Unbalanced and Balanced Heterologous Acrocentric Rearrangements Involving Chromosome 21 at Amniocentesis

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SUMMARY

Objective: To present unbalanced and balanced heterologous acrocentric rearrangements involving chromosome 21 at amniocentesis.

Materials and Methods: Between January 1987 and September 2009, 31,194 amniocenteses were performed at Mackay Memorial Hospital, Taipei, Taiwan. Two cases with an unbalanced heterologous acrocentric rearrangements involving chromosome 21 from two families and seven cases with balanced heterologous acrocentric rearrangements involving chromosome 21 from five families were diagnosed and investigated.

Results: We detected rob(14q21q),+21 (one case), rob(13q21q),+21 (one case), rob(14q21q) (four cases), rob(13q21q) (one case) and rob(15q21q) (two cases). Of the nine cases that underwent parental cytogenetic investigation, one was *de novo* and eight were inherited (five maternal and three paternal). The six families with an inherited acrocentric rearrangement included rob(14q21q) (three families), rob(13q21q) (two families) and rob(15q21q) (one family). Of these six families, three had a known parental carrier status before the first amniocentesis, while the other three were aware of their parental carrier status only after prenatal diagnosis of a fetus with a heterologous acrocentric rearrangement. The seven fetuses with a balanced heterologous acrocentric rearrangement were inherited from two paternal carriers of rob(14q21q), one maternal carrier of rob(14q21q), one maternal carrier of rob(13q21q), and one maternal carrier of rob(15q21q). No uniparental disomy 14 was detected in any of the three cases with rob(14q21q) tested for uniparental disomy.

Conclusion: Concerning heterologous acrocentric rearrangements involving chromosome 21, the frequency of unbalanced rearrangements was 0.0064% and that of balanced rearrangements was 0.0224% at amniocentesis. In this study, rob(14q21q) was the most common, and rob(13q21q) and rob(15q21q) were the second most common rearrangements. Of the six families with an inherited heterologous acrocentric rearrangement involving chromosome 21, 50% (3/6) were aware of their parental carrier status only after prenatal diagnosis of a fetus with a translocation by amniocentesis. [*Taiwan J Obstet Gynecol* 2010;49(1):62–68]

Key Words: acrocentric rearrangement, amniocentesis, Down syndrome, heterologous Robertsonian translocations, trisomy 21, uniparental disomy

Introduction

About 95% of cases of Down syndrome are due to simple trisomy 21 with an extra free chromosome 21, 1–2% are due to mosaicism, and 4% are due to unbalanced heterologous or homologous acrocentric rearrangements

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of which rea(21q21q) and rob(14q21q) are the most common and occur with equal frequencies [1]. In heterologous Robertsonian translocation Down syndrome, rob(14q21q) accounts for 82% of the cases, while rob(13q21q), rob(15q21q) and rob(21q22q) account for the remaining cases [1]. Prenatal diagnosis of Down syndrome due to unbalanced heterologous acrocentric rearrangements involving chromosome 21 by amniocentesis is uncommon.

Fetuses with unbalanced or balanced heterologous acrocentric rearrangements involving chromosome 21 may be associated with trisomies 13, 14, 15, 21 or 22 in cases involving chromosomes 13, 14, 15 or 22, as well as uniparental disomy (UPD) 14 or UPD15 in cases involving chromosomes 14 or 15. In cases of parental non-homologous Robertsonian translocations, there may be a trisomy rescue in an initially trisomic zygote or a monosomy rescue after fertilization of a normal gamete by a nullisomic gamete. Such trisomy rescue or a monosomy rescue may result in UPD from the parent that does not carry the translocation [2]. In cases of *de novo* non-homologous Robertsonian translocations, UPD from the parent whose chromosomes are involved in the translocation is also likely [2]. Maternal and paternal UPD14 and UPD15 are syndromic. Maternal UPD14 is characterized by short stature, muscular hypotonia, precocious puberty, truncal obesity, and variable psychomotor retardation [2,3]. Paternal UPD14 is characterized by severe psychomotor retardation, polyhydramnios, mild contractures of the fingers, and a bell-shaped thorax with a "coat-hanger" sign [2,3]. Maternal UPD15 is associated with Prader-Willi syndrome, which is characterized by muscular hypotonia, feeding difficulties in infancy followed by hyperphagia and subsequent obesity, moderate mental retardation, hypogonadotropic hypogonadism, facial dysmorphisms including almond-shaped eyes, and short hands and feet [2,3]. Paternal UPD15 is associated with Angelman syndrome, which is characterized by severe mental retardation, ataxia, seizures, electroencephalographic abnormalities, jerky movements, and inappropriate laughter [2,3].

