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Research Letter

Prenatal diagnosis of *de novo* monosomy 7q33-qter associated with hydrops fetalis, semilobar holoprosencephaly, and premaxillary dysgenesis

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A 30-year-old nulligravida woman was referred to Taipei Veteran General Hospital for genetic amniocentesis at 21 weeks of gestation due to multiple abnormalities detected in routine prenatal ultrasound since 20 weeks of gestation. The woman and her 30-year-old husband were healthy, and there was no family history of congenital malformations. Down syndrome risk was less than 1/3000 at her 18-week gestation.

A detailed high-resolution ultrasound examination revealed semilobar holoprosencephaly, premaxillary dysgensis (bilateral cleft lip/cleft palate), massive left pleural effusion, and ascites (Fig. 1A–D). Routine cytogenetics with GTG-banding (G-banding obtained by trypsin and Giemsa) documented the presence of a 46,XX,del(7)(pter → q32:) *dn* (Fig. 2A) in all the 20 metaphases examined (from 13 colonies) because both parents' chromosome examinations revealed normal findings. The other parameters of the fetus were as follows: estimated body weight, 576 g (>97th percentile); biparietal diameter, 45.5 mm (<2nd percentile); femoral length, 35.3 mm (20th percentile), and abdominal circumference, 211 mm^2 (>98th percentile). After genetic counseling with parents, termination of pregnancy was performed at 22 weeks of gestation and a 510-g fetus with bilateral cleft lip and palate, hydrops fetalis, flat/broad nasal bridge, and upslanting palpebral fissures was delivered (Fig. 3A–C). Further investigation of abnormality was suggested; oral informed consent was obtained from the parents, but they refused autopsy. The tissue from the fetal skin was sent for further molecular studies in order to determine the breakpoints. Genome-wide oligonucleotide-based array comparative genomic hybridization (array CGH) (SurePrint H3 Human CGH Microarray Kit 60k; Agilent Technologies, Santa Clara, CA, USA) demonstrated a 23.25-Mb deletion at 7q33 to qter (135353693–158602499) × 1 (Fig. 2B). Fluorescent in situ hybridization (FISH) studies on cultured fetal skin cells indicated the deletion of terminal long arm of chromosome 7 (Fig. 2C). The parental origin of the deletion on terminal 7q was analyzed with quantitative fluorescent polymerase chain reaction using the cultured fetal cell and the polymorphic small tandem repeat markers specific for chromosome 7q (Fig. 4). After studying with the microsatellite markers D7S1804, D7S3070, and D7S1823 at 7q32.3, 7q36.1, and 7q36.2, respectively, only D7S3070 and D7S1823 inherited from maternal allele were present. The breakpoint was close to 7q32.3, and the deletion was of paternal origin.

We have presented a case of prenatal diagnosis and molecular characterization of a *de novo* terminal deletion of 7q33-qter. To date, more than 35 cases of partial monosomy 7q32-qter have been reported; the syndrome of 7q was further delineated by Bernstein et al in 1980 [1], which usually arose *de novo*. The variable clinical manifestations of 7q terminal deletion syndrome include growth restriction, developmental

