group reported elsewhere (Potocki et al. 2000) and in four additional families of patients with dup17(p11.2p11.2). We have collected siblings of patients 1006 and 1364, who were reported elsewhere (Potocki et al. 2000), to provide additional evidence of unequal crossovers in those families. The parental origin of the duplication is made evident by duplication of one or both of one parent's alleles for loci D17S2256, D17S2257, and D17S805. Four of the six duplicated chromosomes were of paternal origin, and the remaining two duplications were maternally derived (figs. 1 and 1 and 2; table 1). To determine whether a parent-of-origin bias exists, the data from five families of patients with dup(17)(p11.2p11.2) reported elsewhere (Potocki et al. 2000) were combined with the present data. In total, 8 of the 11 duplications were paternally derived, and three were maternal in origin. The binomial distribution was applied to these data and the apparent parent-of-origin bias was not found to be significant ($P = .227$).

Unequal crossovers between the proximal and distal SMS-REPs were apparent in one informative family with dup(17)(p11.2p11.2) reported by Potocki et al. (2000). To further confirm the duplication is due to unequal crossing over, we analyzed segregation of marker haplotypes in the current six families with dup17(p11.2p11.2). In total, two duplications occurred via interchromosomal recombination and four were a result of intrachromosomal exchange (figs. 1 and 2; table 1). Paternal interchromosomal recombination was demonstrated in one family (HOU 660) by the presence of two distinct paternal alleles and one maternal allele for markers D17S2256, D17S2257, and D17S805 (fig. 2). Paternal intrachromosomal recombination was indicated by the presence of a higher-intensity peak, corresponding to a double dose of one of the paternal alleles for markers D17S2256, D17S2257, and D17S805 in three families (HOU 365, HOU 692, and HOU 724) (figs. 1 and 2). One maternal duplication resulted from interchromosomal recombination (HOU 625), and one duplication arose from maternal intrachromosomal exchange (HOU 532) (fig. 1). Patient 1006 (HOU 365) has an apparent crossover on her maternal chromosome, between markers D17S842 and D17S1871, and loci D17S955 and D17S122 are deleted, as they are in her mother. The *PMP22* gene was deleted in both individuals, and both display a phenotype consistent with