Here, we report our experience of the prenatal diagnosis of unbalanced and balanced heterologous acrocentric rearrangements involving chromosome 21 using amniocentesis.

Materials and Methods

Between January 1987 and September 2009, a total of 31,194 amniocenteses were performed at Mackay Memorial Hospital, Taipei, Taiwan, because of advanced maternal age, abnormal ultrasound findings, abnormal maternal serum screening results, a previous child with a congenital anomaly, a family history of chromosome aberrations, or for other reasons. An unbalanced heterologous acrocentric rearrangements involving chromosome 21 was diagnosed in two cases from two families, and balanced heterologous acrocentric rearrangements involving chromosome 21 were diagnosed in seven cases from five families. Cytogenetic analysis of parental blood lymphocytes was done in seven families. Polymorphic DNA markers were used to investigate UPD in three cases. The clinical data of the nine cases from the seven families are summarized in the Table.

Results

In the 31,194 cases that underwent amniocentesis, the frequency of unbalanced heterologous acrocentric rearrangements involving chromosome 21 was 0.0064% (2/31,194) and the frequency of balanced heterologous acrocentric rearrangements involving chromosome 21 was 0.0224% (7/31,194).

In this study, we detected rob(14q21q),+21 (one case), rob(13q21q),+21 (one case), rob(14q21q) (four cases), rob(13q21q) (one case), and rob(15q21q) (two cases) (Figures 1–5). Of the nine cases that underwent parental cytogenetic investigation, one arose *de novo* and eight were inherited (five maternal and three paternal). The six families with an inherited acrocentric rearrangement included rob(14q21q) (three families), rob(13q21q) (two families) and rob(15q21q) (one family). Of these six families, three had a known parental carrier status before the first amniocentesis, while the other three were aware of a parental carrier status only after prenatal diagnosis of a fetus with a heterologous acrocentric rearrangement. The seven fetuses with a balanced heterologous acrocentric rearrangement were inherited from two paternal carriers of rob (14q21q), one maternal carrier of rob(14q21q), one maternal carrier of rob(13q21q), and one maternal carrier of rob(15q21q). No UPD14 was detected in any of the three cases with rob(14q21q) tested for UPD.

The two cases with heterologous Robertsonian translocation Down syndrome prenatally manifested fetal ascites or hydrops. The fetus of rob(13q21q),+21 was inherited from a maternal carrier, and the fetus of rob(14q21q),+21 arose *de novo*. The two cases with heterologous Robertsonian translocation Down syndrome are described below.

Case 1

This was the second pregnancy of a 31-year-old, gravida 2, para 1, woman. One year previously, she underwent

Table. Clinical data for cases with unbalanced and balanced heterologous acrocentric rearrangements involving chromosome 21, as diagnosed by amniocentesis

Case	Indication for amniocentesis	Maternal age (yr)	Gestational age at amniocentesis (wk)	Fetus karyotype	Parental karyotype	UPD test	Carrier status	Inheritance
1*†	Fetal ascites, hepatosplenomegaly; a previous child with translocation Down syndrome; maternal carrier	31	34	46,XX,der(13;21)(q10;q10),+21	46,XY 45,XX,der(13;21)(q10;q10)	–	K	Maternal
2	Maternal serum screening, Down risk of 1/56; hydrops fetalis	27	18	46,XY,der(14;21)(q10;q10),+21	46,XY 46,XX	No UPD14	UK	*De novo*
3	AMA	38	19	45,XY,der(14;21)(q10;q10)	45,XY,der(14;21)(q10;q10) 46,XX	No UPD14	UK	Paternal
4	AMA; paternal carrier	39	19	45,XY,der(14;21)(q10;q10)	The same as Case 3	–	K	Paternal
5‡	AMA; paternal carrier	36	18	45,XY,der(14;21)(q10;q10)	45,XY,der(14;21)(q10;q10) 46,XX	No UPD14	K	Paternal
6	AMA	37	16	45,XX,der(14;21)(q10;q10)	46,XY 45,XX,der(14;21)(q10;q10)	–	UK	Maternal
7	AMA	37	18	45,XY,der(13;21)(q10;q10)	46,XY 45,XX,der(13;21)(q10;q10)	–	UK	Maternal
8‡	Maternal carrier	27	31	45,XX,der(15;21)(q10;q10)	46,XY 45,XX,der(15;21)(q10;q10)	–	K	Maternal
9‡	Maternal carrier	28	16	45,XX,der(15;21)(q10;q10)	The same as Case 8	–	K	Maternal