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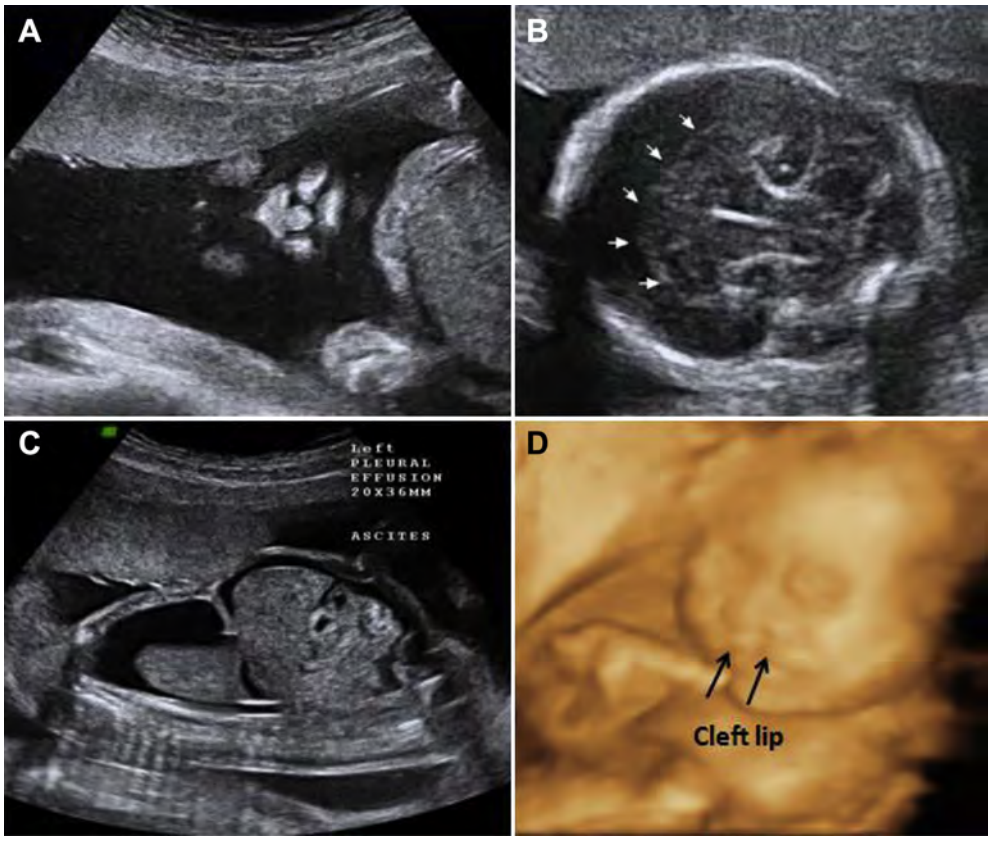

Fig. 1. Prenatal ultrasound: (A) Premaxillary dysgenesis: bilateral cleft lip; (B) semilobar holoprosencephaly; (C) hydrops fetalis: ascites and pleural effusion; and (D) fetal facial structure by three-dimensional ultrasound confirmation.

retardation, microcephaly, holoprosencephaly, bilateral cleft palate and/or lip, ocular abnormalities, abnormal palm/sore crease, caudal dysgenesis, dental abnormalities, and congenital heart defect [1–10]. The present case with hydrops fetalis, including ascites, pleural effusion, and pericardial effusion, is very rare. Finley et al [7] described a female fetus at 27 weeks of gestation that had intrauterine growth restriction, microcephaly, single semilunar valve, a ventricular septal defect (VSD), a large atrial septal defect, a single outflow tract and truncus arteriosus, and ascites, but no pericardial or pleural effusion. The cytogenetic result yielded a 46,XX,del(7q)(q32-qter). Fetal ascites had resolved by 32 weeks. After delivery, the small for gestational age (SGA) infant had symmetric growth restriction and complex heart defects with type III truncus arteriosus, VSD, atrial septal defect, a right aortic arch, and a persistent left superior vena cava entering the coronary artery. The infant had episodes of bradycardia and hypoxia, and died at the age of 8 weeks. Finley et al [7] suggested that fetal ascites were due to cardiac defect. Congenital heart defect has been reported in up to 20% of 7q deletion. Tiller et al [11] reported a preterm male infant with deletion of 7q34-qter that had hypoplasia of the main pulmonary artery, absent pulmonary valve, VSD, and anomalous right pulmonary artery, and Chen et al [12] reported a prenatal case with deletion of 7q35-qter that showed microcephaly and tetralogy of Fallot characterized by an overriding aorta, a small VSD, and a small pulmonary trunk. In the present case, no cardiac defect was detected in prenatal ultrasound that could have caused hydrops fetalis; however, cardiac defect could be assessed if autopsy was allowed by parents.

