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Report

Preferential Paternal Origin of Microdeletions Caused by Prezygotic Chromosome or Chromatid Rearrangements in Sotos Syndrome

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Sotos syndrome (SoS) is characterized by pre- and postnatal overgrowth with advanced bone age; a dysmorphic face with macrocephaly and pointed chin; large hands and feet; mental retardation; and possible susceptibility to tumors. It has been shown that the major cause of SoS is haploinsufficiency of the *NSD1* gene at 5q35, because the majority of patients had either a common microdeletion including *NSD1* or a truncated type of point mutation in *NSD1*. In the present study, we traced the parental origin of the microdeletions in 26 patients with SoS by the use of 16 microsatellite markers at or flanking the commonly deleted region. Deletions in 18 of the 20 informative cases occurred in the paternally derived chromosome 5, whereas those in the maternally derived chromosome were found in only two cases. Haplotyping analysis of the marker loci revealed that the paternal deletion in five of seven informative cases and the maternal deletion in one case arose through an intrachromosomal rearrangement, and two other cases of the paternal deletion involved an interchromosomal event, suggesting that the common microdeletion observed in SoS did not occur through a uniform mechanism but preferentially arose prezygotically.

Sotos syndrome (SoS [MIM 117550]), cerebral gigantism, is an overgrowth syndrome characterized by generalized overgrowth with advanced bone age, macrocephaly, frontal bossing, prominent jaw, high hairline, downslanting palpebral fissures, mental retardation, and possible susceptibility to tumors. We have shown that haploinsufficiency of the *NSD1* gene at 5q35 is the major cause of SoS. Two-thirds of Japanese patients with SoS had a common deletion involving the whole *NSD1* gene (Kurotaki et al. 2002), and a subset of patients had truncate type of *NSD1* point mutations. Such frequent, common deletions are seen in many genomic disorders and may occur by low copy repeat (LCR)–mediated chromosomal rearrangements (Shaffer and Lupski 2000). Recently, another group reported a high rate of *NSD1* point mutations but a low rate of microdeletions in patients with SoS (Douglas et al. 2003). This difference in deletion frequency needs further investigation.

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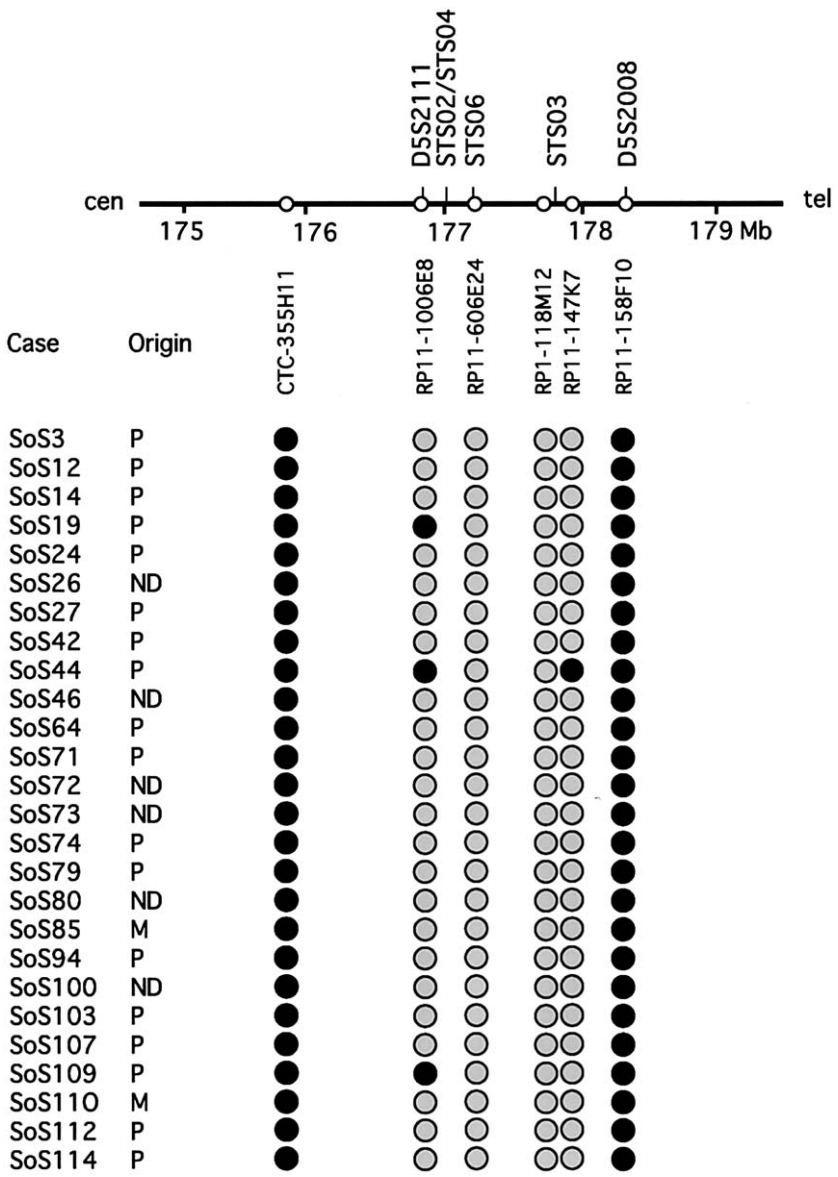