**Cordocentesis was performed simultaneously; †known parental carrier status because of a previous child with heterologous Robertsonian translocation Down syndrome; ‡known parental carrier status because of habitual abortions. AMA = advanced maternal age; carrier = carrier of Robertsonian translocation, UPD = uniparental disomy, – = not checked, UK = unknown at amniocentesis, K = known at amniocentesis.*

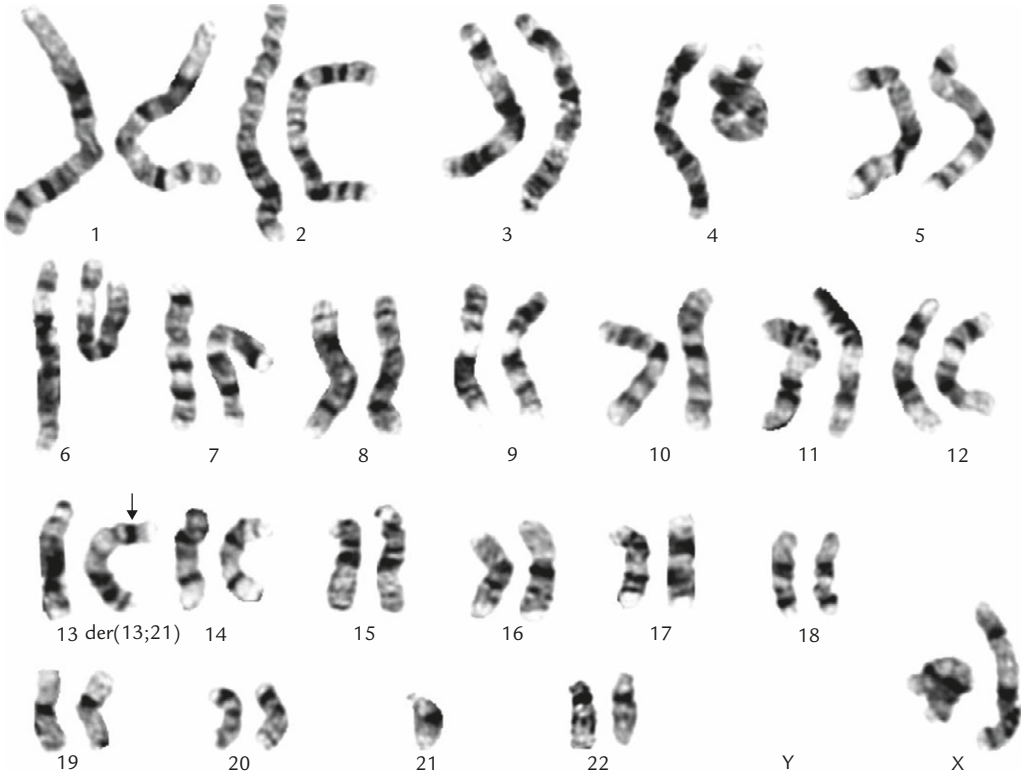

Figure 1. A case with a balanced heterologous Robertsonian translocation rob(13q21q) carrier and a 45,XX,der(13;21)(q10;q10) karyotype. The case has one free chromosome 13, one free chromosome 21, and one derivative chromosome der(13;21) (arrow) containing one translocated chromosome 13q and one translocated chromosome 21q.

