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Short Communication

Mosaic ring chromosome 21, monosomy 21, and isodicentric ring chromosome 21: Prenatal diagnosis, molecular cytogenetic characterization, and association with 2-Mb deletion of 21q21.1–q21.2 and 5-Mb deletion of 21q22.3

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Abstract

Objective: To present the perinatal findings and molecular cytogenetic characterization of prenatally detected mosaic r(21).
Materials, Methods, and Results: A 29-year-old primigravid woman underwent amniocentesis at 22 weeks' gestation because of hyperechogenic cardiac foci and intrauterine growth restriction. Amniocentesis revealed a karyotype of 46,XY,r(21)[15]/45,XY,−21[5]. The parental karyotypes were normal. The woman requested repeat amniocentesis. Oligonucleotide-based array comparative genomic hybridization was applied to the uncultured amniocytes, rapidly detecting a 2.09-Mb deletion of 21q21.1–q21.2 (21,495,262–23,580,815 bp) and a 5.03-Mb deletion of 21q22.3–q22.3 (41,887,412–46,914,715 bp). Cytogenetic analysis revealed a karyotype of 46,XY,r(21)[8]/45,XY,−21[3]/46,XY,idic r(21)[1]. The pregnancy was terminated, and a malformed fetus was delivered with clinodactyly, short big toes, separation between the first and second toes, prominent nasal bridge, downward slanting palpebral fissures, protuberant occiput, prominent forehead, broad anteverted nasal tip, long philtrum, thin upper lip, small mouth, and micrognathia. The placenta had a karyotype of 46,XY,r(21)[83]/45,XY,−21[11]/46,XY,idic r(21)[6], and the cord blood lymphocytes had a karyotype of 46,XY,r(21)[88]/45,XY,−21[9]/46,XY,idic r(21)[3]. Polymorphic DNA marker analysis determined a maternal origin for the deletion.
Conclusion: An extra interstitial 21q deletion can be associated with mosaic r(21) in addition to a terminal 21q deletion. aCGH is useful in determining the breakpoints and associated subtle structural abnormalities in cases of prenatally detected ring chromosome in order to facilitate genetic counseling.

Keywords: 21q interstitial deletion; 21q terminal deletion; mosaicism; prenatal diagnosis; ring chromosome 21

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Introduction

A ring chromosome 21, or r(21) exhibits breakage and reunion at the breakpoints on the long and short arms of chromosome 21, with possible deletions of the chromosomal segments distal to the breakpoints [1]. An r(21) has been found in children and their mothers, implying that the r(21) can be transmitted from parents to their children [1−6]. An r(21) has also been found in a boy with a derivative chromosome 21 in the mother [7]. Further, dicentric (dic) r(21) has been found in the children of parents with an r(21), indicating that the r(21) is susceptible to tandem duplication [8,9]. The r(21) can present with a deletion/duplication of r(21) in the form of mosaic monosomy 21 and dic r(21) [1]. The sequelae in patients with an r(21) are variable, including spontaneous abortions, phenotypically normal offspring with or without r(21), phenotypically abnormal offspring with r(21), infants with Down syndrome with dic r(21) or +r(21), infertility in female carriers, or azoospermia in male carriers [10,11].

Prenatal diagnosis of r(21) is very rare, and to date, only three cases have been reported [6,12,13]. Stetten et al [12] first reported the prenatal diagnosis of 46,XY,r(21)/45,XY,−21 with mosaicism for majority of the r(21) in a fetus with a normal outcome. In that case, amniocentesis was performed because of the risk of sickle cell anemia. Melnyk et al [6] reported the prenatal diagnosis of 46,XX,r(21) (77%)/45,XX,−21 (23%) in a fetus with a normal outcome. In that case, amniocentesis was performed because of the carrier status of r(21) in the normal mother. Papoulidis et al [13] recently reported the prenatal diagnosis of 46,XY,r(21)[34]/45,XY,−21[4]/46,XY[14] in a fetus with a normal outcome. In that case, amniocentesis was performed because of maternal anxiety. Here, we report the perinatal findings and molecular cytogenetic characterization of an additional case with mosaic r(21).

