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Letter to the Editor

Klinefelter and Trisomy X Syndromes in Patients With Prader-Willi Syndrome and Uniparental Maternal Disomy of Chromosome 15—A Coincidence?

To the Editor:

We report on two patients (a 7-year-old boy and a 12-year-old girl) with Klinefelter syndrome and mosaic trisomy X syndrome, respectively, and Prader-Willi syndrome (PWS) due to uniparental maternal disomy of chromosome 15. Both patients were born to mothers with advanced maternal age. To our knowledge only one patient has been reported with PWS and 47,XXX syndrome [Ferrante et al., 1986], while several patients with PWS and Klinefelter syndrome have been reported [Dunn, 1968; Bray et al., 1983; Trent et al., 1991; Tu et al., 1992]. Previous studies have not examined whether or not their phenotypes were due to concerted missegregation of both chromosome 15 and X. Herein, we describe the phenotypes of these two patients and determine the probable etiology of their nondisjunction events.

CLINICAL REPORTS
Patient A

Patient A was born to a 36-year-old gravida 1 mother and weighed 2,483 g (15th centile) and was 47 cm (25th centile) long. Hypotonia was noted immediately after delivery with inability to nurse or suck. He was gavage fed in intensive care for 3 weeks. CT scan and MRI of the head and EEG were normal, as were results of evaluations for primary neuromuscular or metabolic disease. He was on home oxygen therapy for the first 3 months after discharge. He grew slowly until age 3 years, at which time rapid weight gain was noted, although there was no reported change in appetite. He was evaluated for possible growth hormone deficiency at age 2 years when he was found to be short and had a bone age of one year. Thyroid and renal function tests were normal. The family history was unremarkable.

Developmental delays were noted. He sat at 11 months, crawled at 14 months, and had his first words at 19 months and sentences at 2 years. He walked at 2 years. He had articulation problems noted at 3 1/2 years of age, and he received occupational, physical, and speech therapy. His overall health has been good. Because of development delay and minor anomalies, a chromosome study was performed previously at age 2 years and a 47,XXY karyotype was found in all peripheral blood cells analyzed.

A genetic evaluation was requested at 3 years 8 months of age at which time his height was 96 cm (5th centile), weight was 20 kg (95th centile), and head circumference was 51 cm (70th centile). His blood pressure was 94/50 mm Hg. He had mild generalized hypotonia. He had a midline hair whorl, which was anteriorly displaced. His bifrontal diameter was narrow. He had epicanthal folds and almond-shaped palpebral fissures with left esotropia. He had broad alveolar ridges with normal saliva. His abdomen was obese. He had a small penis (stretched length of 2.8 cm) with a small, flat scrotum. The testicles were retractile. His gait was flat-footed and somewhat broad-based.

Because of findings of Prader-Willi syndrome (see Fig. 1), molecular genetic studies were performed on blood from the mother, father, and child. Maternal uniparental disomy of chromosome 15 was found using DNA probe MS620 (D15S586) from the 15q25 region (mother: 5.5 kb, 5.5 kb; father: 4.0 kb, 4.1 kb; and child:

The trisomy X syndrome patient was presented at the 45th annual meeting of the American Society of Human Genetics, October 24-28, 1995, Minneapolis, MN.

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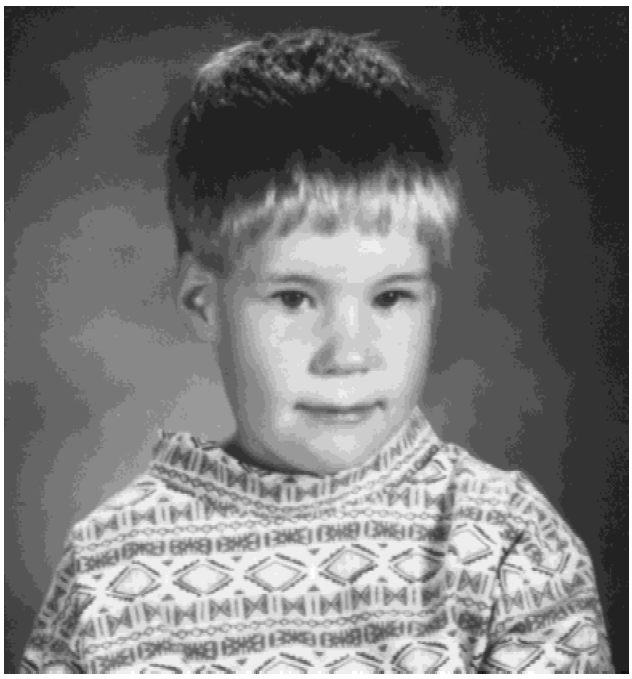

Fig. 1. Frontal view of patient A with Prader-Willi and Klinefelter syndromes at 7 years of age.

