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Case Report

Prenatal diagnosis and molecular cytogenetic characterization of a pure ring chromosome 21 with a 4.657-Mb 21q22.3 deletion

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ABSTRACT

Objective: We present diagnosis and molecular cytogenetic characterization of a pure ring chromosome [r(21)] with a 4.657-Mb 21q22.3 deletion.

Case report: A 44-year-old woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Amniocentesis revealed a karyotype 46,XX,r(21)(p11.2q22.3). Prenatal ultrasound findings were unremarkable. Simultaneous array comparative genomic hybridization (aCGH) analysis on uncultured amniocytes revealed a 4.657-Mb deletion at 21q22.3. The parental karyotypes were normal. The pregnancy was subsequently terminated, and a malformed fetus was delivered with facial dysmorphism and clinodactyly. Postnatal cytogenetic analysis of umbilical cord revealed a karyotype of 46,XX,r(21)(p11.2q22.3). aCGH analysis of umbilical cord revealed the result of arr 21q22.3 (43,427,188–48,084,156) × 1.0 with a 4.657-Mb 21q22.3 deletion encompassing 57 Online Mendelian Inheritance in Man (OMIM) genes including *TRPM2*, *TSPEAR*, *COL18A1*, *COL6A1*, *COL6A2*, *LSS*, *PCNT*, *DIP2A*, *S100B* and *PRMT2*. Metaphase fluorescence *in situ* hybridization (FISH) analysis of the umbilical cord fibroblasts confirmed a 21q22.3 deletion.

Conclusion: Prenatal diagnosis of an r(21) should include molecular cytogenetic characterization such as aCGH and FISH to determine the extent of the 21q22.3 deletion.

Introduction

We previously reported present diagnosis of mosaic ring chromosome 21 [r(21)] associated with a 21q22.3 deletion [1,2]. Here, we present an additional case of a pure r(21) with a 4.657-Mb 21q22.3 deletion.

Case report

A 44-year-old, gravida 2, para 0, woman underwent amniocentesis at 18 weeks of gestation because of advanced maternal age. Her husband was 44 years old. Amniocentesis revealed a karyotype 46,XX,r(21)(p11.2q22.3). Prenatal ultrasound findings were unremarkable. Simultaneous array comparative genomic hybridization (aCGH) analysis on uncultured amniocytes revealed a 4.657-Mb deletion at 21q22.3. The parental karyotypes were normal. The pregnancy was subsequently terminated, and a malformed fetus was delivered with facial dysmorphism of hypertelorism, prominent nasal bridge, protuberant occiput, prominent forehead, broad anteverted nasal tip, long philtrum, thin upper lip, low-set ears, wide mouth and micrognathia (Fig. 1) and clinodactyly. Postnatal cytogenetic analysis of umbilical cord revealed a karyotype 46,XX,r(21)(p11.2q22.3) (Fig. 2). aCGH analysis of umbilical cord revealed the result of arr 21q22.3 (43,427,188–48,084,156) × 1.0 with a 4.657-Mb 21q22.3 deletion encompassing 57 Online Mendelian Inheritance in Man (OMIM) genes including *TRPM2*, *TSPEAR*, *COL18A1*, *COL6A1*, *COL6A2*, *LSS*, *PCNT*, *DIP2A*, *S100B* and *PRMT2* (Fig. 3). Metaphase fluorescence *in situ* hybridization (FISH)

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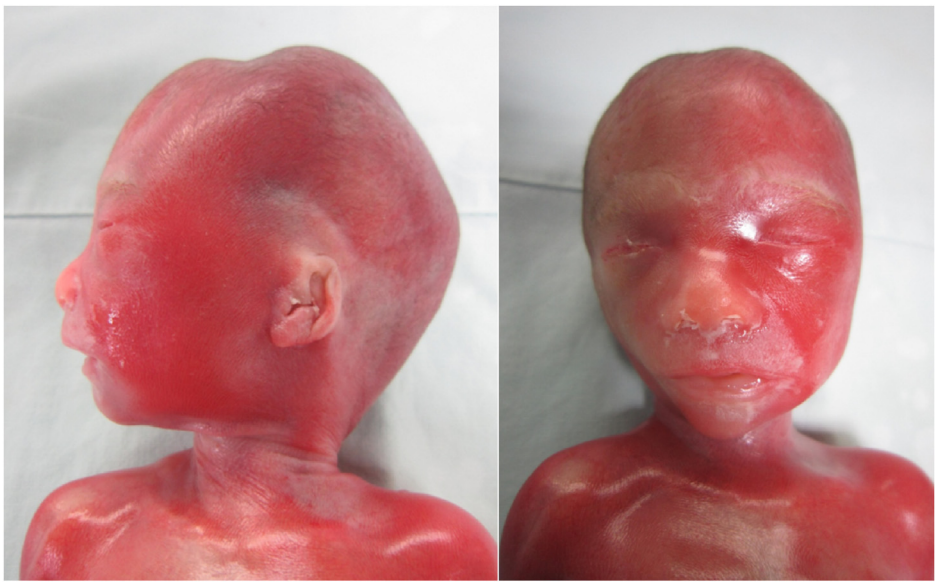