Materials, methods, and results

A 29-year-old primigravid woman underwent amniocentesis at a community obstetric clinic because of hyperechogenic cardiac foci and intrauterine growth restriction. Her husband was also 29 years of age. Amniocentesis at 22 weeks' gestation revealed a male fetus with mosaicism for ring chromosome 21 [r(21)] and monosomy 21, or 46,XY,r(21)[15]/45,XY,−21[5]. The parental karyotypes were normal. Prenatal ultrasound findings at 24 weeks' gestation were unremarkable except for IUGR, dolichocephaly, protuberant occiput, prominent forehead, prominent nasal bridge, and micrognathia (Fig. 1). The fetal biometry was equivalent to 22 weeks' gestation. The woman requested repeat amniocentesis.

Oligonucleotide-based array comparative genomic hybridization (aCGH) using CytoChip Oligo Array (BlueGnome, Cambridge, UK) was applied to the uncultured amniocytes. aCGH rapidly detected a gene dosage decrease at 21q21.1−q21.2 and 21q22.3 in the uncultured amniocytes. There were a 2.09-Mb deletion of 21q21.1−q21.2 (21,495,262−23,580,815 bp) and a 5.03-Mb deletion of 21q22.3−q22.3 (41,887,412−46,914,715 bp) (Fig. 2) [UCSC genome browser on March 2006 (NCBI build 36/hg18) assembly]. Conventional cytogenetic analysis revealed a karyotype of 46,XY,r(21)[8]/45,XY,−21[3]/46,XY,idic r(21)[1] (Figs. 3−5).

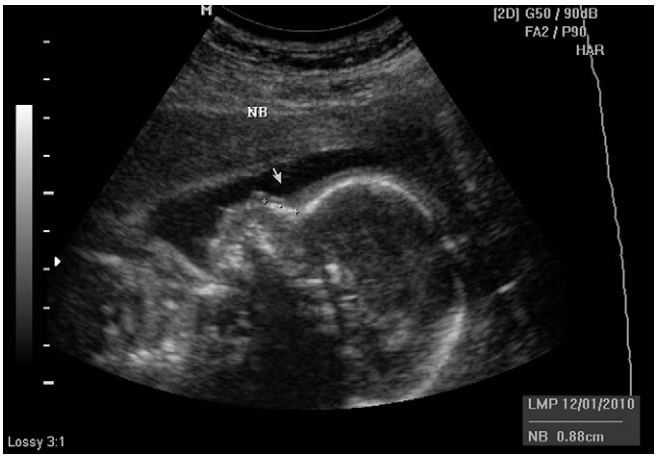

Fig. 1. Prenatal ultrasound at 24 weeks' gestation shows a protuberant occiput, prominent forehead, prominent nasal bridge, and micrognathia.

The parents elected to terminate the pregnancy, and a malformed 750-g fetus was delivered with clinodactyly, short big toes, separation between the first and second toes, prominent nasal bridge, downward slanting palpebral fissures, protuberant occiput, prominent forehead, broad anteverted nasal tip, long philtrum, thin upper lip, small mouth, and micrognathia (Fig. 6). Conventional cytogenetic analyses of the cord blood and placenta were carried out. The placenta had a karyotype of 46,XY,r(21)[83]/45,XY,−21[11]/46,XY,idic r(21)[6]. The cord blood lymphocytes had a karyotype of 46,XY,r(21)[88]/45,XY,−21[9]/46,XY,idic r(21)[3]. Polymorphic DNA marker analysis determined a maternal origin of the deletion (Fig. 7 and Table 1).