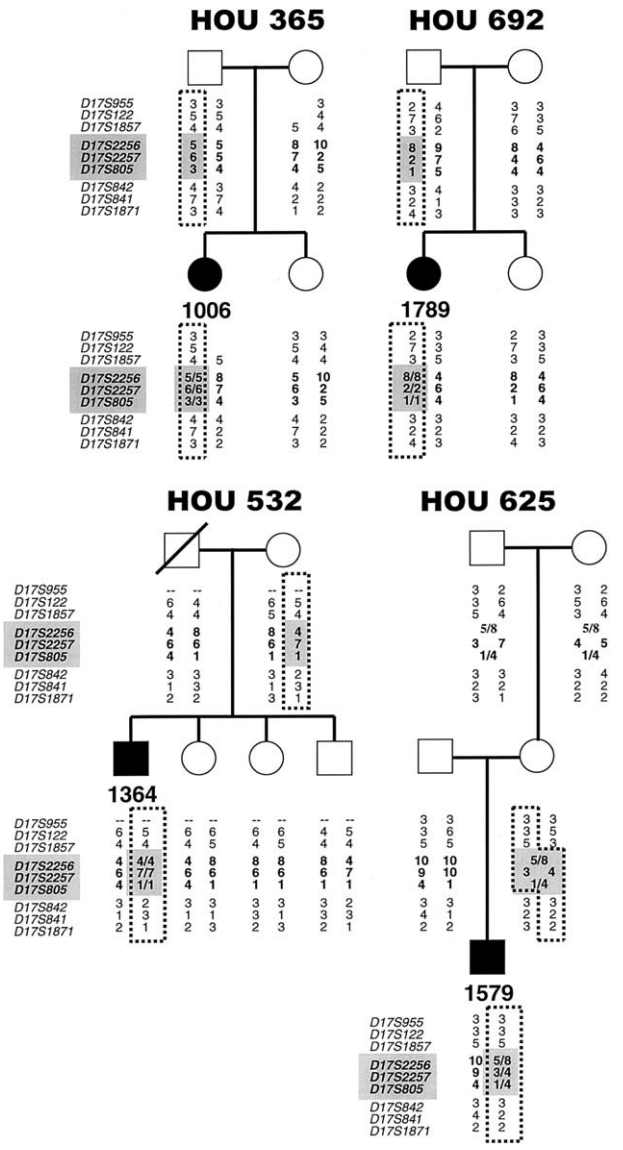


Figure 1 Haplotypes of four patients with dup(17)(p11.2p11.2) and their families. Blackened symbols indicate affected individuals. To the left of each pedigree is a list of microsatellite markers used for genotyping; those within the SMS common-deletion region are shaded and in bold. The allele numbers are located under each family member. The genotypes of markers within the SMS common-deletion region are in bold and are shaded in each patient and the parent of origin. The dotted lines outline alleles inherited by the patient from the parent of origin. Loci D17S955 and D17S122 are deleted in the mother and patient in family HOU 365. D17S955 was not informative for family HOU 532. (The allele numbers for HOU 365 and HOU 532 that were reported elsewhere [Potocki et al. 2000] were changed to remain consistent with those in the present report.)

HNPP (Potocki et al. 1999). Locus D17S955 was uninformative in family HOU 532. The haplotype of the deceased father is inferred from those of his children. A sister of patient 1364 has an apparent crossover on her paternal chromosome, between markers D17S1857 and D17S2256, and patient 1618 (family HOU 660; fig. 2) has a crossover on his maternal chromosome between loci D17S2257 and D17S842. Phasing of the patient, maternal, and grandparental chromosomes was not possible for markers D17S2256 and D17S805 in family HOU 625.

Genetic Evidence That Unequal Crossovers Generate del(17)(p11.2p11.2)

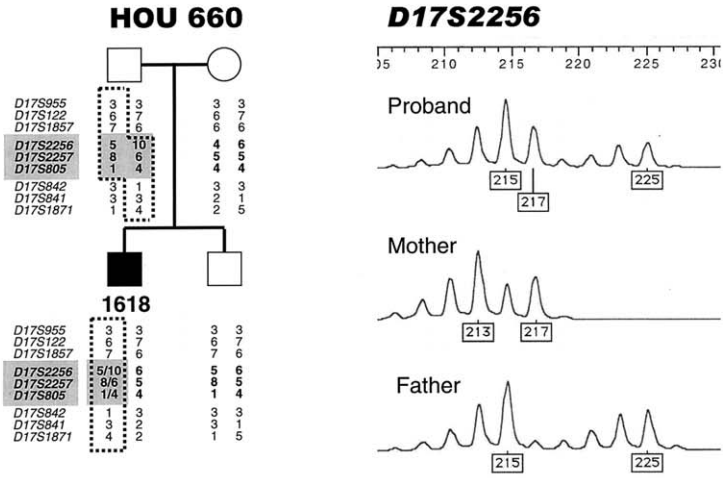
Because of the paucity of genetic markers between the proximal SMS-REP and the centromere, previous haplotype analysis of families with SMS has not been performed. Here we have determined the parent-of-origin and recombination mechanism of the SMS deletion in 14 families. All of the patients analyzed were hemizygous for markers D17S2256, D17S2257, and D17S805, located within the common SMS deletion region (fig. 2 and 3). Eight of the rearranged chromosomes were of paternal origin, as is demonstrated by the absence of maternal alleles for markers D17S2256, D17S2257, and D17S805, and six of the deletions were maternal in origin (figs. 2 and 3; table 2).

