Unbalanced and Balanced Acrocentric Rearrangements Involving Chromosomes Other Than Chromosome 21 at Amniocentesis

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SUMMARY

Objective: To investigate unbalanced and balanced acrocentric rearrangements involving chromosomes other than chromosome 21 at amniocentesis.

Materials and Methods: From January 1987 to September 2009, 31,194 amniocenteses were performed at Mackay Memorial Hospital, Taipei, Taiwan. Two cases with unbalanced acrocentric rearrangements involving chromosomes other than chromosome 21 from two families, and 24 cases with balanced acrocentric rearrangements involving chromosomes other than chromosome 21 from 21 families were diagnosed and investigated.

Results: We detected i(13q13q), +13 (one case), rob(13q14q), +13 (one case), rob(13q14q) (16 cases), rob(14q15q) (five cases), rob(13q15q) (one case), rob(15q22q) (one case), and mosaic rob(14q22q) (one case). Of the 25 cases that underwent parental cytogenetic investigation, six arose *de novo* and 19 were inherited (10 maternal and nine paternal). The 16 families with an inherited Robertsonian translocation included rob(13q14q) (11 families), rob(14q15q) (four families), and rob(15q22q) (one family). Of these 16 families, only two had known parental carrier status prior to the first amniocentesis, while the other 14 were aware of a parental carrier status only after prenatal diagnosis of a fetus with a heterologous Robertsonian translocation. The 18 fetuses with balanced heterologous Robertsonian translocations inherited them from six maternal carriers of rob(13q14q), four paternal carriers of rob(13q14q), four paternal carriers of rob(14q15q), and one maternal carrier of rob(15q22q). Neither UPD14 nor UPD15 was detected in any of the 16 cases tested for UPD.

Conclusion: Concerning acrocentric rearrangements involving chromosomes other than chromosome 21, we found a frequency of 0.0064% for unbalanced rearrangements and 0.0769% for balanced rearrangements at amniocentesis in this study. rob(13q14q) was the most common and rob(14q15q) the second most common rearrangement. Of the families with an inherited translocation, 87.5% were aware of parental carrier status only after prenatal diagnosis of a fetus with a translocation by amniocentesis. [*Taiwan J Obstet Gynecol* 2009;48(4): 389–399]

Key Words: acrocentric rearrangements, amniocentesis, Robertsonian translocation, trisomy 13, uniparental disomy

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Introduction

Trisomy 13 can occur as free trisomy 13 with a free extra chromosome 13 (as in 47,XY, +13 or 47,XX, +13), as a Robertsonian translocation [such as rob(13q13q), rob(13q14q), rob(13q15q), rob (13q21q) or rob(13q22q) involving chromosome 13], or as isochromosome i(13q). Trisomy 13 syndrome or Patau syndrome is the third most common autosomal chromosome trisomy after trisomy 21 and trisomy 18. The incidence of mutant translocation trisomy 13 has been estimated at 0.012 per 1,000 live births (1/80,000) to 0.018 per 1,000 live births (1/56,000), while the incidence of familial translocation trisomy 13 has been estimated to be 0.024 per 1,000 live births (1/42,000) to 0.03 per 1,000 live births (1/33,000) [1]. In a study of spontaneous abortions, Jacobs et al [2] reported that 26% of trisomy 13 cases were translocation trisomy 13. They also found that the most common Robertsonian translocation causing interchange trisomy 13 was rob(13q14q) and that the most common translocation causing secondary trisomy 13 was rea(13q;13q) in the form of either rob(13q13q) or i(13q). The majority of cases of rea(13q13q) trisomy 13 have been identified as i(13q) following DNA polymorphism analysis [3]. Hook [4] found that the mutant proportion was about 90% for rea(13q13q) trisomy 13 cases and about 45% for rob(13q14q) trisomy 13 cases. The prevalence of the rob(13q14q) carrier is about 1 in 1,300, and the frequencies of rob(13q13q), rob(13q14q), rob(13q15q), rob(13q21q) and rob(13q22q) among all balanced Robertsonian translocations have been estimated to be 2%, 74%, 2%, 1% and 2%, respectively, by unbiased ascertainment [5].