Figure 1 Panel of 26 sporadic SoS cases of microdeletions that were confirmed by FISH analysis. Upper row shows locations of clones used for FISH (*open circle*) and polymorphic markers mapped to the deleted regions. Black circle shows a clone that was not deleted in each patient, and gray circle indicates a clone deleted. P = paternal origin of deletion; M = maternal; ND = not determined.

We observed phenotypic differences between patients with SoS with microdeletions and those with point mutations (Nagai et al. 2003). Dysmorphic craniofacial abnormalities, overgrowth, and mental retardation were present in both types of patients, whereas major anomalies in the central nervous, cardiovascular, and urinary systems were predominantly exhibited by patients with the deletion. These different phenotypes could mainly be due to deletion of other genes in addition to *NSD1*.

To unravel the underlying mechanisms for the common deletion, such as the parental origin and the type of chromosome/chromatid rearrangements, we performed genotype and haplotype analyses of polymorphic marker loci in 26 families with 26 patients with sporadic SoS, 7 of whom were reported elsewhere (Kurotaki et al. 2002).

All 26 subjects (see fig. 1) in this study were referred to us after a possible diagnosis of SoS was made and written informed consent forms were obtained from their parents. Three main symptoms, such as craniofacial dysmorphology, mental retardation, and a history of over-

growth, were basically observed in all the patients, but the diagnostic criteria might not be consistent. Advanced bone age that could be one diagnostic symptom, as suggested by Cole and Hughes (1994), was not evaluated, because sufficient data were not available. DNA samples and chromosome preparations from patients and both of their parents were available in 21 families. In the other five families, the samples were available in only patients and their mothers. Experimental protocols were approved by the Committee for the Ethical Issues on Human Genome and Gene Analysis, Nagasaki University.

Microdeletions of all 26 patients with SoS were confirmed by FISH analysis (fig. 1). Six BAC/PAC clones (CTC-355H11, RP11-1006E8, RP11-606E24, RP1-118M12, RP11-147K7, and RP11-158F10) were selected for FISH probes, according to the UCSC genome browser. Cloned DNA was labeled with SpectrumGreen-11-dUTP or SpectrumOrange-11-dUTP (Vysis) by nick translation and denatured at 76°C for 10 min. Probe-hybridization mixtures (10 μl) were applied on the chromosomes, were incubated at 37°C for 16 h, and then were washed. Fluorescence photomicroscopy was performed under a Zeiss Axioskop microscope equipped with a quad filter set with single band excitation filters (84000, Chroma Technology). Images were collected and merged using a cooled CCD camera (TEA/CCD-1317-G1, Princeton Instruments) and IPLab/MAC software (Scanalytics). RP11-606E24 and RP1-118M12 involving *NSD1* were deleted in all cases. RP11-1006E8 was deleted in all but three cases (SS19, SS44, and SS109). RP11-147K7 is not deleted in SS44 but is deleted in others. Thus, 23 patients had the same deletion spanning a region at least from RP11-1006E8 to RP11-147K7 (fig. 1). The size of the common deletion was originally reported as 2.2 Mb, but it turned out to range from 1.3 Mb to 2.7 Mb, according to the most current UCSC database (November 2002). A de novo microdeletion in 21 individuals and normal karyotypes in both of their respective parents were confirmed by FISH. Mothers of the remaining five patients also showed a normal FISH karyotype.