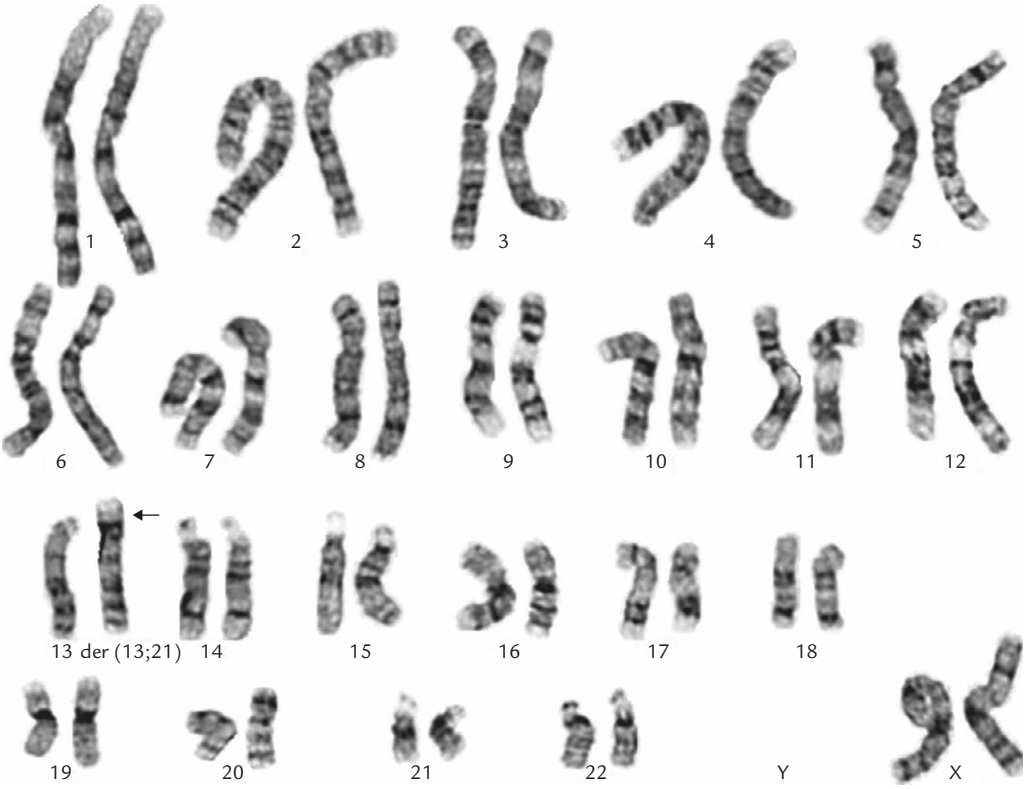

Figure 2. A case with heterologous Robertsonian translocation rob(13q21q),+21 Down syndrome and a 46,XX, der(13;21)(q10;q10),+21 karyotype. The case has one free chromosome 13, two free chromosomes 21, and one derivative chromosome der(13;21) (arrow) containing one translocated chromosome 13q and one translocated chromosome 21q.