In cases of parental non-homologous Robertsonian translocations, trisomy rescue may occur in an initially trisomic zygote or monosomy rescue after fertilization of a normal gamete by a nullisomic gamete, and such trisomy or monosomy rescues can result in uniparental disomy (UPD) from the parent that does not carry the translocation [6]. In cases of *de novo* non-homologous Robertsonian translocations, UPD from the parent whose chromosomes are involved in the translocation is also possible [6]. Maternal and paternal UPD14 and UPD15 are syndromic, whereas maternal and paternal UPD13, UPD21 and UPD22 have no apparent phenotypic effects [6,7]. Shaffer et al [8] suggested that UPD testing should be considered, especially in cases with prenatally identified Robertsonian translocations involving chromosomes 14 and 15. Kotzot [6] suggested that prenatal UPD testing was justified following genetic counseling if paternal UPD14, maternal UPD15 or paternal UPD15 were suspected. Maternal UPD14 is characterized by short stature, muscular hypotonia, precocious puberty, truncal obesity, and variable psychomotor retardation [6,7]. Paternal UPD14 is characterized by severe psychomotor retardation, polyhydramnios, mild contractures of the fingers, and bell-shaped thorax with a coat-hanger sign [6,7]. 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 [6,7]. Paternal UPD15 is associated with Angelman syndrome which is characterized by severe mental retardation, ataxia, seizures, electroencephalographic abnormalities, jerky movements, and inappropriate laughter [6,7].

Fetuses with unbalanced or balanced acrocentric rearrangements involving chromosomes other than chromosome 21 may be associated with trisomy 13, UPD14 and/or UPD15 in cases involving chromosomes 13, 14 and/or 15. Here, we present our experience of the prenatal diagnosis of unbalanced and balanced acrocentric rearrangements involving chromosomes other than chromosome 21 using amniocentesis.

Materials and Methods

From January 1987 to September 2009, 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. Two cases with unbalanced acrocentric rearrangements involving chromosomes other than chromosome 21 from two families, and 24 cases with balanced acrocentric rearrangements involving chromosomes other than chromosome 21 from 21 families were diagnosed. Cytogenetic analysis of parental blood lymphocytes was performed in 22 families. Polymorphic DNA markers were used to investigate UPD14 and/or UPD15 in 16 cases. The clinical data of the 26 cases from 23 families are summarized in the Table.

Results

In the 31,194 cases with amniocentesis, the frequency of unbalanced acrocentric rearrangements involving chromosomes other than chromosome 21 was 0.0064% (2/31,194), and the frequency of balanced

acrocentric rearrangements involving chromosomes other than chromosome 21 was 0.0769% (24/31,194).

In this study, we detected i(13q13q), +13 (one case), rob(13q14q), +13 (one case), rob(13q14q) (16 cases), rob(14q15q) (five cases), rob(13q15q) (one case), rob(15q22q) (one case), and mosaic rob(14q22q) (one case) (Figures 1–7). Of the 25 cases with parental cytogenetic investigation, six arose *de novo* and 19 were inherited (10 maternal and nine paternal). The 16 families with an inherited Robertsonian translocation included rob(13q14q) (11 families), rob(14q15q) (four families), and rob(15q22q) (one family). Among these 16 families, only two (Cases 5 and 13) had a known parental carrier status prior to the first amniocentesis, while the other 14 were aware of parental carrier status only after prenatal diagnosis of a fetus with a heterologous Robertsonian translocation. The 18 fetuses with balanced heterologous Robertsonian translocations showed inheritance from six maternal carriers of rob(13q14q), four paternal carriers of rob(13q14q), four paternal carriers of rob(14q15q), and one maternal carrier of rob(15q22q). Neither UPD14 nor UPD15 was detected in any of the 16 cases tested for UPD.

The two cases of trisomy 13 with unbalanced acrocentric rearrangements (Cases 1 and 2) prenatally manifested holoprosencephaly (HPE). The case of trisomy 13 associated with i(13)(q10) arose *de novo*. The other case of trisomy 13 associated with rob(13q14q) was inherited from a maternal carrier. The details of these two cases are as follows.

