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A child with 45,X/46,X,del(Y)(q12) identified with a Y-specific probe

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We report a 4-month-old girl with normal length and weight, cleft lip and palate, congenital heart disease, and normal female genitalia. Chromosome studies indicated a mosaic 45,X/46,X, + frag pattern. Parental chromosomes were normal. Several chromosome banding procedures and, ultimately, deoxyribonucleic acid (DNA) studies were performed to identify the centric chromosome fragment.

Case Report

This girl was born at 36 weeks' gestation to a 20-year-old primagravida whose pregnancy was complicated by urinary tract infections. The mother did not smoke or consume alcohol during the pregnancy. Labor was prolonged, with the first stage 20 hours in duration. The Apgar scores were 7 at 1 minute and 8 at 5 minutes. Birth weight, length, and occipitofrontal circumference (OFC) were 2.6 kg (25th percentile), 49 cm (60th percentile), and 33 cm (20th percentile), respectively. At birth, multiple anomalies were noted, including left cleft lip and palate, prominent me-topic suture, prominent ears, heart murmur, decreased femoral pulses, and normal female genitalia without clitoral enlargement. No gonads were palpable in the labial folds or inguinal canals. The rest of the physical examination was normal. Radiographs, echocardiograms, and cardiac catheterization indicated a coarctation of the aorta, patent ductus arteriosus (PDA), and ventricular septal defect. The child underwent repair of her coarctation, with ligation of the PDA, during the neonatal period, without complications. The family history was negative for consanguinity or similarly affected relatives.

Leukocytes were cultured for chromosome studies. The patient was found to be mosaic, with 60% of the 85 cells analyzed having a 45,X chromosome complement and 40% 46,X, + frag. The chromosome studies were repeated at 4 months of age, and a similar percentage of mosaicism was noted. G —, Q —, C —, AgNOR, and G — 11 banding procedures were

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used for the identification of the origin of the centric fragment, but the studies were not definitive (Fig. 1). The centric fragment was smaller than a Y chromosome and did not fluoresce. Parental chromosomes, including the father's fluorescent Y chromosome, were normal.

Because of the possibility that the marker was a Y chromosome, blood was obtained from the proband and parents for DNA studies. With the use of standard methods, DNA restriction patterns from the father, mother, and proband were studied following digestion with *Eco* RI, blotting, and hybridization to the radiolabeled 3.3 kb insert from clone 4B-2, which is specific for the proximal long arm of the Y chromosome.^{1, 2} Patterns of 3.3 and 2.3 and 1.8 kb hybridizing fragments were seen after digestion of the father's and proband's DNA with *Eco* RI and *Hind* III, respectively (Fig. 2). The DNA studies confirmed the presence of proximal Yq-specific sequences, indicating that the proband's actual karyotype was 45,X/46,X,del(Y)(q12).

Because of possible gonadal dysgenesis, with its increased risk for malignancy,³ ultrasound studies were done to locate the position and to determine the size of the gonads and uterus. The results indicated no identifiable gonads, consistent with rudimentary streak gonads, and a normal-for-age-sized uterus. The child died at 6 months of age from cardiac complications. An autopsy was not performed.

Discussion

This patient had multiple congenital anomalies, including cleft lip and palate, prominent ears, congenital heart defects, and unidentifiable gonads and died at 6 months of age. The patient's coarctation of the aorta, prominent ears, and gonads unidentifiable by ultrasound are consistent with the diagnosis of Turner's syndrome, but no short stature, lymphedema, or neck webbing was noted. Although Turner's syndrome patients may not have short stature at this early age, cleft lip and palate are not reported features of this syndrome.

The confirmed cytogenetic findings, normal female genitalia, and absence of masculinization suggest that the intraabdominal structures are bilateral rudimentary streak gonads.⁴ A mosaic 45,X/46,X,del(Y)(q12) karyotype was observed in 60% and 40% of the cells, respectively. Because the origin of the centric fragment could not be identified with certainty with the use of G —, Q —, C —, AgNOR, and G — 11 banding techniques, restriction patterns of DNA from the father, mother, and proband were determined with hybridization with a Y chromosome-specific probe (4B-2). Clone 4B-2 was isolated from a rodent × human cell line in which the only cytologically identifiable human chromosome was the Y. This clone contains single copy sequences from the human Y chromosome that has been mapped to the region between band Yq11 to the centromere through the use of DNA from individuals with Y chromosome deletions or translocations.