About 87% of patients with *de novo* terminal 7q deletions are associated with holoprosencephaly and 45% with caudal deficiency sequence [13–15]. The 7q terminal region is believed to contain genes that "play a critical role in differentiation of midline mesoderm at both ends of the developing notocord" [16]. Schwartz et al [9] reported a newborn infant with 46,XX,del(7)(pter → q32:) that had cebocephaly with holoprosencephaly. McMorrow et al [17] described a male infant with deletion of 7q32-qter having hydrocephalus with a prominent forehead, horizontal palpebral fissures; bilateral anophthalmos; elongated, narrow nose; a flat nasal bridge; agenesis of the nasal septum; a completely cleft palate; a small mouth; a wide nasal philtrum; low-set, deformed ears; a webbed neck; bilaterally undescended testes; and a left club foot. Chuang et al [18] reported two fetus with der (7)t(1;7)(q32;q32)pat inherited from the father with double translocations, 46,XY, t(1;7)(q32;q32), t(14,15) (q32.1;q26.3) that had alobar holoprosencephaly and cleft palate. Several genes involved in normal brain development were mapped in the region of 7q36, such as sonic hedgehog gene (*SHH*), or *HPE3* [19], *En2* [20,21], and *HTR5A* [22]. Haploinsufficiency of these genes in the present patient severely affected brain function and facial