To trace the parental origin of the deletion in the 26 families, we carried out PCR-based microsatellite analysis using four markers (STS02 [GenBank accession number BV005166], STS03 [GenBank accession number BV005165], STS04 [GenBank accession number BV 005168], and STS06 [GenBank accession number BV 005167]) that were newly generated from BAC clones mapped to the common deletion (figs. 1 and 2) and that showed high heterozygosity among 10 normal Japanese control individuals. Twelve other markers included D5S2111 within the common deleted region, and D5S436, D5S410, D5S422, D5S400, D5S429, D5S677, D5S2008, D5S2073, D5S1354, D5S408, and D5S2006, which flank the deletion, were also used (fig. 2). PCR amplification was performed in a 20-μl PCR mixture containing 50 ng genomic DNA, 10 pM of each fluorescent primer and reverse primer, 250 μM dNTP, 0.5 U Ex *Taq* polymerase (Takara), and 10 × PCR buffer (Takara). PCR was cycled 40 times at 98°C for 10 s, 55–60°C for 30 s, and 72°C for 30 s. PCR products were electrophoresed in ABI PRISM 377 automated sequencer (PE Applied Biosystems) and analyzed with fragment analysis software (PE Applied Biosystems). As a result, 20 of the 26 families were informative for the parent-of-origin (fig. 1). In 18 of the 20 families, microdeletions had occurred in the paternally derived chromosome 5, whereas the occurrence of deletions in the maternally derived chromosome was confirmed in only two informative cases. In addition, all the patients from the other five families in which only the maternal DNA was available retained the maternally derived alleles at the marker loci examined; therefore, the finding supports the paternal origin of their microdeletions.

We then genotyped six 3-generation families and two 2-generation families with an unaffected sib. Haplotype analysis disclosed the type of chromosome/chromatid rearrangements in the patients. Five instances of paternal deletion and an instance of maternal deletion had intrachromosomal type of rearrangements, whereas rearrangements in the other two instances of paternal deletion were interchromosomal type (fig. 2). Occurrence of double recombination between the two closest markers flanking the microdeletion is very unlikely, because the genetic distance between them is only 7.8 (D5S677–D5S2008) to 15.8 cM (D5S429–D5S2073). Therefore, it is reasonable that the rearrangements in the former six subjects are interpreted to be intrachromosomal (fig. 2). The absence of somatic mosaicism was confirmed in 100 mitotic cells by FISH in each of these eight subjects.

Parental origin of microdeletions and/or duplications have been investigated in several genomic disorders. Deletions in Williams syndrome (WS) at 7q11.23 and velocardiofacial syndrome (VCFS) at 22q11.2 were of equally paternal and maternal origin (Nickerson et al. 1995; Dutly and Schinzel 1996; Urban et al. 1996; Baumer et al. 1998). Deletions at 17p11.2 in Smith-Magenis syndrome (SMS) and their reciprocal chromosomal events, duplications of 17p11.2, tended to occur more frequently in the paternally derived chromosomes than the maternally derived chromosomes, but a significant parent-of-origin bias was not observed (Shaw et al. 2002). Instead, duplications in Charcot-Marie-Tooth disease type 1A (CMT1A) at 17p11.2–p12 (Palau et al. 1993; Bort et al. 1997; Lopes et al. 1997) were of preferential paternal origin. In contrast, microdeletions in neurofibromatosis type 1 (NF1) at 17q11.2 were of predominantly maternal origin (Lazaro et al. 1996; López Correa et al. 2000). A 15q11–q13 deletion occurring in the paternally and the maternally derived chromosome results