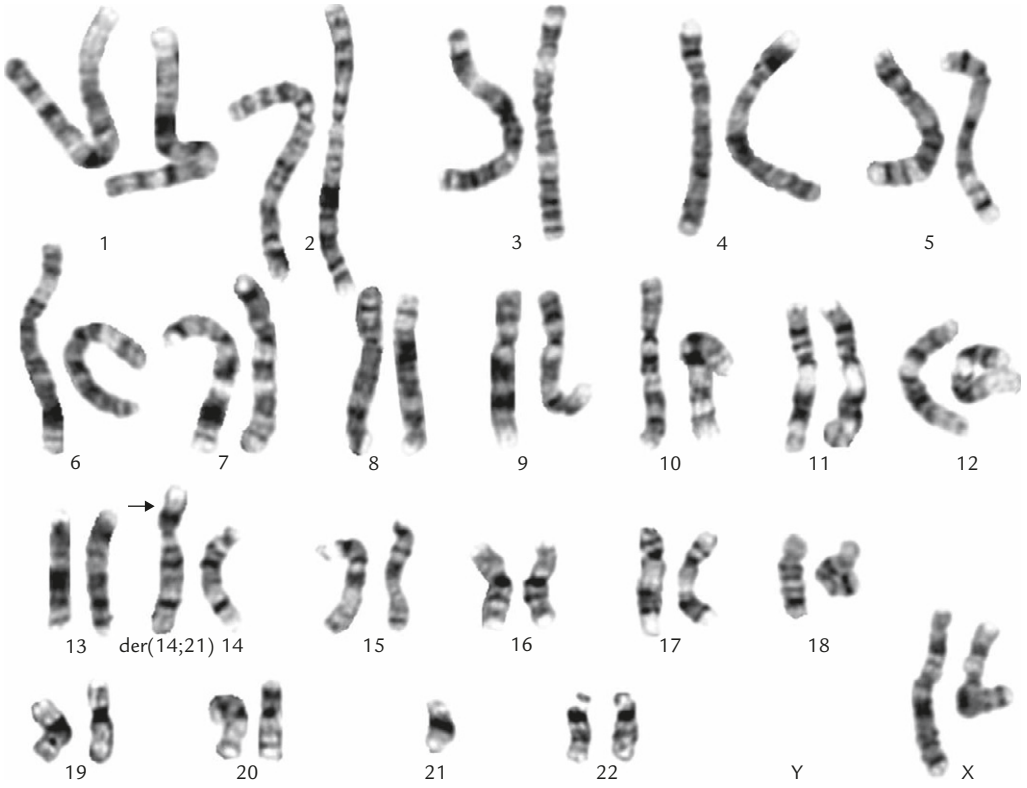

Figure 3. A case with a balanced heterologous Robertsonian translocation rob(14q21q) carrier and a 45,XX, der(14;21)(q10;q10) karyotype. The case has one free chromosome 14, one free chromosome 21, and one derivative chromosome der(14;21) (arrow) containing one translocated chromosome 14q and one translocated chromosome 21q.

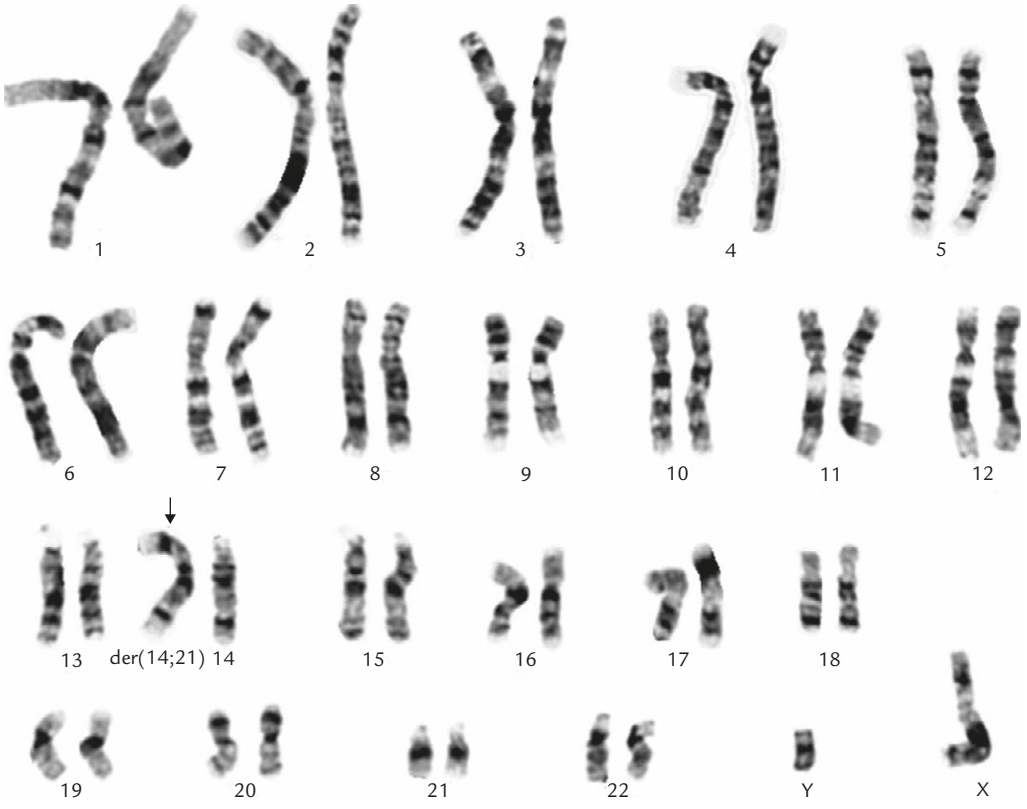

Figure 4. A case with heterologous Robertsonian translocation rob(14q21q),+21 Down syndrome and a 46,XY, der(14;21)(q10;q10),+21 karyotype. The case has one free chromosome 14, two free chromosomes 21, and one derivative chromosome der(14;21) (arrow) containing one translocated chromosome 14q and one translocated chromosome 21q.