Case 1

This was the first pregnancy of a 31-year-old, gravida 1, para 0, woman who was referred for amniocentesis at 26 weeks' gestation because of abnormal sonographic findings of HPE, cebocephaly, and a ventricular septal defect. Amniocentesis revealed a 46,*XX*, +13, der(13;13)(q10;q10) karyotype. The parental karyotypes analyzed from blood lymphocytes were normal. Polymorphic DNA marker analysis showed that the rea(13q13q) was isochromosome 13 and was of maternal origin [9]. The karyotype was 46,*XX*,i(13)(q10). The pregnancy was subsequently terminated, and a dysmorphic fetus with cebocephaly and polydactyly was delivered. Her second pregnancy resulted in a healthy daughter with a 46,*XX* karyotype. Her third pregnancy resulted in a healthy boy with a 46,*XY* karyotype.

Case 2

This was the fifth pregnancy of a 39-year-old, gravida 5, para 1, woman. She had experienced three abortions and had a healthy 13-year-old boy. During her current pregnancy, she underwent amniocentesis at 20 weeks' gestation because of advanced maternal age, and the result revealed a 46,*XX*, +13,der(13;14)(q10;q10) karyotype. The paternal karyotype was 46,*XY*. The maternal karyotype was 45,*XX*,der(13;14)(q10;q10). Ultrasound at 24 weeks' gestation showed polydactyly, cebocephaly, and intrauterine growth restriction [10]. The pregnancy was subsequently terminated. The proband manifested all the prenatally observed abnormalities.

Discussion

Concerning acrocentric rearrangements involving chromosomes other than chromosome 21, we found frequencies of 0.0064% for unbalanced rearrangements and 0.0769% for balanced rearrangements among the patients undergoing amniocentesis. In our study, rob(13q14q) was the most common and rob(14q15q) the second most common rearrangement. Of the families with an inherited translocation, 87.5% (14/16) were aware of parental carrier status only after prenatal diagnosis of a fetus with a translocation. Our results show that unbalanced acrocentric rearrangements involving chromosomes other than chromosome 21 can be detected by amniocentesis performed because of advanced maternal age (Case 2) or fetal anomalies, especially HPE (Cases 1 and 2). Balanced acrocentric rearrangements involving chromosomes other than chromosome 21 may also be detected by amniocentesis performed for advanced maternal age (Cases 3–8, 13, 14, 16, 19 and 21–23), abnormal maternal serum screening results (Cases 10–12, 17, 20-1), maternal carrier status (Cases 13, 16-2 and 16-3), paternal carrier status (Cases 5 and 20-2), abnormal ultrasound findings (Case 9), or an elective cause (Case 15).

In our study, neither UPD14 nor UPD15 was detected among 16 cases tested for UPD. The risk of UPD in offspring of non-homologous Robertsonian translocation carriers has been shown to be low but not negligible. In a meta-analysis of 477 cases of prenatally detected non-homologous Robertsonian translocations, Shaffer [11] found only three cases (0.63%) with UPD. The author also found no significant difference in the frequency of UPD among the groups of paternally derived, maternally derived and *de novo* nonhomologous Robertsonian translocations. Shaffer [11] suggested that families carrying a fetus with a nonhomologous Robertsonian translocation may be advised that the risk of UPD is less than 1% (about 0.6–0.8%). Gualandi et al [12] found no UPD among 23 fetuses with balanced Robertsonian translocations and summarized an additional 55 cases with no UPD. Jay et al

Table. Clinical data for cases with unbalanced and balanced acrocentric rearrangements involving chromosomes other than chromosome 21 diagnosed by amniocentesis