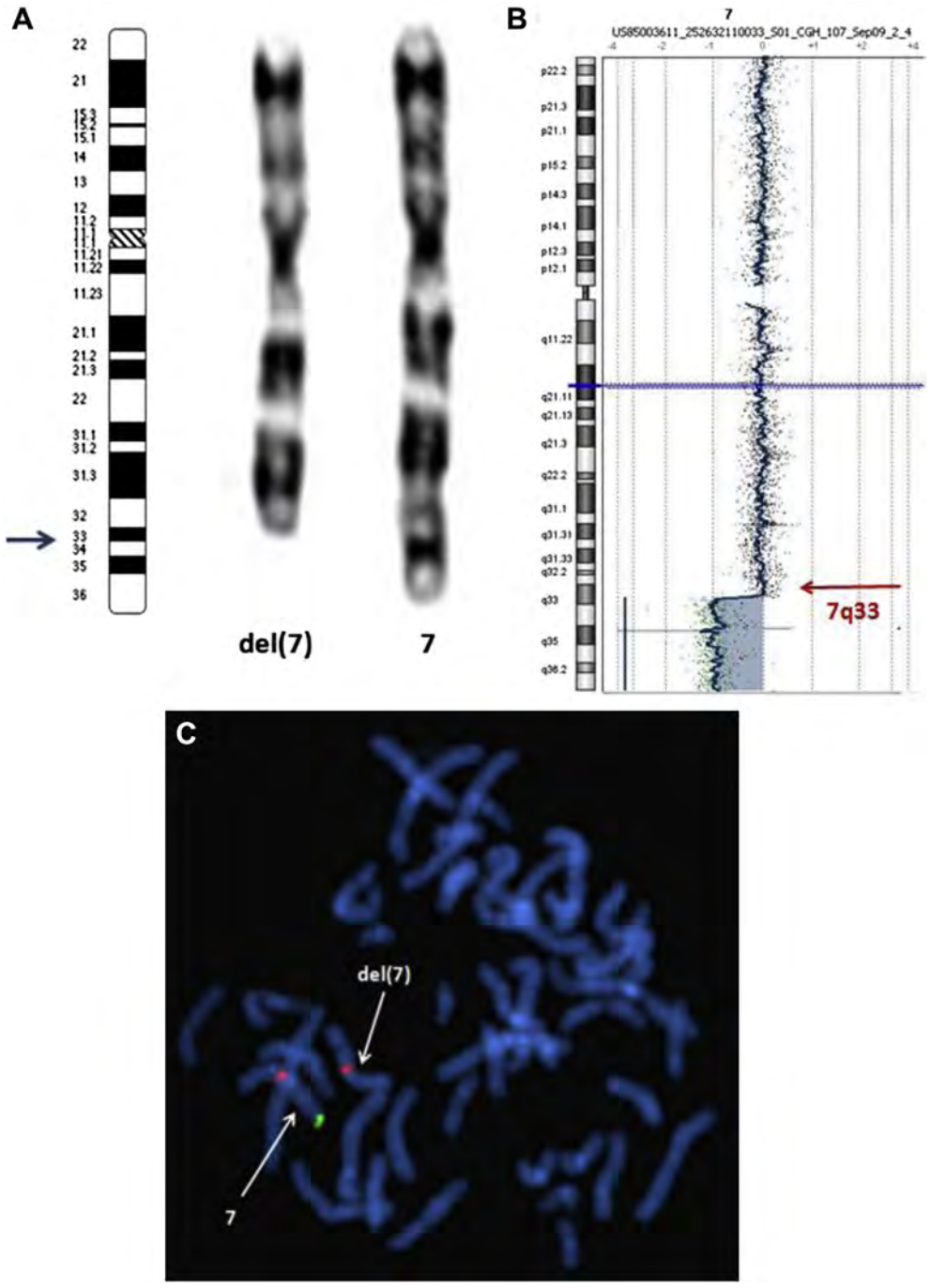

Fig. 2. (A) G-banded chromosome 7 and del(7q33). (B) Array CGH analysis with the Human CGH Microarray Kit 8 × 60 k array showed 23.25-Mb terminal deletion at 7q33(135353693–158602499) × 1, which was indicated by a red arrow. (C) FISH metaphase from amniotic fluid cells hybridized with a 7 centromere probe (PR11-41F22; red) and loss of signal of 7q telomere probe (RP11-477A19; green) on chromosome 7.

structure, as reported previously. The gene for caudal development, *HLXB9* [16,23], was also mapped in the deleted region, but perinatal investigations on sacral vertebrae did not reveal remarkable abnormalities. Haploinsufficiency of HLXB9 in our patient seems not to cause severe consequences of sacral development.

The breakpoint and the parental origin of the deletion on terminal 7q were analyzed with quantitative fluorescent polymerase chain reaction using the skin cells and the polymorphic small tandem repeat markers specific for chromosome 7q (Fig. 3). With the microsatellite marker D7S1804, two alleles inherited from the parents were seen in the proband, but with the markers D7S3070 and D7S1823, only one maternal allele was detected. The deletion was of paternal origin. Numerous studies of the parental origin of syndromes associated with cytogenetically detectable deletions have been published, including the 4p deletion associated with Wolf–Hirschhorn syndrome [24], deletion of 5p associated with the cri-du-chat syndrome [25], deletions of 18q [26], and terminal deletion associated with the 9p deletion

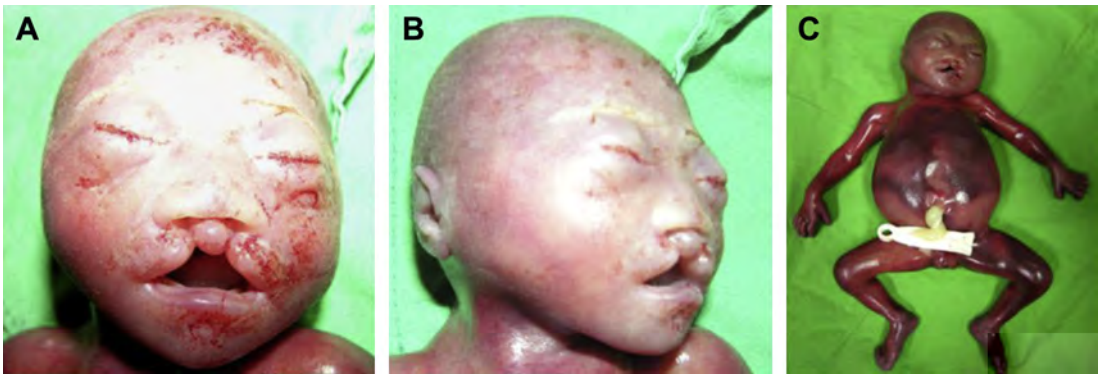

Fig. 3. (A) Anterior view of the face: bilateral cleft lip; (B) lateral view of the face; and (C) whole-body view: hydrops fetalis.

