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Identification of Complex Chromosome 18 Rearrangements by FISH and Array CGH in Two Patients With Apparent Isochromosome 18q

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TO THE EDITOR:

Most cases of Edwards syndrome result from an extra copy of chromosome 18 (Trisomy 18) [Edwards et al., 1960], however, a small fraction of individuals have unbalanced translocations or isochromosome 18q (i(18q)) [Bass et al., 1979; Froster-Iskenius et al., 1984], reviewed in Bugge et al. [2004]. The observation of i(18q) generally indicates a deletion of the entire short arm of chromosome 18 and a gain of the entire long arm; however, we have identified two unique cases in which cytogenetically apparent isochromosomes 18q were in fact complex rearrangements involving portions of both 18p and 18q. In one case, chromosome studies were initially performed in the newborn period, and low resolution banding failed to identify the complex nature of the rearrangement. In the second case, array CGH initially identified the complex rearrangement, however, follow up chromosome studies revealed an isochromosome-like appearance of the derivative 18. Thus, the results presented here demonstrate that patients with isochromosomes identified by conventional chromosome analysis could benefit from more detailed molecular cytogenetic studies such as FISH and array CGH.

The first patient was delivered at 33.5 weeks gestation by cesarean section for abnormalities in fetal heart monitoring. A routine fetal ultrasound revealed an enlarged right atrium, and a fetal echocardiogram revealed a mobile mass in the left ventricular outlet. Birth weight was 1,353 g and head circumference was 23 cm, both well below the 5th percentile for gestational age. Features included prominent occiput with a large posterior fontanelle, posteriorly rotated ears, clenched hands, hypoplasia of the nails, a short sternum, and mild rocker-bottom feet. An echocardiogram revealed multiple abnormalities, including a large patent ductus arteriosus, a large muscular ventricular septal defect, and aneurismal redundant tricuspid valve tissue. G-tube/Nissen fundoplication, bilateral inguinal hernia repair, and tracheostomy placement were performed at 4½ months of age. At 4 years of age, the child was nonverbal and could sit but not crawl or walk. He weighed 13.1 kg and received a mixture of G-tube feeds and oral feeds. He no longer required mechanical ventilation; however, he had a tracheostomy in place and required oxygen at night.

The initial low-resolution GTG-banded chromosome analysis performed in the newborn period identified an abnormal male karyotype with one normal chromosome 18 and one

apparent isochromosome 18q, consistent with the clinical diagnosis of Edwards syndrome (Fig. 1a). Follow-up high-resolution studies of the maternal chromosomes were performed which identified a pericentric inversion of one chromosome 18 between bands 18p11.31 and 18q12.2 (Fig. 1b). Given this result, a repeat high-resolution chromosome analysis combined with FISH studies was performed on Patient 1, which revealed that the child had in fact one normal chromosome 18 and one complex chromosome 18 made up of one q arm and one arm consisting of the proximal portion of 18p from 18p11.31 to the centromere and the distal portion of 18q from 18q12.2 to qter (Fig. 1c,e). Based on this data, the karyotype was redefined as 46,XY,rec(18)dup(18q)inv(18)(p11.31q12.2). Following a genetics consultation, it was noted that the mother had 5 previous pregnancies, 4 of which resulted in spontaneous abortions and 1 that produced a child with dextrocardia and congenital diaphragmatic hernia who died in the first 24 hr of life. Karyotype analysis on that child revealed an abnormal chromosome 18, reported as 46,XY,i(18)(q10) by an outside lab. A third child (sibling 2) has since been born following an abnormal prenatal chromosome analysis which revealed the same recombinant chromosome 18 as the proband (Fig. 1d).

The second patient was born prematurely at 34 weeks gestation to a G1P0→1 mother via cesarean. Birth weight was 1,490 g (10th centile) and head circumference was 29.5 cm (10th–25th centile). Clinical features included a triangular facies, prominence of the forehead, intact high-arched palate, malformed ears with incomplete folding of bilateral helices, abnormal tragus and a cup-shaped right pinna. She had a III/VI harsh holosystolic cardiac murmur, patent foramen ovale, atrial septal defect and a large subaortic ventriculoseptal defect. The digits were without the typical overlapping seen in complete Trisomy 18 patients. A weak suck was noted, and swallow studies demonstrated moderate-to-severe dysphagia with nasopharyngeal aspiration. The perinatal course was complicated by prematurity, intrauterine growth retardation, respiratory distress, periodic breathing, hyperbilirubinemia, metabolic acidosis, hyponatremia, hypokalemia, and feeding intolerance. At 3 months of age, the child passed away due to complications related to congestive heart failure.

Array-based comparative genomic hybridization (array CGH) analysis was performed at 40 days of age and revealed a gain in copy number in the subtelomeric region of the short arm of chromosome 18 at band 18p11.32 to 18p11.31 (Fig. 2a,b). The duplication spanned a minimum of 4.7 Mb and a maximum of 4.8 Mb and was confirmed by FISH analysis. Additionally, there was a gain in copy number in the long arm of chromosome 18 at band 18q12.3 to 18q23, encompassing a segment of 38.7 Mb in size. GTG-banded chromosome analysis was subsequently performed to further characterize the chromosomal rearrangements. This analysis revealed the presence of one normal chromosome 18 and one apparent isochromosome 18q which, based on array CGH data, was in fact a derivative chromosome 18 consists of a duplication of band 18p11.32 to 18p11.31 and a duplication of band 18q12.3 to 18q23. FISH studies using probes specific to the regions 18p11.31, 18q12.3, 18q23, and 18cen confirmed the inverted nature of the dup (18p) and the dup (18q) (Fig. 3b–d). Based on this data, the infant's karyotype was designated according to ISCN 2009 and the hg18 build of the human genome as 46,XX,der-(18)dup(18)(p11.32p11.31)dup(18)(q12.3q23).nuc ish 18p11.31(RP11-838N2×3).arr 18p11.32p11.31(121700–4832613)×3, 18q12.3q23(37401561–76103255)×3. Paternal partial chromosome analysis showed no evidence of a rearrangement involving chromosome 18; however, the maternal sample was not available for analysis.

