Maternal origin and clinical findings in a case with trisomy 22

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We report a newborn girl with multiple congenital anomalies whose chromosomal analysis showed complete trisomy 22. Her phenotype included microcephaly, epicanthus, hypertelorism, micrognathia, cleft palate, microtia, and preauricular tag. She died in the 24th post-natal hour. Trisomy 22 was shown by fluorescence in situ hybridization technique and the parental origin of the extra chromosome was found to be maternal by DNA microsatellite marker analysis of chromosome 22. Postmortem examination revealed the presence of atrioseptal defect and stasis in the biliary canals. We believe that this patient will contribute to the literature both by clinical findings and short life span associated with maternal origin of extra chromosome 22.

Key words: trisomy 22, atrioseptal defect (ASD), fluorescence in situ hybridization (FISH), cleft palate, newborn infant, maternal origin.

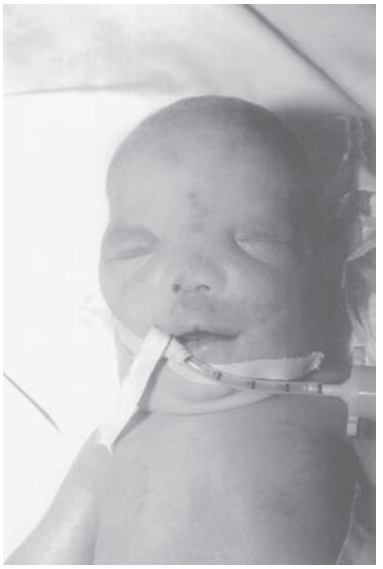
Trisomy 22, which can be seen either in mosaic or non-mosaic form, is a rare chromosome anomaly in live born infants[1-4]. Non-mosaic trisomy is a frequent finding and is the second most common trisomy determined in spontaneous abortions, comprising 10% of the cases. However, survival beyond the first trimester of gestation appears to be rare[5-7] and survival to term may occur in very exceptional cases, with severe malformations and short life span.

"Trisomy 22 phenotype", consisting of mental and growth retardation, microcephaly, preauricular pits and tags, apparently low-set or malformed ears, micrognathia, cleft palate, cardiac and renal malformations, long slender fingers, proximally placed or finger-like thumbs, and hypoplasia of the male genitalia, was first described by Hsu et al. in 1971[2].

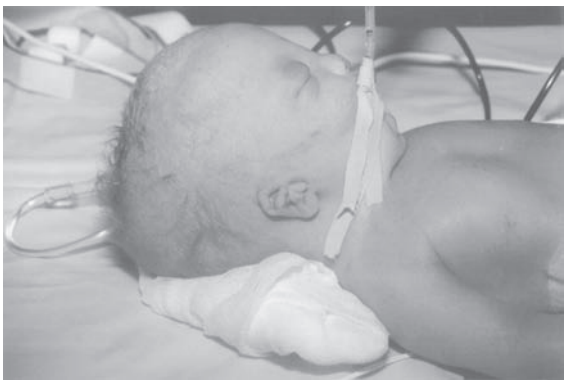
In this report, we describe a new case of trisomy 22, shown by chromosome painting probes, and the parental origin of the extra chromosome in a malformed newborn female who died on her second day of life.

Case Report

A two-day-old girl was born at 35 weeks of gestation to a G2P1 mother after an uncomplicated pregnancy. The mother was 37 and the father was 31 years of age at the time of birth. Her previous gestation has ended in abortion for unknown reasons. The baby's weight was 1,440 g (<3rd percentile), length 37 cm (<3rd percentile), and head circumference 28 cm (<3rd percentile). In her physical examination, her nasal bridge was high and large with bilateral epicanthal folds and apparent lateral displacement of the orbits. The supraorbital ridges were hypoplastic and the orbits were shallow, giving relative prominence to the globes. There were also micrognathia, cleft palate, small and apparently low-set malformed ears, bilateral preauricular depression, and atresia of the left external auditory canal. The right ear had preauricular tags (Fig. 1a, b, c, d). She had limb anomalies including polydactyly between the first and second phalanges on the right hand and bilateral transverse palmar creases. A midline sacral



(a)



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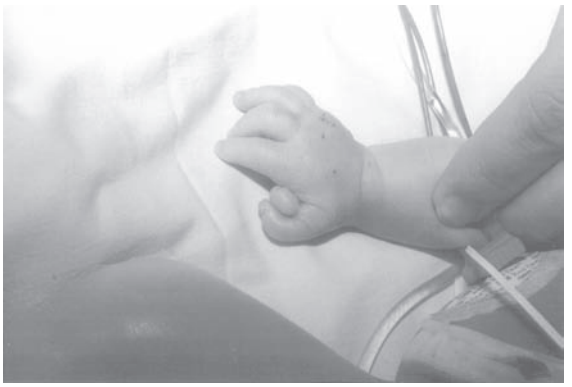