Discussion

We previously demonstrated the utility of aCGH in the molecular cytogenetic characterization of mosaic r(18) [14]. In this report, we also demonstrate the use of aCGH to determine the breakpoints and the interstitial microdeletion of a small ring chromosome in a case in which the ring chromosome comprises the majority of the mosaicism. The present case was initially found to have high-level mosaicism for r(21) and low-level mosaicism for r(21) deletion/duplication. aCGH further identified a 2.09-Mb interstitial deletion of 21q21.1−q21.2 and a 5.03-Mb terminal deletion of 21q22.3.

The 2-Mb 21q21.1−q21.2 interstitial deletion in this case encompasses the genes *NCAM2*, *C21orf74*, and *ZNF299P*, and has *NCAM2* haploinsufficiency. Neural cell adhesion molecule 2 (NCAM2; OMIM 602040) belongs to the NCAM family, which is highly expressed in the nervous system and participates in mediating cell adhesion, neurite outgrowth, cell migration, differentiation and survival, and the formation and plasticity of synapses [15,16]. Molloy et al [17] suggested that *NCAM2* may be a candidate gene for autism. Haldeman-Englert et al [18] reported an autistic male with a *de novo*

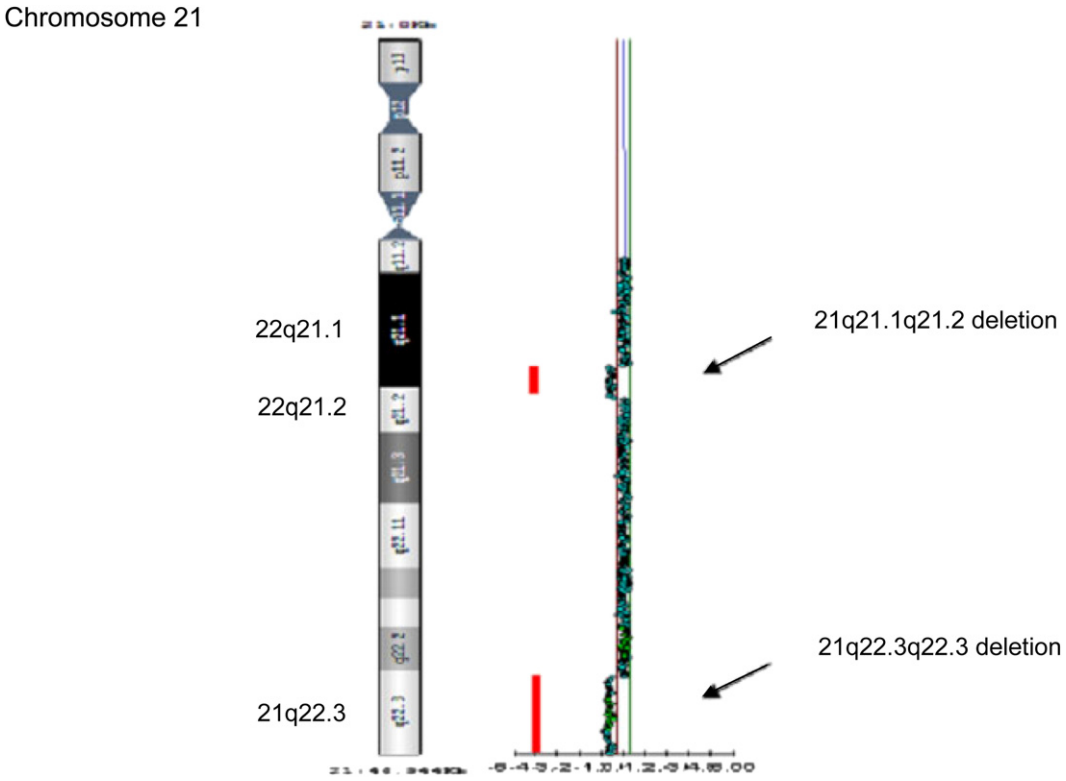

Fig. 2. Oligonucleotide-based array comparative genomic hybridization shows a 2.09-Mb deletion of 21q21.1–q21.2 (21,495,262–23,580, bp) and a 5.03-Mb deletion of 21q22.3–q22.3 (41,887,412–46,914, bp) (NCBI build 36/hg18).