In summary, the cases presented here demonstrate the extent to which molecular studies can further elucidate chromosomal abnormalities that are detected by karyotype. In the first case, molecular studies allowed for the identification of a recombinant chromosome 18 found in both the proband (Patient 1) and his sibling, resulting from a maternal inversion (Fig. 1).

This is consistent with previously reported chromosome 18 rearrangements in individuals born to normal parents, one of whom carries a pericentric inversion of chromosome 18 [Vianna-Morgante et al., 1976]. In the second case (Patient 2), array CGH identified multiple duplications of chromosome 18 material, and FISH studies revealed the nature of the complex rearrangement (Figs. 2 and 3). It is important to note that, cytogenetically, both patients had an apparent i(18q). Low-resolution GTG-banded chromosome analysis, which is common for newborn blood specimens or prenatal specimens, could easily have failed to detect these complex rearrangements. Given their cryptic nature, it is easy to predict that similar rearrangements may be more common in “apparent” isochromosomes than previously appreciated. For this reason, cases of i(18q) and other isochromosomes should be interpreted with caution, especially in the case of prenatal chromosome analysis when band resolution is low. Detailed molecular studies such as array CGH and FISH analysis may provide valuable information about the composition of an apparent isochromosome and should be used whenever possible.

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REFERENCES

- Bass HN, Sparkes RS, Miller AA. Features of trisomy 18 and 18p-syndromes in an infant with 45,XY,i(18q). *Clin Genet.* 1979; 16:163–168. [PubMed: 487637]
- Bugge M, Brandt CA, Petersen MB. DNA studies of mono- and pseudodicentric isochromosomes 18q. *Am J Med Genet Part A.* 2004; 127A:230–233. [PubMed: 15150771]
- Edwards JH, Harnden DG, Cameron AH, Crosse VM, Wolff OH. A new trisomic syndrome. *Lancet.* 1960; 1:787–790. [PubMed: 13819419]
- Froster-Iskenius U, Coerdts W, Rehder H, Schwinger E. Isochromosome 18q with karyotype 46,XX,i(18q). *Cytogenetics and pathology.* *Clin Genet.* 1984; 26:549–554. [PubMed: 6499266]
- Vianna-Morgante AM, Nozaki MJ, Ortega CC, Coates V, Yamamura Y. Partial monosomy and partial trisomy 18 in two offspring of carrier of pericentric inversion of chromosome 18. *J Med Genet.* 1976; 13:366–370. [PubMed: 1003448]

FIG. 1.

Partial karyotypes and ideograms of the three family members included in Case 1. Red and green highlighted areas on the ideograms correspond to FISH probes in (e). a: Initial low-resolution chromosomes 18 from Patient 1. b: Maternal chromosomes 18 showing a pericentric inversion of one chromosome 18 at bands 18p11.31 and 18q12.2. Red arrows point to proposed inversion breakpoints. c: Patient 1 and his sibling (d) each have one normal chromosome 18 and one complex chromosome 18 made up of one q arm and one arm consisting of the proximal portion of 18p from 18p11.31 to the centromere and the distal portion of 18q from 18q12.2 to qter. e: FISH analysis for patient 1 using probes RP11-193E15 (18p11.31, red, coordinate 2.9–3.1 Mb), RP11-540M4 (18q11.2, green,

coordinate 21.3–21.5 Mb), and D18Z1 (cen18, aqua). The normal chromosome 18 is shown in the inset

FIG. 2.

Array CGH analysis of Patient 2. a: Whole genome plot (left) depicting gain in copy number at 18p11.32-p11.31 and 18q12.3-q23. The enlarged segment of both 18p11.32-p11.31 (~5 Mb) and 18q12.3-q23 (38.7 Mb) is shown on the right. Each point represents a 60mer oligonucleotide clone on the array. The gain on 11q25 (0.2–0.7 Mb, arrowhead) is a known CNV. b: Chromosome 18 ideogram showing regions of duplication in green.

FIG. 3.

Cytogenetic and FISH analyses of Patient 2. a: Partial karyotype showing the normal chromosome 18 and the derivative 18 (arrows). b: Interphase FISH using probes RP11-183C12 (18p11.31, green, 4.4–4.6 Mb) and RP11-838N2 (18p11.31, red, 3.3–3.5 Mb) shows the adjacent duplicated regions of 18p11.31. c,d: Metaphase FISH analysis using probes RP11-183C12 (green) and RP11-687E1 (18q12.3, red, 37.8–37.9 Mb) show the junction of band 18p11.32 with band 18q12.3 on the duplicated long arm. The centromere is detected with a D18Z1 centromere probe (aqua) in (c). The subtelomere region 18q23 (RP11-90L3, 73.4–73.6 Mb) is detected in orange in (d).