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Pallister-Killian Syndrome Detected by Fluorescence In Situ Hybridization

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To the Editor

The Pallister-Killian syndrome is a rare cytogenetic condition first described in 1977 by Pallister et al. in 3 adults; the first affected child was reported in 1981 [Teschler-Nicola and Killian, 1981]. This syndrome (also known as Pallister mosaic aneuploidy syndrome or isochromosome 12p mosaicism) is characterized by postnatal growth retardation, seizures, hypotonia, deafness, profound mental retardation, minimal speech development, and a distinctive facial appearance (high prominent forehead, ocular hypertelorism, sparse anterior scalp hair, prominent lower lip, large ears with thick protruding lobules, cupid-bow shaped upper lip, and a long philtrum) [Pallister et al., 1977; Teschler-Nicola and Killian, 1981; Reynolds et al., 1987; Bergoffen et al., 1993]. A chromosome 12 abnormality (tetrasomy 12p) has been reported in skin biopsies from these patients but this chromosome anomaly is usually not found (or in only a small proportion, e.g., <0.5%, of blood cells) in peripheral blood [Raffel et al., 1986; Warburton et al., 1987; Larramendy et al., 1993; Ohashi et al., 1993].

We report on an additional patient with Pallister-Killian syndrome confirmed with fluorescence in situ hybridization (FISH) using an alpha satellite DNA probe for chromosome 12. This report further illustrates the application of FISH in identifying the source of chromosomal markers of unknown origin in infants with multiple congenital anomalies specifically before the natural history of a condition allows for definitive diagnosis based on clinical findings.

CLINICAL REPORT

B.R. was born at term to a 30-year-old G4P2 black woman by C-section due to cephalopelvic disproportion. Apgar scores were 2 at one minute and 8 at 5 minutes. The pregnancy was complicated by cocaine use. At birth she weighed 3,575 g (75th centile). Multiple congenital anomalies, hypotonia, and cyanosis were noted at birth. She was subsequently placed on 30% oxygen and had an oxygen saturation of 95%. The family history was unremarkable. At birth the white blood cell count was 38,200/mm³ with increased immature

forms and thrombocytosis (platelet count was 658,000/mm³). The hemoglobin was 19 gm%, hematocrit was 59, and the direct Coomb's test was negative. Electrolyte and glucose levels were normal. An echocardiogram showed mitral and tricuspid regurgitation and a small ventricular septal defect. She had good air exchange but the respiratory rate was 80 to 100/min. Chest radiograph showed an enlarged heart suggestive of congestive heart failure and she was treated with diuretics. She had a grade II/VI systolic heart murmur heard best over the left sternal border and her liver was palpated 2–3 cm below the right costal margin. By the 6th day of life, the respiratory rate had improved and evidence for congestive heart failure had decreased. Because of multiple congenital anomalies, facial appearance “reminiscent of Down syndrome,” and an apparent leukemoid reaction sometimes seen in patients with Down syndrome, this diagnosis was considered the most likely explanation before clinical genetics evaluation. At one day of age, chromosome studies showed a 47,XX,+mar karyotype from unstimulated peripheral blood cultures. At 11 days of age, unstimulated blood cultures showed a 46,XX/47,XX,+mar (50% of cells) karyotype while both phytohemagglutinin and pokeweed-stimulated blood cultures showed only 46,XX cells. Parental chromosomes were normal. A skin biopsy obtained at age 16 days showed 46, XX (in 15 cells)/47,XX,+mar (in 12 cells). Mosaicism was also seen at the 4th, 8th, and 16th cell passages. The extra chromosome was also negative with AgNOR staining. Because the extra chromosome marker also resembled an isochromosome 12p and the clinical findings of the infant were suggestive of the Pallister-Killian syndrome, an alpha satellite DNA probe was studied for chromosome 12 following manufacturer's guidelines (Oncor, Gaithersburg, MD). FISH showed the origin of the marker chromosome to be from chromosome 12 and further supported tetrasomy 12p in this infant (Fig. 1). She was discharged on the 16th day of life, and was eating well on formula with iron and weighed 3,277 g (50th centile). The mother was instructed on feeding and infant care. The infant was stable on Lanoxin with a heart rate of 120 and had no signs of congestive heart failure. The respiratory rate was 40 per min. Her white blood count was 15,300/mm³, hemoglobin was 15, and hematocrit was 46.