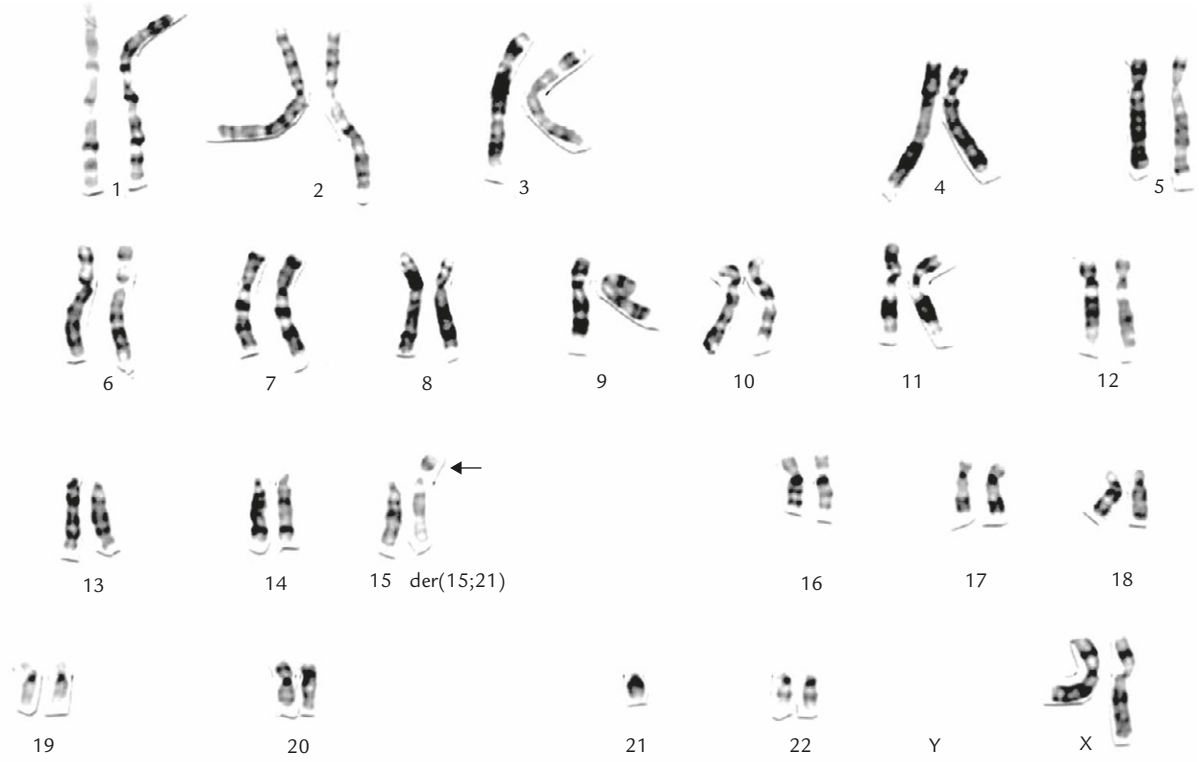

Figure 5. A case with a balanced heterologous Robertsonian translocation rob(15q21q) carrier and a 45,XX,der(15;21)(q10;q10) karyotype. The case has one free chromosome 15, one free chromosome 21, and one derivative chromosome der(15;21) (arrow) containing one translocated chromosome 15q and one translocated chromosome 21q.

amniocentesis because of an abnormal maternal serum screening result, and amniocentesis revealed Robertsonian translocation Down syndrome with der(13;21)(q10;q10),+21 in the fetus. Subsequent parental karyotyping showed that the mother was a carrier of der(13;21)(q10;q10). During this pregnancy, she underwent amniocentesis at 16 weeks of gestation, but the physician unsuccessfully performed the procedure and the woman declined a repeated amniocentesis. However, at 32 weeks of gestation, fetal ascites and hepatosplenomegaly developed. cordocentesis and amniocentesis revealed a 46,XX,der(13;21)(q10;q10),+21 karyotype. The cord blood also showed transient abnormal myelopoiesis [4]. The fetus died and the pregnancy was terminated at 36 weeks of gestation. Familial cytogenetic investigation showed that the woman's father and sister were also carriers of der(13;21)(q10;q10).