Case	Indication for amniocentesis	Maternal age (yr)	Gestational age at amniocentesis (wk)	Karyotype of fetus	Parental karyotype	UPD test	Carrier status	Inheritance
1	HPE	31	26	46,XX,i(13)(q10)	46,XY 46,XX	–	UK	*De novo*
2	HPE, AMA	39	20	46,XX, +13,der(13;14)(q10;q10)	46,XY 45,XX,der(13;14)(q10;q10)	No UPD14	UK	Maternal
3	AMA	34	18	45,XX,der(13;14)(q10;q10)	46,XY 45,XX,der(13;14)(q10;q10)	No UPD14	UK	Maternal
4	AMA	35	20	45,XX,der(13;14)(q10;q10)	46,XY 45,XX,der(13;14)(q10;q10)	No UPD14	UK	Maternal
5*	AMA, paternal carrier	34	19	45,XY,der(13;14)(q10;q10)	45,XY,der(13;14)(q10;q10) 46,XX	No UPD14	K	Paternal
6	AMA	36	20	45,XY,der(13;14)(q10;q10)	46,XY 46,XX	No UPD14	UK	*De novo*
7	AMA	37	18	45,XY,der(13;14)(q10;q10)	46,XY 46,XX	No UPD14	UK	*De novo*
8	AMA	34	17	45,XY,der(13;14)(q10;q10)	46,XY 45,XX,der(13;14)(q10;q10)	No UPD14	UK	Maternal
9†	Polyhydramnios, CDH	30	34	45,XY,der(13;14)(q10;q10)	–	–	–	–
10	Down risk of 1/253	31	21	45,XY,der(13;14)(q10;q10)	45,XY,der(13;14)(q10;q10) 46,XX	–	UK	Paternal
11	Down risk of 1/177	34	25	45,XX,der(13;14)(q10;q10)	45,XY,der(13;14)(q10;q10) 46,XX	–	UK	Paternal
12	Down risk of 1/202	31	19	45,XY,der(13;14)(q10;q10)	46,XY 45,XX,der(13;14)(q10;q10)	–	UK	Maternal
13‡	AMA, maternal carrier	40	16	45,XX,der(13;14)(q10;q10)	46,XY 45,XX,der(13;14)(q10;q10)	No UPD14	K	Maternal

14	AMA	35	17	45,XX,der(13;14)(q10;q10)	46,XY 46,XX	No UPD14	UK	*De novo*
15	Maternal anxiety	21	23	45,XX,der(13;14)(q10;q10)	45,XY,der(13;14)(q10;q10) 46,XX	–	UK	Paternal
16-1	AMA	34	20	45,XX,der(13;14)(q10;q10)	46,XY 45,XX,der(13;14)(q10;q10)	–	UK	Maternal
16-2	AMA, maternal carrier	36	15	45,XY,der(13;14)(q10;q10)	The same as 16-1	–	K	Maternal
16-3	AMA, maternal carrier	37	16	45,XY,der(13;14)(q10;q10)	The same as 16-1	No UPD14	K	Maternal
17	Down risk of 1/106	30	18	45,XY,der(14;15)(q10;q10)	45,XY,der(14;15)(q10;q10) 46,XX	No UPD14 No UPD15	UK	Paternal
18	Abnormal Down risk	29	18	45,XX,der(14;15)(q10;q10)	45,XY,der(14;15)(q10;q10) 46,XX	No UPD14 No UPD15	UK	Paternal
19	AMA	36	16	45,XX,der(14;15)(q10;q10)	45,XY,der(14;15)(q10;q10) 46,XX	No UPD14 No UPD15	UK	Paternal
20-1	Down risk of 1/5	32	19	45,XX,der(14;15)(q10;q10)	45,XY,der(14;15)(q10;q10) 46,XX	–	UK	Paternal
20-2	Paternal carrier	33	18	45,XX,der(14;15)(q10;q10)	The same as 20-1	No UPD14 No UPD15	K	Paternal
21	AMA	38	17	45,XX,dic(13;15)(p11.2;p11.2)	46,XY 46,XX	No UPD15	UK	*De novo*
22	AMA	38	16	45,XY,der(15;22)(q10;q10)	46,XY 45,XX,der(15;22)(q10;q10)	–	UK	Maternal
23	AMA	37	18	45,XY,der(14;22)(q10;q10)[12]/ 46,XY[14]	46,XY 46,XX	No UPD14	UK	*De novo*

**Known parental carrier status because of infertility and paternal oligospermia; †cordocentesis was performed simultaneously; ‡known parental carrier status because of habitual abortion. UPD = uniparental disomy; carrier = carrier of Robertsonian translocation; HPE = holoprosencephaly; – = not checked; UK = unknown at amniocentesis; AMA = advanced maternal age; K = known at amniocentesis; CDH = congenital diaphragmatic hernia.*