8.8-Mb deletion of 21q21.1–q21.3 encompassing the *NCAM2* gene and suggested that *NCAM2* is a candidate gene for autism and other neurobehavioral disorders.

The 5-Mb 21q22.3 terminal deletion in this case encompasses 94 genes including *TRPM2, C21orf29, PCNT, DIP2A, S100B, PRMT2, COL18A1, COL6A1, COL6A2*, and *LSS*. Specchio et al [19] reported a patient with the karyotype of 46,XY,r(21)(p13q22.3)/45,XY,−21 and the phenotype of generalized epilepsy, intellectual disability, and dysmorphic features. In the mouse model, deficiencies in the region corresponding to human 21q22.3 cause cognitive deficits [20]. McQuillin et al [21] reported that *TRPM2* and *C21orf29* (*TSPEAR*) are candidate genes for bipolar disorder. The positional candidate approach has shown an association between

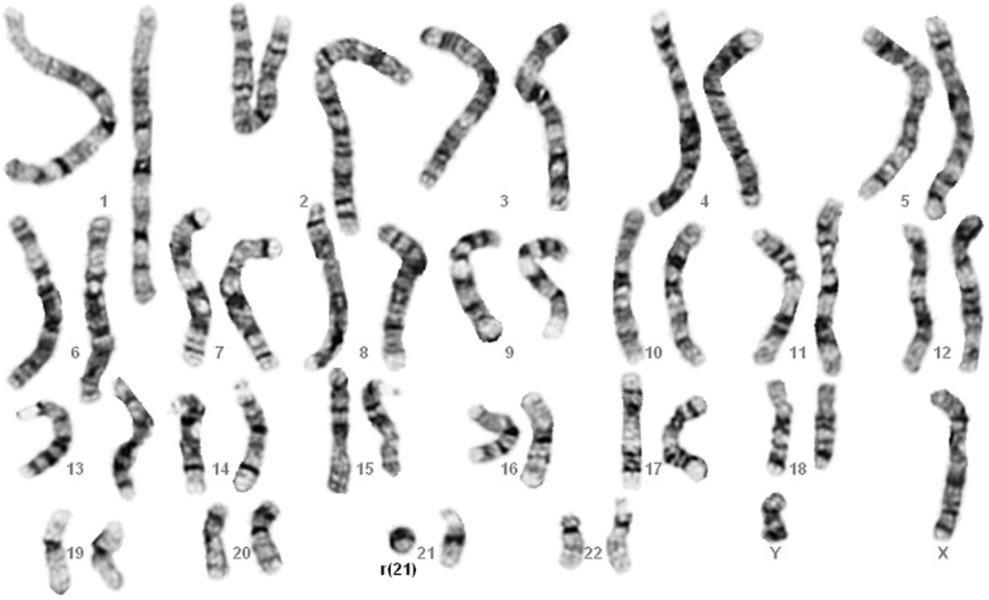

Fig. 3. A karyotype of 46,XY,r(21).