5.5 kb, 5.5 kb; data not shown) following established protocols [Mascari et al., 1992; Lai et al., 1993]. Additional molecular genetic studies were performed at 7 years of age using 15q11q13 microsatellite DNA markers (D15S128, D15S122, GABRB3, GABRA5, and D15S219) and PCR amplification [Malcolm and Donlon, 1994]. In addition, markers from the X chromosome (DXS987, DXS991, DXS992, DXS997, DXS1002, and DXS1003) identified alleles in the child that were not present in his mother. Unfortunately, his father was deceased. These data suggest that X-Y chromosome non-disjunction occurred during male gametogenesis. Two different chromosome 15 alleles were found in the child that were identical to the mother's and consistent with the previous MS620 probe data showing uniparental maternal heterodisomy of chromosome 15.

Patient B

Patient B is a white female born by repeat C-section to a 36-year-old gravida 4, para 2 mother. She weighed 2,100 g (30th centile) and was 45.7 cm (40th centile) long. Fetal activity was decreased. Severe generalized hypotonia was noted at birth with a poor suck reflex and temperature instability. An EEG done at 4 weeks showed an immature pattern but no evidence of seizures. An amino acid screen, cranial CT scan and auditory brain stem evoked potential studies were normal during the neonatal period. Chromosome studies were obtained from peripheral blood cells and 17 of 30 cells (57%) showed a 47,XXX karyotype, while 13 of 30 cells (43%) demonstrated a normal 46,XX female karyotype, with comparable mosaicism observed in fibroblasts. At 20 months of age, her motor function were at the 6–7 month level while social, speech, and language functions were at the 9–12 month level. At 22 months of age, she was 76.8 cm (<5th centile) long, weight was 8.44 kg (<5th centile), and her head circumference was 47.7 cm (50th centile). She had marked hypotonia with hyperextensible joints and decreased deep tendon reflexes. She had dolichocephaly with a prominent forehead, bilateral epicanthal folds, slightly posteriorly rotated ears, prominent lateral palentine ridges, mild micrognathia, a bland expressionless face with a history of staring spells, and mild puffiness of the dorsum of the feet. She began walking at age 36 months. At 4 years 1 month, the family noted rapid weight gain, food related tantrums and sleep disturbances.

At 5 years, 5 months, her height was 100.3 cm (3rd centile), weight was 22.7 kg (90th centile) and head circumference was 51 cm (50th centile). Additional findings noted were enamel hypoplasia, sticky saliva, lumbar lordosis, marked truncal obesity, small hands and feet, hypoplastic labia minora, a small clitoris, joint laxity, an increased carrying angle, and skin picking (see Fig. 2). Currently, she is 12 years old with a height of 142.2 cm (60th centile) and her weight is 70.4 kg (>95th centile). She is in the sixth grade and is approximately one year behind academically. Reading skills are her strengths while math is a weakness.

To confirm the diagnosis of PWS, PCR studies were undertaken using 15q11q13 microsatellite primers as previously described for patient A. PCR analysis using X chromosome markers from both Xq and Xp (DXS987, DXS989, DXS991, DXS992, DXS6789, DXS1001, DXS1105, DXS998, DXS984, DXS6790, DXS988, and AR) was undertaken, and the patient exhibited a single maternal and a single paternal allele at each of the X chromosome loci tested, and no third allele was observed. The sensitivity of detection for a minor allele present in a mosaic cell line is approximately 2% of the predominant alleles [Pangalos et al., 1994]; thus a third allele could have been detected in our patient with trisomy X observed in greater than 50% of cells examined. PCR analysis with several 15q11q13 markers (D15S128, MN-1, GABRB3, D15S541, D15S165, GABRA5, and D15S122) showed maternal heterodisomy of chromosome 15 in the patient. Loci studied from other chromosomes were not compatible with nonpaternity.

The findings in each patient were consistent with PWS [Butler et al., 1986; Butler, 1990], although the girl also had epicanthal folds, a flattened nasal bridge, staring spells, and an increased carrying angle, which can be seen in patients with trisomy X syndrome. The boy with Klinefelter syndrome and PWS had findings consistent with PWS and few, if any, additional anomalies (e.g., tall stature) of Klinefelter syndrome [Jones, 1988]. The major manifestations of PWS predominated in each patient. However, behavior and emotional problems, which can occur in both Klinefelter and trisomy X syndromes, can also overlap in PWS [de la Chapelle, 1983]. It is unclear why the clinical presentation of an imprinted disorder (i.e., PWS) predomi-