Unequal crossing over between the proximal and distal SMS-REPs was obvious in 13 of 14 patients, as evidenced by absence of a parental allele for each of three genetic markers (D17S2256, D17S2257, and D17S805) that map within the common-deletion region. Four of the paternal deletions were due to intrachromosomal exchange (HOU 110, HOU 114, HOU 421, and HOU 554), and four were interchromosomal (HOU 69, HOU 344, HOU 411, and HOU 433) (figs. 2 and 3; table 2). An interchromosomal recombination event was demonstrated by recombination between the markers directly flanking the SMS common-deletion region. Four of the maternal deletions were intrachromosomal (HOU 68, HOU 358, HOU 490, and HOU 540), and one was interchromosomal (HOU 689) (fig. 3 and table 2). The recombination mechanism (i.e., inter- vs. intrachromosomal) that resulted in the remaining maternal deletion (HOU 233), was not obvious. Patient 1402 has an apparent crossover on his maternal chromosome between markers D17S122 and D17S1857, and patient 1144 has an apparent crossover on his maternal chromosome between markers D17S1857 and D17S2256.

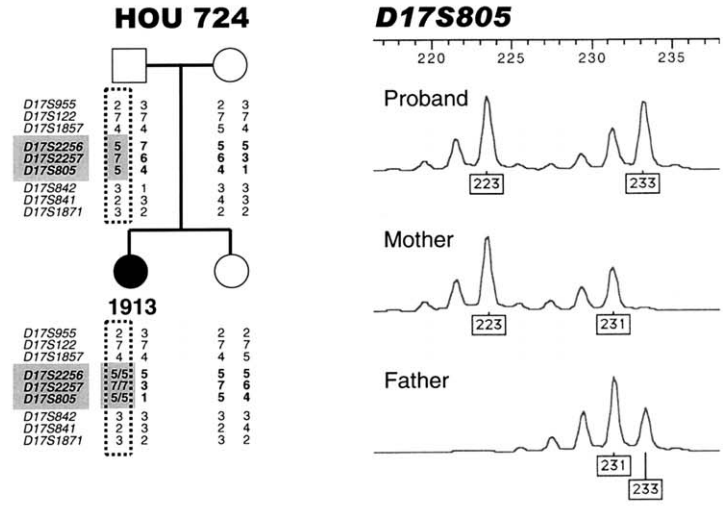
Discussion

One patient with dup(17)(p11.2p11.2) whom we have reported elsewhere (Potocki et al. 2000) demonstrated unequal crossing over between the proximal and distal SMS-REPs, resulting in a paternal interchromosomal duplication. Here, we provide further evidence supporting unequal crossing over in two families from that study