Case 2

This was the first pregnancy of a 27-year-old, gravida 1, para 0, woman. She underwent amniocentesis at 18 weeks of gestation because of an abnormal maternal serum screening result and hydrops fetalis. Amniocentesis revealed a 46,*XY*,der(14;21)(q10;q10),+21 karyotype. The parental karyotypes were normal. The fetus died and the pregnancy was terminated at 20 weeks of gestation.

Discussion

Chen et al [5] previously reported that the frequency of rea(21q21q) Down syndrome was 0.019% of cases with amniocentesis. Chen et al [6] also reported that the frequencies of unbalanced acrocentric rearrangements and balanced acrocentric rearrangements involving chromosomes other than chromosome 21 were 0.0064% and 0.0769%, respectively, of cases undergoing amniocentesis. In this report, the frequency of heterologous Robertsonian translocation Down syndrome was 0.0064% and that of balanced heterologous acrocentric rearrangements involving chromosome 21 was 0.0224% among cases undergoing amniocentesis.

Among these cases, the most common unbalanced heterologous acrocentric rearrangement involving chromosome 21 at amniocentesis was Robertsonian translocation Down syndrome. This is because of the lethality of trisomies 13, 14 and 15, the rarity of rearrangements involving chromosome 22 in early gestation, and the viability of unbalanced translocation Down syndrome progeny at the time of amniocentesis. Heterologous Robertsonian translocation Down syndrome can be detected by amniocentesis because of fetal anomalies (Cases 1 and 2), abnormal maternal serum screening (Case 2), known parental carrier status of Robertsonian

translocation (Case 1), and a previous child with translocation Down syndrome (Case 1). Balanced heterologous Robertsonian translocations involving chromosome 21 may be detected by amniocentesis because of the indications of a parental carrier status (Cases 4, 5, 8 and 9) and advanced maternal age (Cases 3, 4, 5, 6 and 7). In our study, rob(14q21q) was the most common rearrangement, followed by rob(13q21q) and rob(15q21q). Of the families with an inherited heterologous acrocentric rearrangement involving chromosome 21, 50% (3/6) were aware of their parental carrier status only after prenatal diagnosis of a fetus with a translocation by amniocentesis.

In Case 1, the fetus with Robertsonian translocation Down syndrome was inherited from a maternal carrier. Daniel et al [7] suggested that for Robertsonian translocation involving chromosome 21 and D group chromosomes (chromosomes 13, 14 and 15), the rate of unbalanced translocation trisomy 21 progeny is 10–15% among female carriers and 2–5% among male carriers. Daniel et al [7] performed a study of the prenatal results of 144 cases with a parental balanced Robertsonian translocation, including 23 cases with rob(13q21q) (14 maternal carriers and nine paternal carriers), 106 cases with rob(14q21q) (79 maternal carriers and 27 paternal carriers), and 15 cases with rob(15q21q) (nine maternal carriers and six paternal carriers). They found that among 102 cases with maternal carriers, 12 had Robertsonian translocation Down syndrome [10 with rob(14q21q),+21 and two with rob(13q21q),+21]. Meanwhile, among 42 cases with paternal carriers, only one had Robertsonian translocation Down syndrome [one with rob(14q 21q),+21].

In our study, UPD14 was not detected in any of the three cases with rob(14q21q) tested for UPD. The risk of UPD in offspring of non-homologous Robertsonian translocation carriers is low but not negligible. Shaffer et al [8] suggested that UPD testing should especially be considered for cases with prenatally identified Robertsonian translocations involving chromosomes 14 and 15. Maternal and paternal UPD14 and UPD15 are syndromic, whereas maternal and paternal UPD13, UPD21 and UPD22 have no apparent phenotypic effect [2,3]. In a meta-analysis of 477 cases of prenatally detected non-homologous Robertsonian translocations, Shaffer [9] found only three cases (0.63%) with UPD. Shaffer [9] also found no significant difference in the frequency of UPD among cases with paternally derived, maternally derived and *de novo* non-homologous Robertsonian translocations. Shaffer [9] suggested that families carrying a fetus with a non-homologous Robertsonian translocation may be advised that the risk of UPD is less than 1% (about 0.6–0.8%). Kotzot [2] suggested that after genetic counseling, prenatal UPD testing is justified if paternal UPD14, maternal UPD15 and paternal UPD15 are suspected. Prenatal diagnosis of heterologous Robertsonian translocations involving chromosome 21 should include cytogenetic analysis of the parents and UPD testing for cases involving chromosomes 14 and 15.

Acknowledgments

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