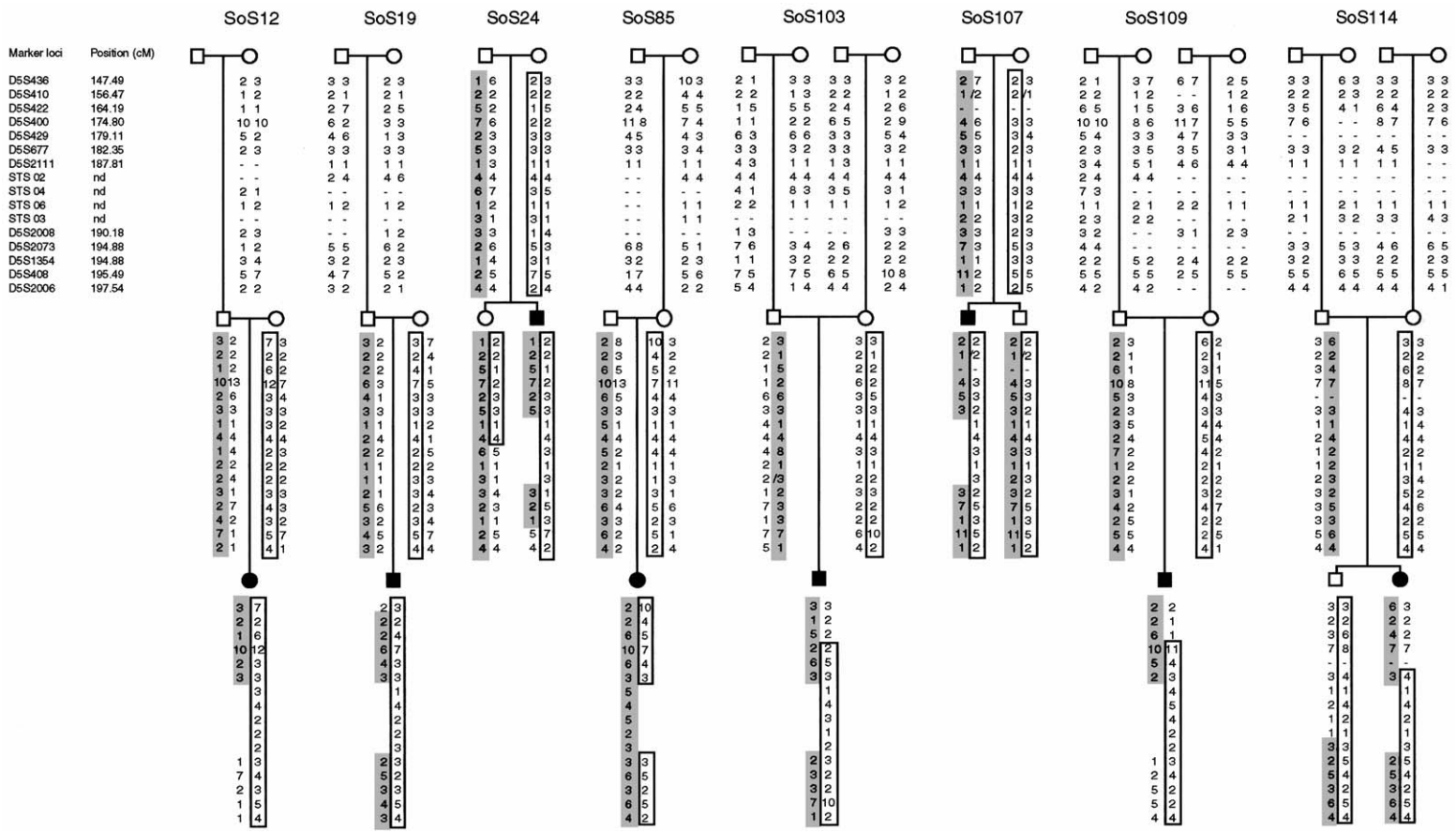

Figure 2 Haplotype analysis in eight families having patients with sporadic SoS at 16 polymorphic marker loci: D5S436, D5S410, D5S422, D5S400, D5S429, D5S677, D5S2111, STS02, STS04, STS06, STS03, D5S2008, D5S2073, D5S1354, D5S408, and D5S2006. Position of markers was also shown according to the Marshfield database. Paternal deletions are recognized in all families but a family of SoS85. Gray and open boxes indicate a haplotype on chromosome 5 transmitted from the father and the mother, respectively. At D5S410 in a family of SoS107, which allele (1 or 2) contributes to a haplotype is unknown.

in Prader-Willi (PWS) and Angelman (AS) syndromes, respectively, because of the imprinting effect at the chromosomal region. Furthermore, some terminal deletion syndromes also showed biased parental origin. Deletions in Wolf-Hirschhorn syndrome (WHS) at 4p16.3 (Quarrell et al. 1991; Tupler et al. 1992; Wieczorek et al. 2000) and cri du chat syndrome (CCS) at 5p15.3 (Mainardi et al. 2001) are of preferential paternal origin, and the 1p36 deletion syndrome showed predominant maternal deletions (Wu et al. 1999). Mechanisms resulting in terminal deletions may be different from those in interstitial deletions in genomic disorders.