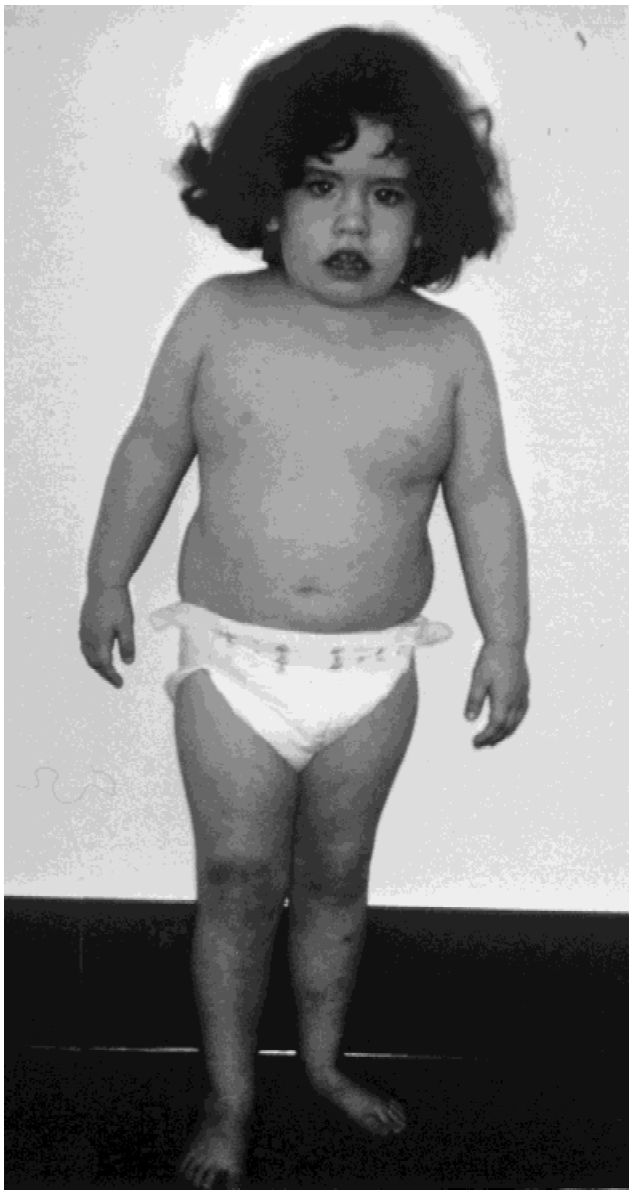

Fig. 2. Frontal view of patient B with Prader-Willi and trisomy X syndromes at 4 years of age.

nated over the sex chromosome aneuploidy in our two patients, although patients with Klinefelter and trisomy X syndromes often have non-specific phenotypes or at least are subtly abnormal. PWS findings are obvious. We suggest that the genetic imbalance results from over-expression of genes on the X chromosome may be less deleterious during development than functional haploinsufficiency (or nullisomy) due to failure to express imprinted alleles on chromosome 15.

Molecular analyses of DNA in these patients indicate that non-disjunction of the X chromosome and of chromosome 15 each occurred independently. The Klinefelter syndrome and PWS patient inherited a non-maternal X chromosome allele at each of the loci studied. X chromosome non-disjunction occurred during male gametogenesis, whereas both chromosome 15s were of maternal origin. Our patient with mosaic trisomy X syndrome and PWS exhibited a single X maternal and a single X paternal allele. Maternal or paternal meiotic non-disjunction is unlikely based on the absence of a third allele at the six polymorphic informative X chromosome loci studied (though it cannot be excluded). If a meiotic error is assumed to have occurred, then reduction of both parental genotypes to homozygosity of X chromosome loci close to the centromere (e.g., at DXS991) would indicate that missegregation is likely to have occurred at meiosis II. By contrast maternal heterodisomy of proximal 15q genetic loci indicates that chromosome 15 non-disjunction occurred during meiosis I. In any case, the observed mosaicism suggests that a meiosis II error would be less likely than a sole postzygotic missegregation event [Pangalos et al., 1994]. The extra X chromosome in the trisomy X cell line presumably arose postzygotically, whereas nondisjunction of the chromosome 15 arose by a meiotic error.

Since cases of non-disjunction of the X chromosome and of chromosome 15 are both viable, one might expect to observe patients with both cytogenetic syndromes by chance alone. The incidence of PWS is about 1 per 15,000 live births and maternal disomy 15 accounts for about 25% of those subjects; therefore the chance for a child to be born with PWS and maternal disomy 15 would be about 1 in 60,000. The chance of having a child with Klinefelter syndrome is 1 in 1,000 live births and 1 in 2,000 for trisomy X syndrome. Assuming that these non-disjunction events occurred independently of one another, the odds of having a child with both PWS (due to maternal disomy 15) and Klinefelter syndrome or trisomy X syndrome would be estimated at 1 in 60,000,000 and 1 in 120,000,000, respectively. We present these patients with hopes that other investigators will report on PWS patients with atypical presentations that include anomalies seen in other genetic syndromes.

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