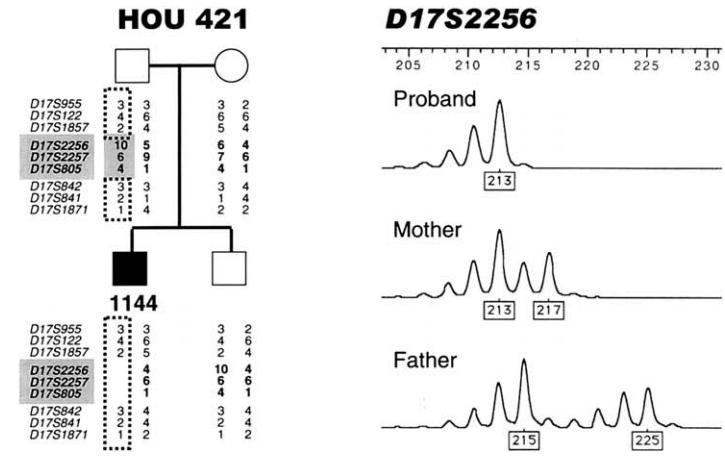
A **Interchromosomal recombination**



B **Intrachromosomal recombination**



C **Intrachromosomal recombination**



(HOU 365 and HOU 532) and four additional families with dup(17)(p11.2p11.2). Of the 11 combined cases (7 from Potocki et al. [2000] and 4 from the present report), 6 resulted from interchromosomal recombination, and 5 were intrachromosomal, indicating that duplication occurs via both mechanisms at an approximately equal frequency (table 1). Likewise, we provide evidence showing that 5 of the 14 SMS deletions occurred via interchromosomal recombination and that 8 resulted from an intrachromosomal event (table 2). Since the SMS deletion and dup(17)(p11.2p11.2) represent reciprocal recombination events resulting from unequal crossing over between proximal and distal SMS-REPs, the data presented here for both can be combined. Of the 24 patients with informative SMS/dup(17)(p11.2p11.2), 11 rearrangements were interchromosomal, and 13 were intrachromosomal, further supporting the hypothesis that NAHR between proximal and distal SMS-REPs occurs as frequently between or within sister chromatids as between homologs.

Potocki et al. (2000) reported six patients with dup(17)(p11.2p11.2) in which the parental origin could be determined, and five of these were paternal in origin. This observation led to the hypothesis that there may be a parent-of-origin bias associated with this duplication. However, when these earlier data were pooled together with data reported here, 8 of 11 duplications were demonstrated to be paternal, and 3 were maternal (table 1). Thus, although a trend is evident (with eight paternal vs. three maternal duplications), these data do not support the significant association of a parent-of-origin bias with dup(17)(p11.2p11.2) ($P = .227$). Similarly, eight SMS deletions were paternal, and six were maternal in origin. The combined SMS and dup(17)(p11.2p11.2) parent-of-origin data show 16 paternal rearrangements and 9 of maternal origin, further indicating that unequal crossovers between proximal and distal SMS-REPs may occur as frequently on the maternal chromosome as the paternal chromosome ($P = .230$).

We show that rearrangements of maternal and paternal origin each occur via both inter- and intrachromosomal unequal crossing over; thus, our data provide no evidence for a significant association of sex-biased recombination mechanisms with SMS/dup(17)(p11.2p11.2). This finding contrasts with similar studies performed on the reciprocal deletion/duplication syndromes HNPP and CMT1A, in which all informative paternal CMT1A duplications ($n = 32$) resulted from unequal interchromosomal crossing over between CMT1A-REPs, whereas the few informative maternal duplications ($n = 2$) and HNPP deletions ($n = 2$) resulted from intrachromosomal recombination (Lopes et al. 1997, 1998). The de novo CMT1A duplication event has been found to occur 10 times more frequently in male than in female patients (Palau et al. 1993; Lopes et al. 1997). Interestingly, genetic mapping in CEPH reference families reveals that male patients exhibit a lower recombination frequency in the CMT1A region than do female patients (.67cM/Mb vs. 5.5cM/Mb) (Inoue et al. 2001). This reduced male recombination frequency was hypothesized to result in an extended region of unsynapsed chromosome segments in meiosis, enabling the chromosomes to slip on each other, thus predisposing to unequal crossovers between misaligned CMT1A-REPs. Thus, reduced recombination has been proposed to potentially enable an increase of unequal crossovers and therefore may explain the high frequency of paternally derived duplications in CMT1A. On the basis of a comparison between the genetic and physical maps of 17p11.2, we reported elsewhere that male and female patients exhibit a reduced but equal rate of recombination in the SMS region (Bi et al. 2002). Therefore, the absence of a parent-of-origin bias for the reciprocal SMS del/dup(17)(p11.2p11.2) could still be consistent with a "reduced recombination/increased unequal crossover" hypothesis. Indeed, SMS deletions occur at a relatively equal frequency in male and female patients.

The molecular mechanisms resulting in several other chromosome deletions and duplications that cause contiguous gene syndromes have been reported elsewhere;

Table 1

Origin and Mechanism of dup(17)(p11.2p11.2) Rearrangement

Parental Origin	Recombination Mechanism		
	Interchromosomal	Intrachromosomal	Unknown
Maternal	2	1	0
Paternal	4	4	0

Note.—Includes data from the article by Potocki et al. (2000).