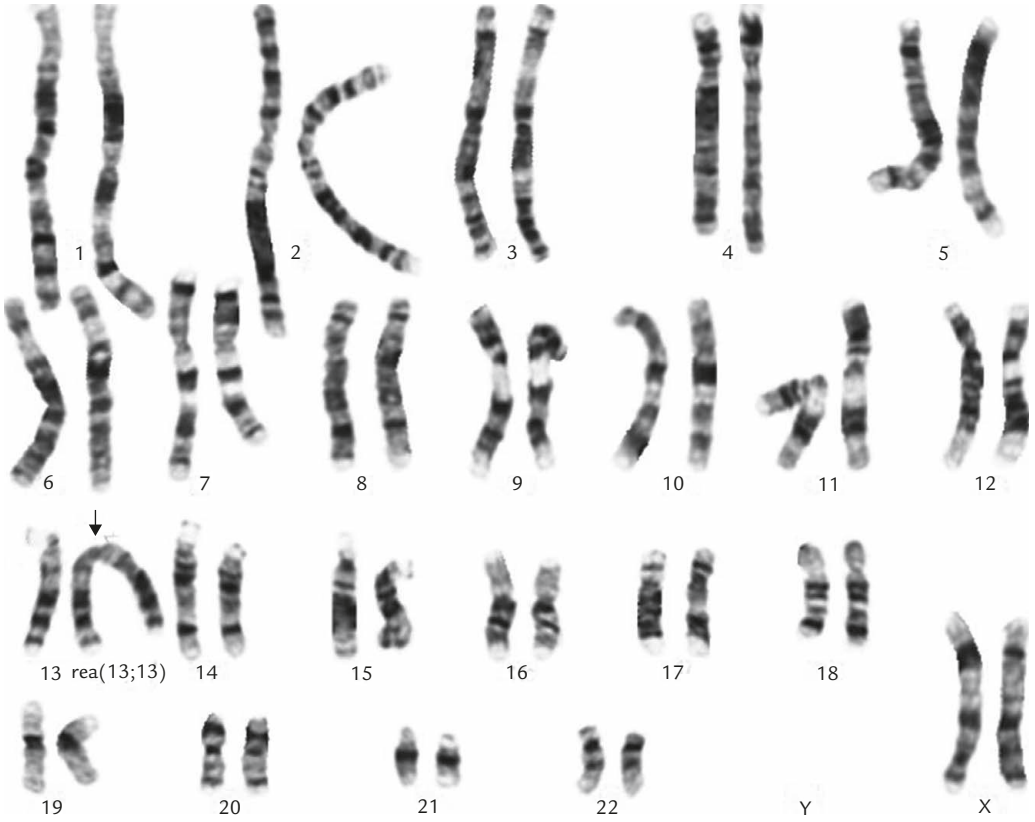

Figure 1. A case of rea(13q13q) trisomy 13 with a 46,XX,i(13)(q10) karyotype. There is one free chromosome 13 and one isochromosome 13 (arrow).