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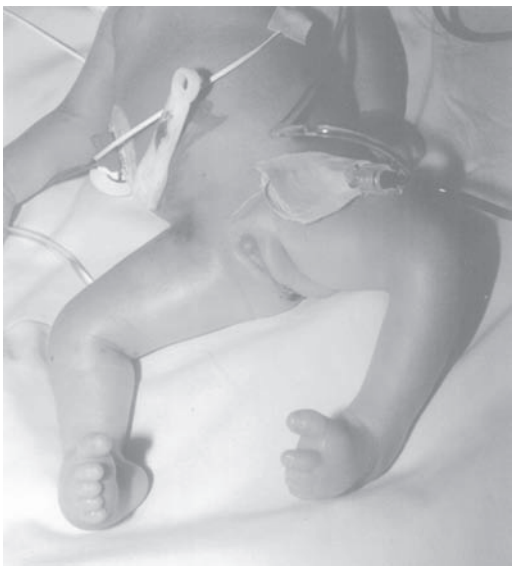

(d)

Fig. 1.

a) Facial profile of the case with the epicanthic fold, prominent eyes, and flat nasal bridge.
b) Lateral view of the face showing the short nose, prominent eyes, low-set ears and preauricular tags with short neck.
c) Limb anomaly showing polydactyly between the first and second phalanges on the right hand of the case.
d) View showing bilateral pes equinovarus deformity and genitalia abnormalities (hypoplasia of the labia majors and clitoromegaly).

dimple was present. Hypoplasia of labia majors and clitoromegaly were present on genital exam. There was bilateral pes equinovarus deformity. Her renal ultrasound was normal. The patient had bradycardia and died in the 24th postnatal hour. Postmortem examination demonstrated the presence of atrioseptal defect (ASD) and minimal stasis in the biliary canals. Karyotyping and molecular analysis were undertaken in our newborn case.

Cytogenetic and Molecular Cytogenetic Analysis

Chromosomal analysis was performed with GTG banding technique according to standard

procedures. Cytogenetic analysis revealed a 47,XX,+ 22 (Fig. 2a). Fluorescence in situ hybridization (FISH) analysis was carried out on metaphase spreads using whole chromosome painting probe for chromosome 22 (Vysis Inc.) We also showed the trisomy 22 karyotype using FISH, as shown in Figure 2b.

Parental DNAs were studied to determine the origin of the extra chromosome 22. Genomic DNAs were isolated from blood samples of both parents and of the case by salting out method. Highly polymorphic (heterozygosity >0.7) and commercially available microsatellites were run on a 6% polyacrylamide gel and visualized by silver staining method (Table I). Results were interpreted by visually comparing the intensity of both alleles (Fig. 3). Two of 12 microsatellite markers showed that the origin of the extra chromosome 22 was maternal.

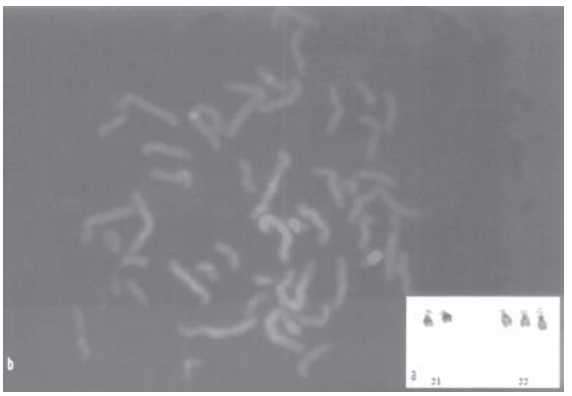

Fig. 2. a) Partial karyotype showing the extra chromosome 22 by GTG banding. b) A metaphase of the proband by FISH analysis using a chromosome 22 library as a painting probe.

Table I. Results of the Investigated Microsatellite Markers of Chromosome 22

Marker	PIC value	Location	Alleles of M/P/F
D22S420	0.77	22q11	aa/aa/aa
D22S258	0.78	22q11.2	ab/aa/ab
D22S270	0.78	22q13-qter	aa/aa/aa
D22S277	0.85	22q13.1	ab/ab/ab
D22S315	0.80	22q11.2-q12.1	aa/ab/ab
D22S1638			aa/aa/aa
D22S427	0.74	22q11	aa/aa/aa
D22S274	0.78	22q13.3	ab/bb/ab
D22S450	0.83	22q13-qter	not very clear
D22S299	0.79	22q12-qter	not very clear
D22S283*	0.88	22q	ac/abc/bd
D22S282*	0.84	22q13.2-13.3	ab/abd/cd

PIC: Polymorphism information content value. M: Mother. P: Proband. F: Father.

Markers in bold, underlined and in italics are informative for trisomy 22. Marker localizations are according to GDB and Genethon Linkage maps.