At age 10 months the patient was evaluated for hydrocephaly because of a large appearing head. A magnetic resonance image (MRI) was performed and showed hydrocephaly but no evidence of masses or structural problems. There was no history of seizures. However, there was a history of feeding difficulties at this time and developmental delay. At age one year she could roll from side to side but did not reach for objects, hold her bottle, sit alone, or smile. She did show head rocking and relatives reported that she slept most of the time.

On physical examination, she was an alert but delayed 12-month-old black girl with abnormal facial appearance and in no acute distress. Her length was 71.8 cm (20th centile), weight 9.6 kg (50th centile), head circumference 47.4 cm (90th centile), ear length 5.2 cm (80th centile), inner canthal distance 3.3 cm (>97th centile), outer canthal distance 7.6 cm (75th centile), hand length 7.5 cm (<3rd centile), and middle finger length 2.8 cm (<3rd centile). Prominent findings (Fig. 2) were: high, prominent forehead with sparse hair anteriorly and sparse eyebrows, upslanting palpebral fissures, delayed dental eruption, ptosis, strabismus, large-appearing ears with prominent lobules, flat nasal bridge with short nose and anteverted nares, coarse-appearing face with long philtrum and cupid bow-shaped mouth, protruding lower lip, prominent appearing jaw, relatively short neck, brachydactyly with bilateral simian creases and mild 5th finger clinodactyly, preaxial polydactyly of left

foot, distal digital hypoplasia including hypoplastic nails, systolic heart murmur (grade II/VI), hydrocephaly, excessive sweating, overlapping of digits, increased pigmentary area on lower back (3 × 4 cm size), and a sacral dimple.

In summary, the patient does show the classical findings of the Pallister-Killian syndrome and the extra chromosome was identified as an isochromosome 12p using FISH. She also demonstrated a leukemoid reaction and the isochromosome 12p in unstimulated blood cultures during the neonatal period. Interestingly, the initial chromosome findings were suggestive of mosaic tetrasomy 21. This cytogenetic interpretation has been previously reported in similar clinical situations (i.e., mosaic tetrasomy 21 is mosaic tetrasomy 12p in some cases [Hall, 1985]). In addition, this infant presented with preaxial polydactyly of the left foot, a ventricular septal defect, hydrocephaly, and a leukemoid reaction which are unusual manifestations in this syndrome. Unlike other patients reported with this syndrome [Reynolds et al., 1987] she did not have cataracts, supernumerary nipples, or severe limb abnormalities although she had preaxial polydactyly of the left foot and distal digital hypoplasia. Hence, this case of a rare cytogenetic syndrome further illustrates the use of FISH in the identification of de novo chromosome abnormalities of unknown origin particularly during early infancy.

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Fig. 1. Photograph showing a GTG banded chromosome number 12 pair and the isochromosome 12p (on the left) and FISH with the alpha satellite chromosome 12 probe showing the chromosome 12 pair and the isochromosome 12p (on the right).

Fig. 2. Frontal (A, C), profile (B), and photographs of the feet (D) from the infant at 12 months of age showing a high, prominent forehead with sparse hair anteriorly, upslanting palpebral fissures, hypertelorism, ptosis, strabismus, large-appearing ears with prominent lobules, a flat nasal bridge with a short nose and anteverted nares, a long philtrum and protruding lower lip, preaxial polydactyly of the left foot, and distal digital hypoplasia.