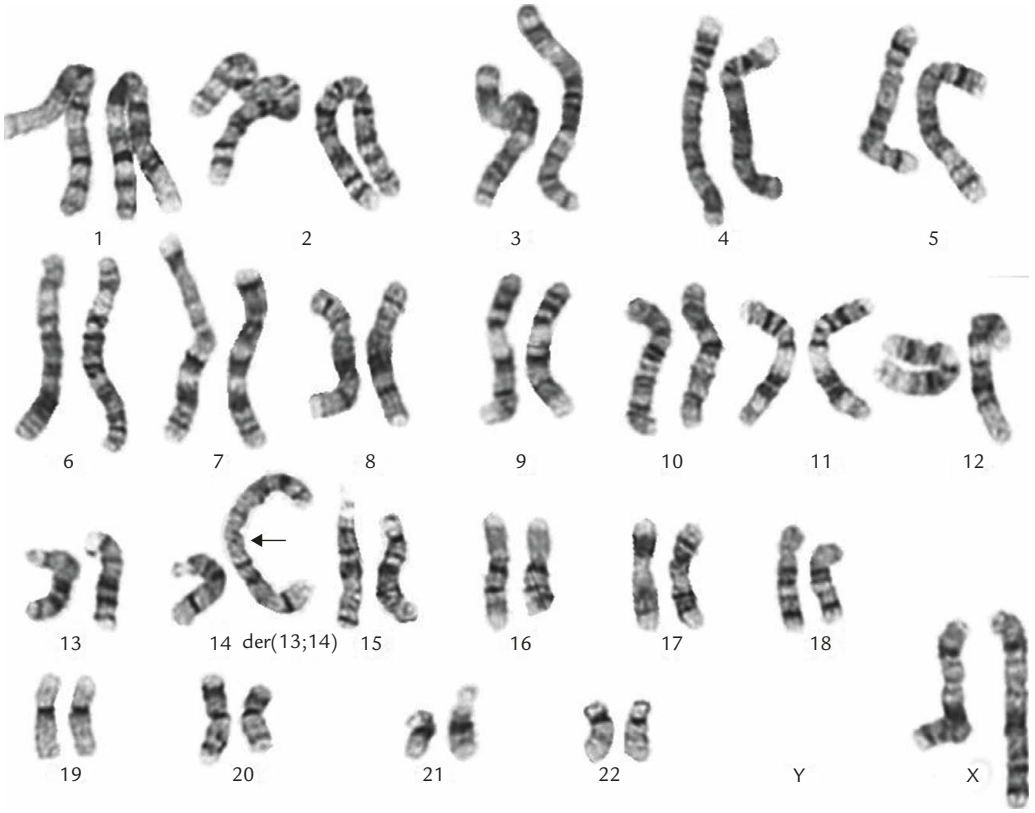

Figure 2. A case of heterologous Robertsonian translocation trisomy 13 with a 46,XX, +13,der(13;14)(q10;q10) karyotype. There are two free chromosomes 13, one free chromosome 14, and one derivative chromosome der(13;14) (arrow) containing one translocated chromosome 13q and one translocated chromosome 14q.