Fig. 1. Craniofacial appearance of the fetus at birth.

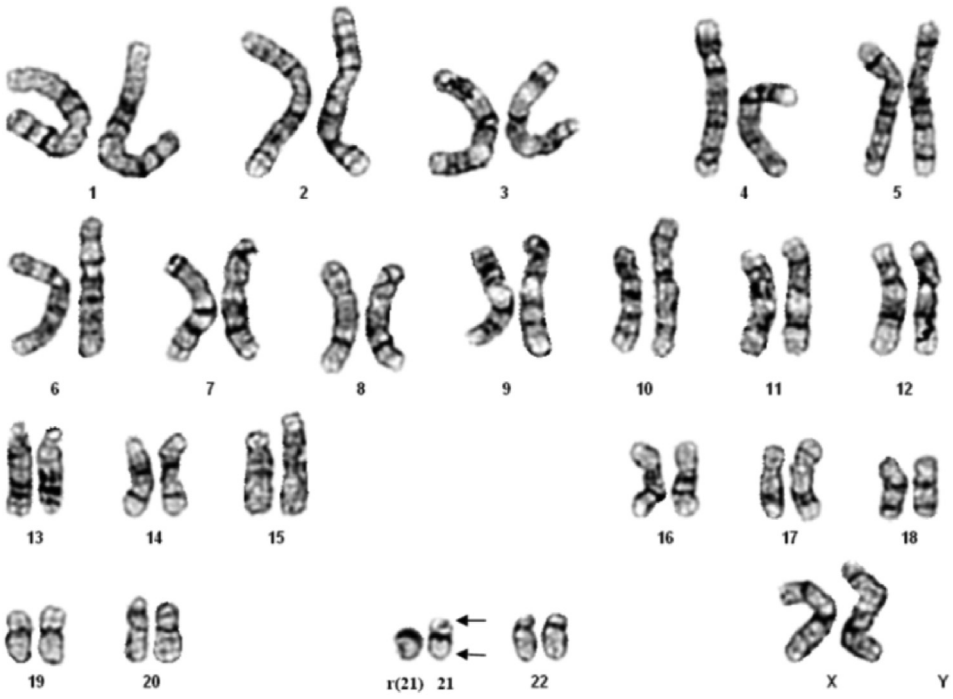

Fig. 2. A karyotype of 46,XX,r(21)(p11.2q22.3). r = ring chromosome. The arrows indicate the breakpoints.

analysis of the umbilical cord fibroblasts confirmed a 21q22.3 deletion (Fig. 4).

Discussion

To date, at least six cases with prenatal diagnosis of r(21) have been reported [1–6]. The phenotype of r(21) is associated with the extent of the 21q deletion. Stetten et al. [3] reported prenatal diagnosis of 46,XY,r(21)/45,XY,-21 by amniocentesis with mosaicism for majority of r(21). The proband was apparently normal except minor developmental delay at 14 months of age. Melnyk et al., [1995] reported prenatal diagnosis of familial r(21) of 46,XX,r(21) (77%)/45,XX,-21 (23%) in the fetal with a normal outcome and a normal mother carrier with r(21). Papoulidis et al. [5] reported prenatal diagnosis of 46,XY,r(21) [34]/45,XY,-21 [4]/46,XY [14] in a fetus with apparently normal phenotype in a pregnancy because of advanced maternal age. Chen et al. [1] reported prenatal diagnosis of 46,XY,r(21) [8]/45,XY,-21 [3]/46,XY,idic r(21) [1] associated with a 2-Mb deletion at 21q21.1-q21.2 and a 5-Mb deletion at 21q22.3 in a fetus with facial dysmorphism. Chen et al. [2] reported prenatal diagnosis of 46,XX,r(21) [12]/45,XX,-21 [5] in a fetus with facial dysmorphism and sacrococcygeal teratoma, and a 0.15-Mb deletion of 21q22.3 encompassing the genes of *DIP2A*, *S100B*, *PRMT2*, *DSTNP1* and *RPL23A4*. Bone et al.