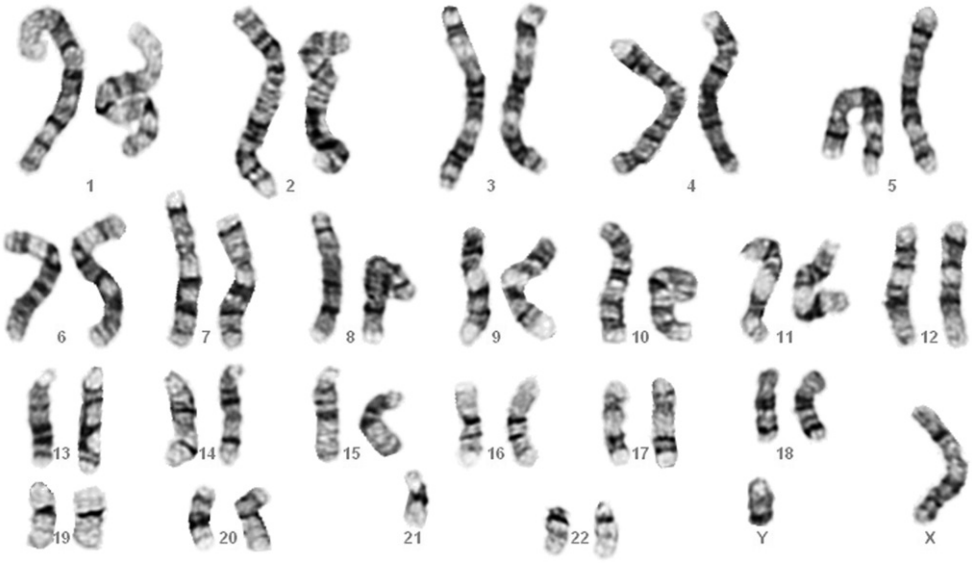

Fig. 4. A karyotype of 45,XY,−21.

bipolar disorder and *TRPM2* [22]. *TRPM2* (OMIM 603749) encodes a transient receptor potential cation channel subfamily M member 2 protein, which is a calcium channel receptor and is associated with oxidative stress-induced cell death and inflammatory processes. *C21orf29* or *TSPEAR* (OMIM 612920) is an epilepsy gene that encodes chromosome 21 open reading frame 29 peptide with epilepsy-associated repeats.

Poelmans et al [23] reported that *PCNT*, *DIP2A*, *S100B*, and *PRMT2* are candidate genes for dyslexia. *PCNT* (OMIM 605925) encodes pericentrin, which is important for cell-cycle progression and for the normal functioning of centrosomes and cytoskeleton. *DIP2A* (OMIM 607711) encodes *Drosophila* homologue of disco-interacting protein 2A protein, which is involved in the AMPA glutamate receptor recycling pathway and is important in the regulation of synaptic plasticity. *S100B* (OMIM 176990) encodes S100 calcium-binding protein, which is a calcium-binding peptide produced mainly by astrocytes and exerts paracrine and autocrine effects on neurons and glial cells. *PRMT2* (OMIM 601961) encodes protein arginine *N*-methyltransferase 2 and is involved in mRNA metabolism.

Rope et al [24] reported a dilated ascending aorta in a child with ring chromosome 21 and suggested that haploinsufficiency of the collagen genes *COL6A1* (OMIM 120220), *COL6A2* (OMIM 120240), and *COL18A1* (OMIM 120328) might be responsible for the phenotype. The *LSS* gene (OMIM 600909) encodes lanosterol synthase, which is required for cholesterol modification of the Sonic hedgehog protein and was considered to be an excellent candidate gene for *HPE1* (OMIM 236100). However, in a mutational analysis of the *LSS* gene in patients with holoprosencephaly (HPE), Roessler et al [25] could not find evidence that *LSS* gene was responsible for HPE1.

Partial deletions of 21q are rare, and the patients display variable phenotypes according to the size and position of the deletion [26–29]. Lindstrand et al [28] suggested that the