Figure 2 Pedigrees and genotype plots of two dup(17)(p11.2p11.2) families and one SMS family. *A,* An example of paternal interchromosomal recombination resulting in a duplication. Pedigree and genotype plots of family HOU 660, showing inheritance by patient 1618 of both alleles from his father and one allele from his mother for marker D17S2256. Peaks labeled 213, 215, 217 and 225 correspond to alleles 4, 5, 6 and 10, respectively, in the pedigree. *B,* dup(17)(p11.2p11.2) patient 1913 who inherited two copies of her father's allele and one copy of her mother's allele for marker D17S805, demonstrating a paternal intrachromosomal event leading to duplication. Peaks labeled 223, 231 and 233 correspond to alleles 1, 4 and 5, respectively, in the pedigree. *C,* Genotype plots and pedigree of family HOU 421 showing inheritance by patient 1144 of one allele from his mother and none from his father for marker D17S2256. Peaks and alleles are labeled as in panel *A*. There is a crossover between D17S1857 and D17S2256 on the patient's maternal chromosome.

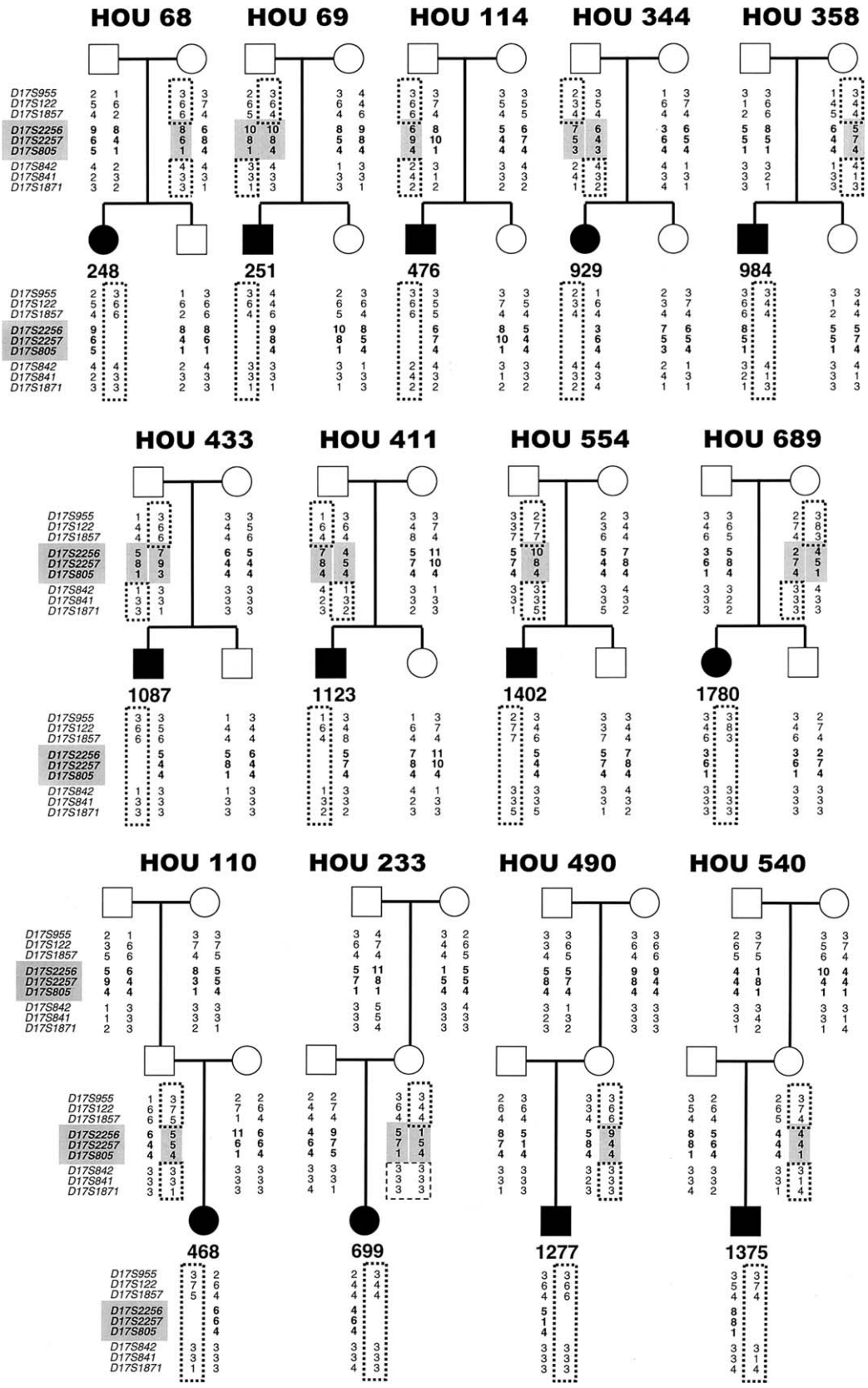


Figure 3 Haplotypes of 13 patients with SMS and their families. The markers within the SMS common-deletion region are shaded and in bold, and their genotypes are shaded and in bold in the parents of origin and are in bold in the patients. The dotted lines outline alleles inherited by the patient from the parent of origin. The dashed lines in pedigree HOU 233 indicate that the deletion mechanism could not be determined for patient 699.

Table 2

Origin and Mechanism of del(17)(p11.2p11.2) Rearrangement

Parental Origin	Recombination Mechanism		
	Interchromosomal	Intrachromosomal	Unknown
Maternal	1	4	1
Paternal	4	4	0

DGS/VCFS, NF1, and PWS/AS deletions occur via both intra- and interchromosomal events (Carrozzo et al. 1997; Baumer et al. 1998; Robinson et al. 1998; Edelmann et al. 1999*a;* López Correa et al. 2000; Trost et al. 2000), whereas the majority of WBS deletions are due to interchromosomal recombination (Urbán et al. 1996). The parental origins of these rearrangements