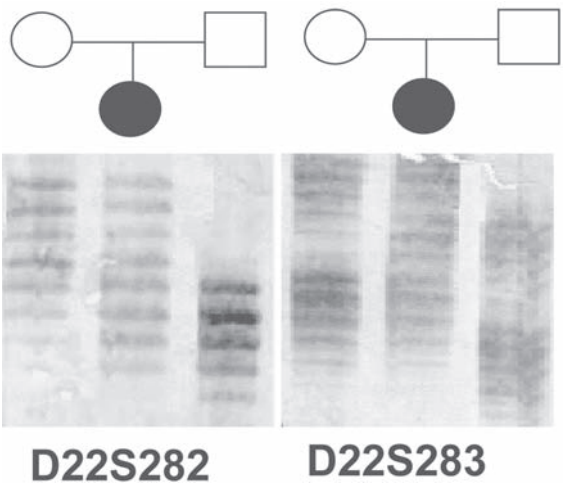

Fig. 3. DNA polymorphism analysis by polymerase chain reaction (PCR) amplification of microsatellite markers with D22S282, D22S283, showing maternal origin for the extra chromosome 22.

Discussion

The clinical phenotype of the trisomy 22 varies widely. The most common presenting features of trisomy 22 are ear anomalies, congenital heart disease, micrognathia, and cleft palate. In our case, all of these features were present (Table II). Although the frequency of trisomy 22 in spontaneous abortions (29/1000) is equivalent to that of trisomy 21 (26/1000), it is rarely found in liveborn infants (1/30,000-1/50,000 live births)[8].

A short postnatal life is characteristic of trisomy 22[9,10]. It is possible that the patient's parents' first child also had trisomy 22, because the mother said her first pregnancy had the same dysmorphological findings and anomalies as our patient. However, these abnormalities were not investigated by any pathological or genetic analysis at that time.

Trisomy 22 has some similar characteristic findings of other clinical genetic diseases. For example, in a previous study, trisomy 22 was reported in a patient with Goldenhar sequence[11]. Our patient had ear abnormalities, which are

Table II. Clinical Comparison of Present Case and Literature Cases

Clinical Features	Kobrynski et al. 1993[11]	Stratton et al. 1993[16]	Sundareshan et al. 1990[17]	Kukolich et al. 1989[18]	Slater et al. 1993[19]	Kim et al. 1992[20]	Feret et al. 1991[21]	McPherson and Setka 1990[22]	Isada et al. 1990[23]	Fahmi et al. 1994[10]	Our case
IUGR	+	+	+	+	+	+	+	+	+	+	+
Microcephaly	+	+	+	+	+	+	+	+	+	+	+
Hypertelorism	+	+	+	+	+	+	?	+	+	+	+
Epicanthal folds	+	+	+	+	?	+	?	+	+	+	+
Hypoplastic or low-set ears	+	+	+	+	?	+	+	+	+	+	+
Ear pits/tags	+	+	–	+	+	–	+	+	–	+	+
Midface hypoplasia	+	+	+	+	?	+	+	+	+	+	–
Cleft lip	–	+	+	–	–	–	+	+	+	+	–
Cleft palate	–	+	+	+	+	–	+	+	+	+	+
Webbed neck/redundant skin	+	+	+	–	+	+	+	+	?	+	–
Cardiac anomalies	–	+	?	+	+	–	+	+	+	?	+*
Renal anomalies	+	–	?	–	+	+	+	+	+		–
Hypoplastic distal phalanges	+	–	+	+	?	?	+	+	?		
Digitalized thumbs	+	+	+	–	?	?	?	–	+	?	+
Anal atresia/stenosis	–	–	–	–	+	–	+	+	–	?	–
Genitalia anomalies	n/a	n/a	n/a	+	n/a	+	n/a	+	–	+	+**

IUGR: Intrauterine growth retardation. *ASD: Atrioseptal defect. PDA: Patent ductus arteriosus. **Clitoromegaly, labia major hypoplasia.

most common in trisomy 22 phenotypes and similar to patients with Goldenhar sequence. In contrast, she did not have eye or vertebral abnormalities.

The most frequent etiology of trisomy 22 is the maternal non-disjunction at the first meiotic division that is correlated with the mother's age[5]. The mother of our case was 37 years old and microsatellite analysis showed that the extra chromosome was maternal in origin. As noted by Zerres et al.[13] in 1988, it is possible that most conceptions with complete trisomy 22 do not progress beyond the first trimester because of the abnormal placental development[12, 3]. Mosaicism for trisomy 22 in placenta with a normal fetal chromosome complement results in growth retardation without structural abnormalities[14]. The rare liveborn child with complete trisomy 22 may survive to term because of placental mosaicism, as found by Spinner et al.[15] [1992] in the terminated pregnancy they reported. In conclusion, our case supplies further proof of the maternal origin of trisomy 22. Although the majority of fetuses with an extra chromosome 22 are spontaneously aborted, rare cases may survive for a short time.

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