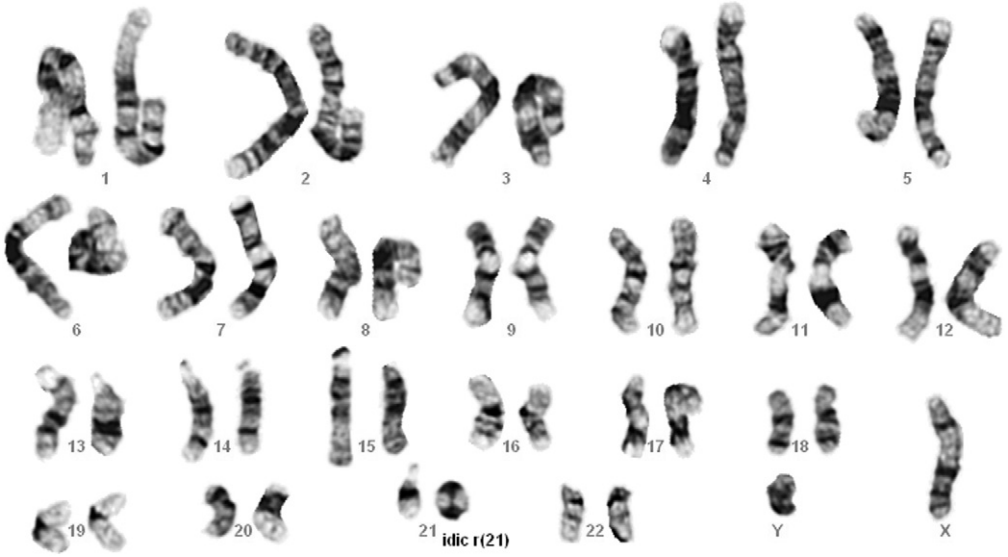

Fig. 5. A karyotype of 46,XY,idic r(21).

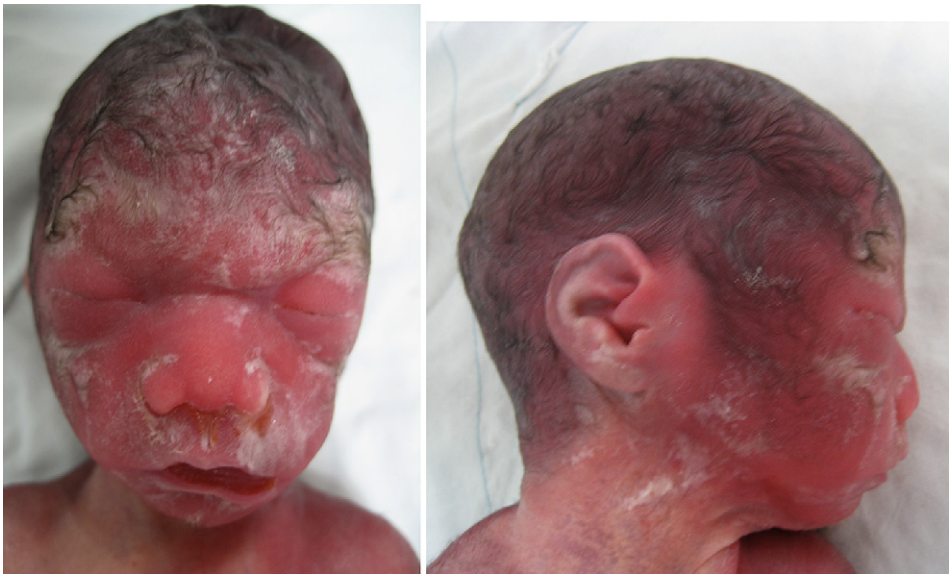

Fig. 6. The craniofacial appearance of the fetus at birth.

ITSN1 gene is involved in severe mental retardation, and that genes *KCNE1*, *DSCR1*, *CLIC6*, and *RUNX1* are associated with severe congenital heart defects in patients with a 21q deletion. Our patient did not have haploinsufficiency of such genes and did not manifest congenital heart defects.

An HPE1 (OMIM 236100) critical region has been suggested on chromosome 21q22.3 [30]. HPE has been reported in patients with ring chromosome 21 [31,32] or a minute deletion of chromosome 21q22.3 [33]. An agenesis of the corpus callosum (ACC) critical region has also been suggested on chromosome 21q22.2–q22.3 [34]. ACC has been reported in patients with satellited 21q [35] and a deletion of 21q22.1→qter [36]. However, the present case did not have any central nervous system abnormality. Therefore, the phenotype associated with the distal 21q deletion encompassing the critical regions of HPE and ACC can be variable.