also have been investigated. The majority of NF1 deletions are maternal in origin (Lázaro et al. 1996), as are reciprocal duplications of the PWS/AS critical region (Browne et al. 1997; Repetto et al. 1998; Thomas et al. 1999; Roberts et al. 2002), but no consistent sex bias has been detected in WBS (Urbán et al. 1996) or DGS/VCFS (Trost et al. 2000).

Several chromosome deletions have been noted to be recurrent and to occur with a higher frequency in specific regions of the human genome. The breakpoints of such rearrangements, including all of those mentioned above, have been found to fall within recombination-prone LCR regions (Lopes et al. 1996; Chen et al. 1997; Lupski 1998; Pérez Jurado et al. 1998; Amos-Landgraf et al. 1999; Edelmann et al. 1999*b;* López Correa et al. 2000; Potocki et al. 2000). Since duplications are predicted to occur at the same frequency as deletion events resulting from LCR-mediated unequal crossing over, it remains a distinct possibility that most microdeletion syndromes have corresponding microduplication syndromes that represent the reciprocal recombination product.

In summary, our data provide genetic evidence that the SMS deletion and reciprocal duplication (17)(p11.2p11.2) occur by unequal crossing over, presumably mediated through NAHR between the proximal and distal SMS-REPs. These chromosomal rearrangements occur on paternal and maternal chromosomes and arise from both inter- and intrachromosomal exchange events. The present study provides further evidence for a model in which reciprocal deletion and duplication syndromes arise from unequal crossing over between LCRs.

Acknowledgments

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Electronic-Database Information

Accession number and URLs for data presented herein are as follows:

Genome Database, The, http://gdbwww.gdb.org/
Lupski Lab Web site, http://imgen.bcm.tmc.edu/molgen/lupski/
National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for SMS [MIM 182290])
Whitehead Institute, http://www-genome.wi.mit.edu/

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