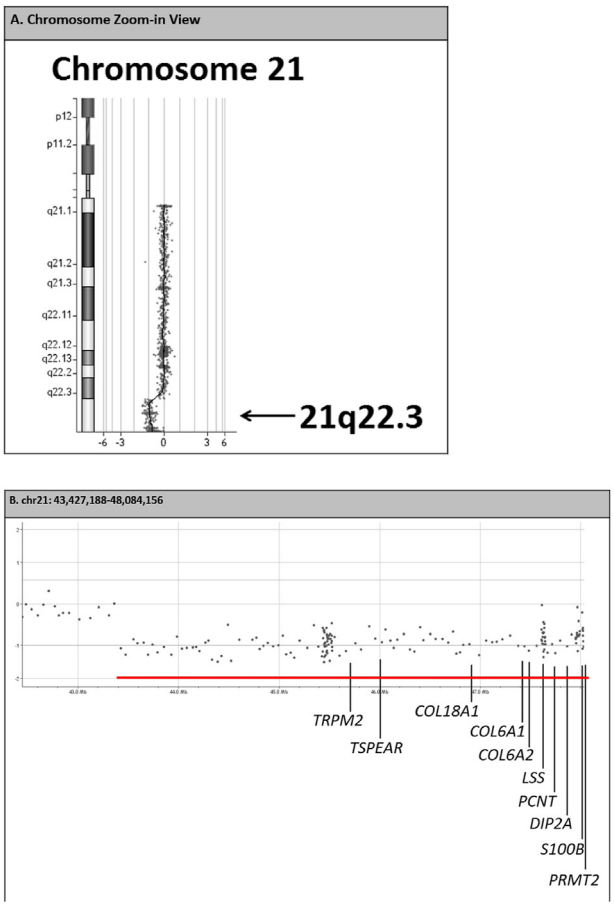

Fig. 3. (A) and (B) Array comparative genomic hybridization analysis on the DNA extracted from the umbilical cord using SurePrint G3 Unrestricted CGH ISCA v2, 8 × 60K (Agilent Technologies, Santa Clara, CA, USA) shows the result of arr 21q22.3 (43,427,188–48,084,156) × 1.0 [GRCh37 (hg19)] with a 4.657-Mb 21q22.3 deletion encompassing the genes of *TRPM2*, *TSPEAR*, *COL18A1*, *COL6A1*, *COL6A2*, *LSS*, *PCNT*, *DIP2A*, *S100B* and *PRMT2*.

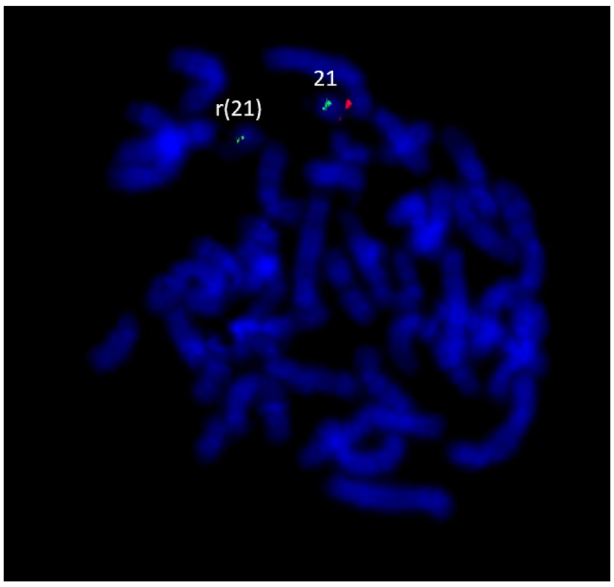

Fig. 4. Metaphase fluorescence *in situ* hybridization analysis on the fibroblasts of umbilical cord using the bacterial artificial chromosome (BAC) probes of RP11-762K21 [21p11.2; fluorescein isothiocyanate (FITC), spectrum green] and RP11-135B17 (21q22.3; Texas Red, spectrum red) shows that the normal chromosome 21 contains one red signal and one green signal, whereas the ring chromosome 21 [r(21)] contains only one green signal, indicating a 21q22.3 deletion.