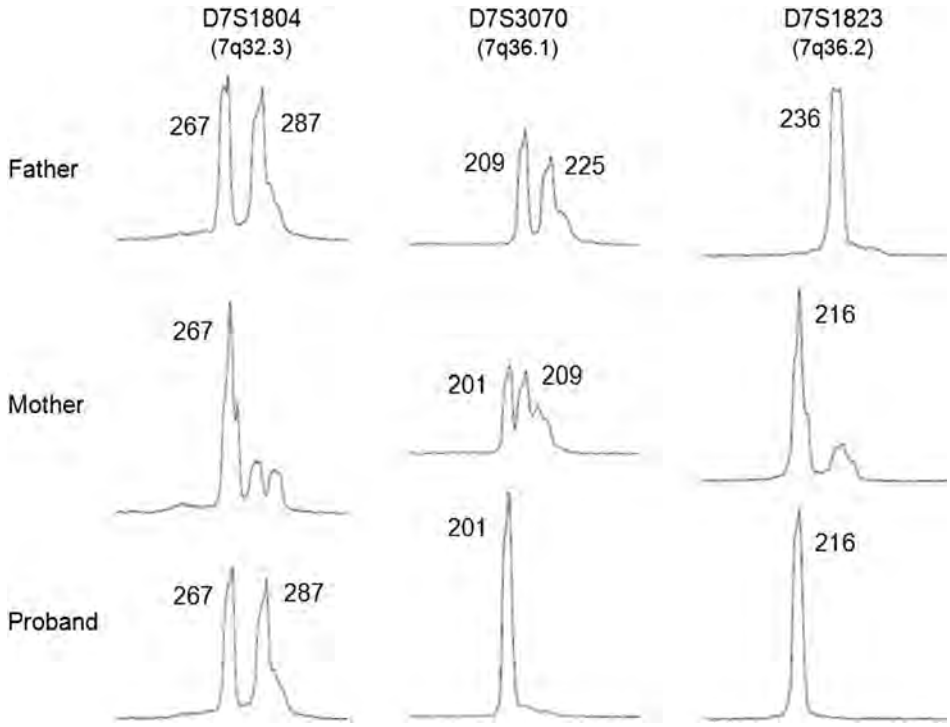

Fig. 4. According to the electropherograms on amplified PCR products using chromosome 7 specific STRs and genomic DNAs, the proband lost paternal markers at 7q36.1 and 7q36.2, which indicated the terminal deletion was inherited from paternal side. PCR = polymerase chain reaction; STR = small tandem repeat.

syndrome [27]. All have been shown to be paternal in origin in the majority of patients studied. Thomas et al [28] summarized parental origin and, wherever possible, the chromosomal origin of 115 *de novo* unbalanced structural chromosome abnormalities detectable by light microscopy. Simple terminal deletions were approximately 70% paternal and 30% maternal in origin in the 39 cases with terminal deletion studied. For chromosome 7q, two cases were reported: Case 112 with del(7)(q36.1) was of paternal origin and Case 115 with del(7)(q36.2) was of maternal origin. Chen et al [12] reported del(7)(q35) in a female fetus, which was of maternal origin. The terminal deletion of chromosome 7q does not appear to be derived from paternal origin predominantly.

In summary, a great variety of phenotypes can be detected in terminal 7q deletion syndrome. The present case provided evidence that monosomy of 7q33-qter is associated with hydrops fetalis, and congenital cardiac defect should be examined carefully.

Acknowledgments

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