Apparently, the two events that led to the proband's 45,X/46,X,del(Y)(q12) karyotype were: (1) a de novo Y chromosome deletion, because father's Y chromosome was normal; and (2) mosaicism due to nondisjunction after fertilization. We anticipate that the recurrence risk in

future pregnancies would be low, but a slight possibility of mosaicism of the Y chromosome deletion exists in the father's gonadal tissue.

In general, all 45,X/46,XY subjects reared as girls should have prophylactic gonadectomy.³ The rudimentary streak gonads with or without ipsilateral testis that are present in these individuals are repositories for tumor formation, and the testis may further masculinize the patient at puberty. The potential endocrine and exocrine function of the testis may be determined by measuring serum follicle-stimulating hormone. An elevated hormone level for age would indicate testicular failure, and nothing would be gained by retaining the functionless gonad. The only real therapeutic dilemma is the person who maintains normal-forage serum follicle-stimulating and luteinizing hormone levels. Perhaps there is a place for testicular preservation under these circumstances. If the latter is elected, then annual determinations of beta subunit human chorionic gonadotropic hormone and alpha feto protein should be performed as biochemical markers for tumor formation. Periodic testicular sampling for tumor surveillance by random biopsy study in such individuals is often impractical.

Y-specific DNA probes will be valuable in detecting Y DNA in putative 45,X subjects and in clarifying the nature of a chromosome fragment suspected to be a structurally abnormal Y chromosome. This case demonstrates the utility of precise identification of the Y chromosome using specific chromosome DNA probes in patients with chromosome markers of unknown origin.

We have reported a child with cleft lip and palate, coarctation of the aorta, patent ductus arteriosus, ventricular septal defect, prominent ears, and normal female genitalia with a mosaic 45,X/46,X,del(Y)(q12) karyotype. The chromosome fragment was identified as a Y with the use of DNA studies with clone 4B-2, which is specific for the proximal long arm of the Y chromosome (Yq subcentromeric to Yq12).

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References

1. George DL, Phillips JA III, Franke U, Seeburg PH. The genes for growth hormone and chorionic somatomammotropin are on the long arm of human chromosome 17 in region q21 qter. *Hum Genet.* 1981; 57:138. [PubMed: 6262212]
2. Burk RD, Patrick MA, Smith KD. Characterization and evolution of a single-copy sequence from the human Y chromosome. *Mol Cell Bio.* 1985; 5:576. [PubMed: 3990685]
3. Muller J, Skakkebaek NE, Ritzen M, Ploen L, Pettersen KE. Carcinoma in situ of the testis in children with 45, X/46, XY gonadal dysgenesis. *J Pediatr.* 1985; 106:431. [PubMed: 3973780]
4. Gantt PA, Byrd JR, Greenblatt RB, McDonough PG. A clinical and cytogenetic study of fifteen patients with 45,X/46,XY gonadal dysgenesis. *Fertil Steril.* 1979; 34:216.

Figure 1. Selection of Y chromosomes from the proband and father stained with the GTG procedure to show G-bands (a); the QFA procedure to show Q-bands (b); the CBG procedure to show C-bands (c) and G-11 procedure (d).

Figure 2.

Autoradiogram patterns of DNA from the father, mother proband, and female control following digestion with either *Eco* RI and *Hind* III and hybridization to the radiolabeled 3.3-kb insert from clone 4B-2, which is specific for the proximal long arm of Y chromosome. The relative amounts of Y-specific sequences homologous to clone 4B-2 in the proband's DNA (3.3-, 2.3-, and 1.8-kb [kilobase] fragments) appeared to be about one-half of the father's, in agreement with the degree of mosaicism observed in the proband's cytogenetic studies.