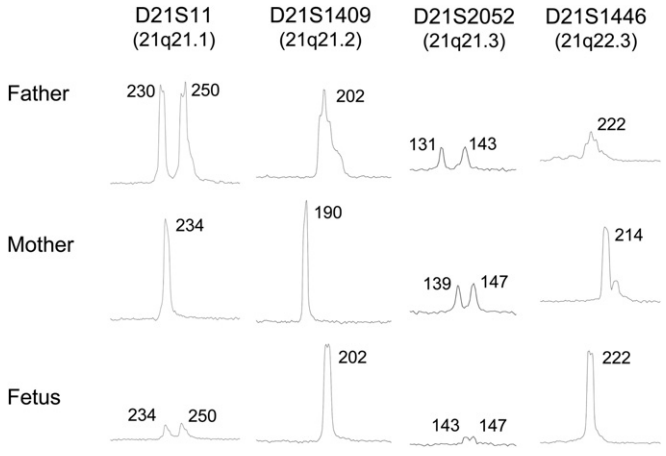

Fig. 7. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays at short tandem repeat markers specific for chromosome 21q using fetal and parental DNAs. With the markers D21S11 (21q21.1) and D21S2052 (21q21.3), two alleles of 234 bp: 250 bp (maternal:paternal) and 147 bp: 143 bp (maternal:paternal), respectively, in the fetus, have a ratio of 1:1 (maternal:paternal), indicating a biparental inheritance in 21q21.1 and 21q21.3. With the markers D21S1409 (21q21.2) and D21S1446 (21q22.3), only one allele of 202 bp (paternal) and 222 bp (paternal), respectively, in the fetus, is present, indicating paternal inheritance in 21q21.2 and 21q22.3 and a maternal origin of the deletion in 21q21.2 and 21q22.3.

Recently, several reports have been published describing the atypical ring chromosome in which aCGH showed not only the deletions at the chromosomal ends but also an extra deletion or duplication [37–39]. Glass et al [37] reported loss of the 15q subtelomeric clone and a discontinuous interstitial bacterial artificial chromosome clone on distal 15q in a patient with r(15). Knijnenburg et al [38] reported inverted duplication and terminal deletion in a patient with r(14). In a study of 33 ring chromosomes, Rossi et al [39] found that seven had duplications in addition to terminal deletions. The seven atypical duplication/deletion chromosomes include a single case of r(13) with inv dup del 13q, r(13) with dup del 13q, r(15) with inv dup del 15q, r(21) with dup 21q21.3q22.2 and trp 21q22.2q22.3, r(22) with dup del 22q, and two cases of r(18) with dup del 18 p.

To our knowledge, the case presented here is the first report of mosaic r(21) with a terminal deletion/interstitial duplication of 21q. Our case provides evidence for an extra interstitial 21q deletion in addition to terminal 21q deletion in the case with mosaic r(21). It can be concluded that aCGH is useful in determining the breakpoints and the associated subtle

Table 1
Molecular results using polymorphic DNA markers specific for chromosome 21q.[a]

Markers	Father	Mother	Proband	Location[b]
D21S1432	142, 142	134, 134	134, 142	16,265,317–16,265,448
D21S11	230, 250	234, 234	234, 250	19,476,130–19,476,352
D21S1409	202, 202	190, 190	202	23,270,598–23,270,778
D21S2052	131, 143	139, 147	143, 147	27,740,433–27,740,559
D21S2054	174, 174	178, 178	174, 178	29,978,408–29,978,580
D21S1446	222, 222	214, 214	222	46,862,013–46,862,233

[a] Alleles (base pair sizes) are listed below each individual; [b] Location according to NCBI build 36/hg18.

structural abnormalities in case of prenatally detected ring chromosome in order to facilitate the genetic counseling.

Acknowledgments

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