[6] reported prenatal diagnosis of 46,XY,r(21)(p11.2q22) with a 6.2-Mb deletion at 21q22.2-q22.3, hydrops fatalis, nuchal edema and ascites.

The present case was associated with a 4.657-Mb 21q22.3 deletion encompassing 57 OMIM genes including *TRPM2*, *TSPEAR*, *COL18A1*, *COL6A1*, *COL6A2*, *LSS*, *PCNT*, *DIP2A*, *S100B* and *PRMT2*. Patients with 21q22.3 deletion have been reported to be associated with holoprosencephaly, corpus callosum agenesis, microcephaly, intellectual disability, cognitive deficits and cardiovascular disorders. Lafabregue et al. [7] reported a patient with alopecia, deformed ear, mental retardation and an r(21) with a 3.6-Mb 21q22.3 terminal deletion. Orru et al. [8] reported a patient with autism spectrum disorder, anxiety and severe depression with deletion and duplication in the 21q22.3 region including the deletion of *COL6A2*, *LSS*, *PCNT*, *DIP2A* and *S100B*. Falik-Borenstein et al. [9] reported growth retardation and microcephaly in patients associated with familial translocation of r(21)(p13q22) and the deletion of *COL6A2* and *S100B*. McGinniss et al. [10] reported mild mental retardation, growth retardation, short stature and microcephaly in a patient with r(21) and a longer deletion including *COL6A1*. Roberson et al. [11] reported a 4-year-old boy with 46,XY,del(21)(q22.3) and a 5.68-Mb 21q22.3 terminal deletion presenting speech delay and moderate mental retardation. Specchio et al. [12] reported a patient with 46,XY,r(21)(p13q22.3)/45,XY,-21 and the phenotype of epilepsy, intellectual disability and dysmorphic features. Yu et al. [13] reported that deficiencies in the region syntenic to human 21q22.3 cause cognitive deficits in mice. McQuillin et al. [14] suggested that *TRPM2* and *TSPEAR* are candidate genes for bipolar disorder. Kato [15] suggested an association between bipolar disorder and *TRPM2*. Poelmans et al. [16] suggested that *PCNT*, *DIP2A*, *S100B* and *PRMT2* are candidate genes for dyslexia. Rope et al. [17] reported dilated ascending aorta in a child with an r(21) and suggested that *COL6A1*, *COL6A2* and *COL18A1* are responsible for the phenotype. Ciocca et al. [18] reported hypoplastic left heart syndrome in a patient with a 21q22.3 deletion. *PCNT* has been associated with schizophrenia [19,20]. *S100B* has been associated with schizophrenia, bipolar depression and autism [21–25]. *DIP2A* has been associated with autism and dyslexia [23,26–28].

The holoprosencephaly candidate gene of *HPE1* (OMIM 236100) has been suggested to be located at 21q22.3 [29]. Aronson et al. [30] reported a male infant with holoprosencephaly and an r(21). Estabrooks et al. [31] reported holoprosencephaly in an infant with a 21q22.3 deletion. Mallick et al. [32] reported holoprosencephaly in a neonate with 21q22 deletion. Tran Mau-Them et al. [33] reported middle interhemispheric variant of holoprosencephaly in a patient with partial 21q monosomy of del(21q22.2-q22.3). Chen et al. [34] reported a 3-year-old boy with *de novo* satellited 21q associated with 21q22.3 deletion, corpus callosum dysgenesis, colpocephaly, a concealed penis, congenital heart defects and developmental delay. Guion-Almeida et al. [35] reported frontonasal dysplasia, callosal agenesis, basal encephalocele and eye anomalies in a girl with 46,XX,r(21) and a 219-kb interstitial deletion of 21q22.3.

In summary, we present diagnosis and molecular cytogenetic characterization of a pure r(21) with a 4.657-Mb 21q22.3 deletion. Prenatal diagnosis of an r(21) should include molecular cytogenetic characterization such as aCGH and FISH to determine the extent of the 21q22.3 deletion.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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