Preferential paternal origin of microdeletions in our patients with SoS may be explained by either (1) the influence of the parental origin of microdeletions on the SoS phenotype or (2) more susceptibility of a region at or around the microdeletion on the paternally derived chromosomes to abnormal chromosomal rearrangements than that on the maternally derived chromosome. Since the two patients with the maternal deletion had typical clinical manifestations for the syndrome, and no imprinted genes have been identified in the region (Brzustowicz et al. 1994; Ledbetter and Engel 1995; Morison and Reeve 1998), the first possibility is unlikely. We favor the second hypothesis. Predominant paternal origin of de novo point mutations as well as of de novo structural chromosome abnormalities has repeatedly been reported (Chandley 1991; Moloney et al. 1996; Wirth et al. 1997). Most of such de novo mutations may arise at spermatogenesis, and paternal age effect has been documented in many diseases (Wirth et al. 1997). The average paternal age in our patients with paternal deletions is 32.3 years (range 27–43 years), not significantly deviating from 31.8 years for the general Japanese population (Web site of Ministry of Health, Labor and Welfare of Japan). Chromosomal rearrangements mediated by possible LCR may not be affected by paternal age.

There have been several studies on the type of chromosomal rearrangements. In WS, VCFS, CMT1A, and NF1, most deletions/duplications were associated with interchromosomal rearrangements (Urban et al. 1996; Lopes et al. 1997; Baumer et al. 1998; López Correa et al. 2000). Deletions and duplications of 17p11.2 in SMS were caused by either intra- or interchromosomal events (Potocki et al. 2000; Shaw et al. 2002) and by deletions in PWS, as well (Carrozzo et al. 1997; Robinson et al. 1998). It is most likely that interchromosomal rearrangements arise by an unequal crossing-over at the meiosis I through paralogous LCRs between homologous chromosomes. However, intrachromosomal type of rearrangements may occur by an LCR mispairing–mediated unequal sister-chromatid exchange. Alternatively, the rearrangements arise through the formation of an intrachromosomal loop that is also mediated by LCRs within a chromatid. Although both events may occur in a somatic cell, and possibly in a spermatogonial cell (Lopes et al. 1997), its occurrence during meiosis remains unknown. Since somatic mosaicism for deletion was never observed in our patients with SoS, the postzygotic occurrence of the intrachromosomal rearrangements is unlikely, and thus all these abnormalities in our series of patients may have arisen at a prezygotic period.

An interesting correlation between the parental origin and the type of deletion/duplication has been recognized (Lopes et al. 1997). Paternal duplications in CMT1A are always associated with interchromosomal rearrangements, whereas maternal duplications/deletions, both in CMT1A and in hereditary neuropathy with liability to pressure palsies, are associated with intrachromosomal rearrangements. Thus, the mechanism for such rearrangements occurring in females and males may be different in these diseases. However, this is not the case for SoS, since both events were observed in our series of patients.

In conclusion, we observed that microdeletions in SoS are mostly of paternal origin, and intra- or interchromosomal rearrangements are both involved in the microdeletion. A physical map construction that covers the common deleted region and its flanking regions is now in progress. It remains to be seen whether LCRs or other repetitive sequences present in the 5q35 region mediate the deletion.

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Electronic-Database Information

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

GenBank, http://www.ncbi.nlm.nih.gov/GenBank/ (for markers deposited: STS02 [accession number BV005166], STS03 [accession number BV005165], STS04 [accession number BV005168], and STS06 [accession number BV005167])

Marshfield genetic map, http://research.marshfieldclinic.org/genetics

Ministry of Health, Labor and Welfare in Japan, http://wwwdbtk.mhlw.go.jp/toukei/cgi/j_kensaku (for average parental age at birth in Japan) (in Japanese)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for Sotos syndrome)

UCSC genome informatics, http://genome.ucsc.edu/ (for human, mouse, and rat genomes)

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