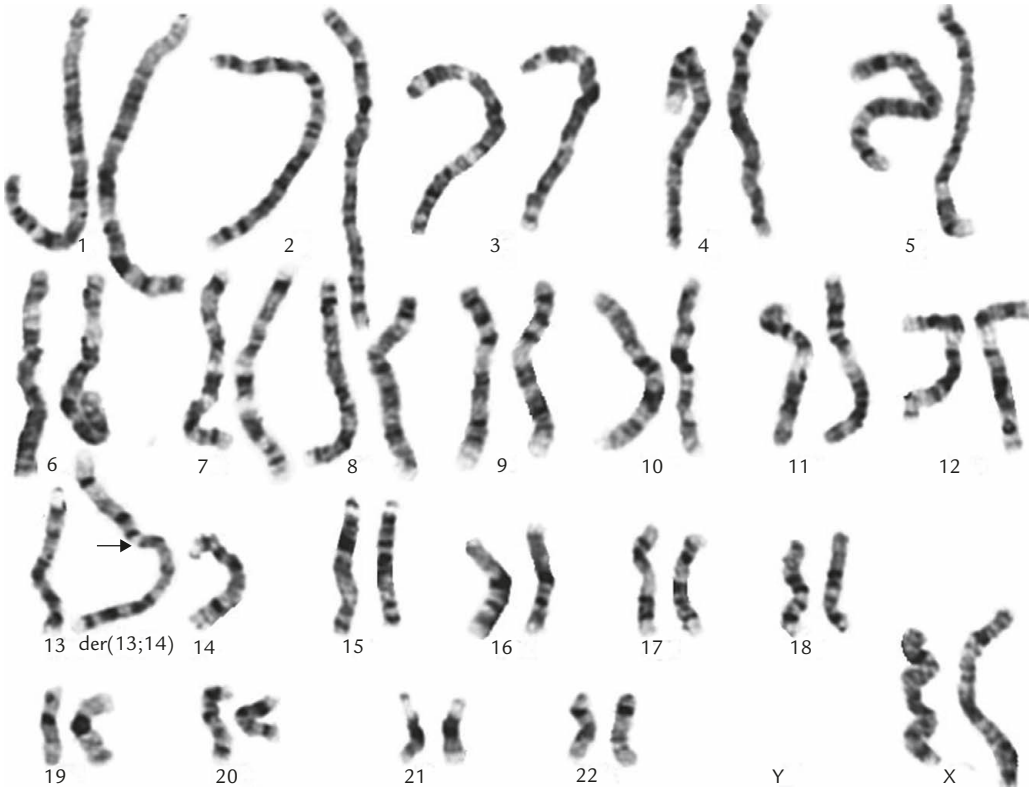

Figure 3. A case of balanced heterologous Robertsonian translocation rob(13q14q) carrier with a 45,XX,der(13;14)(q10;q10) karyotype. There is one free chromosome 13, one free chromosome 14, and one derivative chromosome der(13;14) (arrow) containing one translocated chromosome 13q and one translocated chromosome 14q.

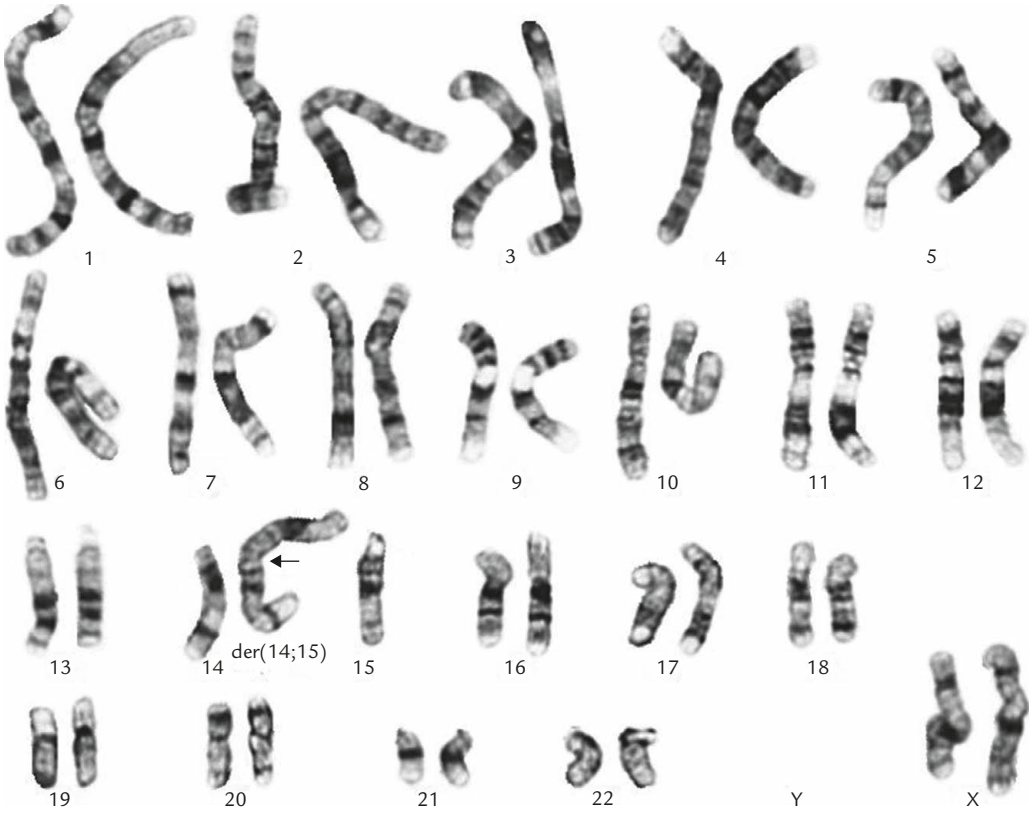

Figure 4. A case of balanced heterologous Robertsonian translocation rob(14q15q) carrier with a 45,XX,der(14;15)(q10;q10) karyotype. There is one free chromosome 14, one free chromosome 15, and one derivative chromosome der(14;15) (arrow) containing one translocated chromosome 14q and one translocated chromosome 15q.

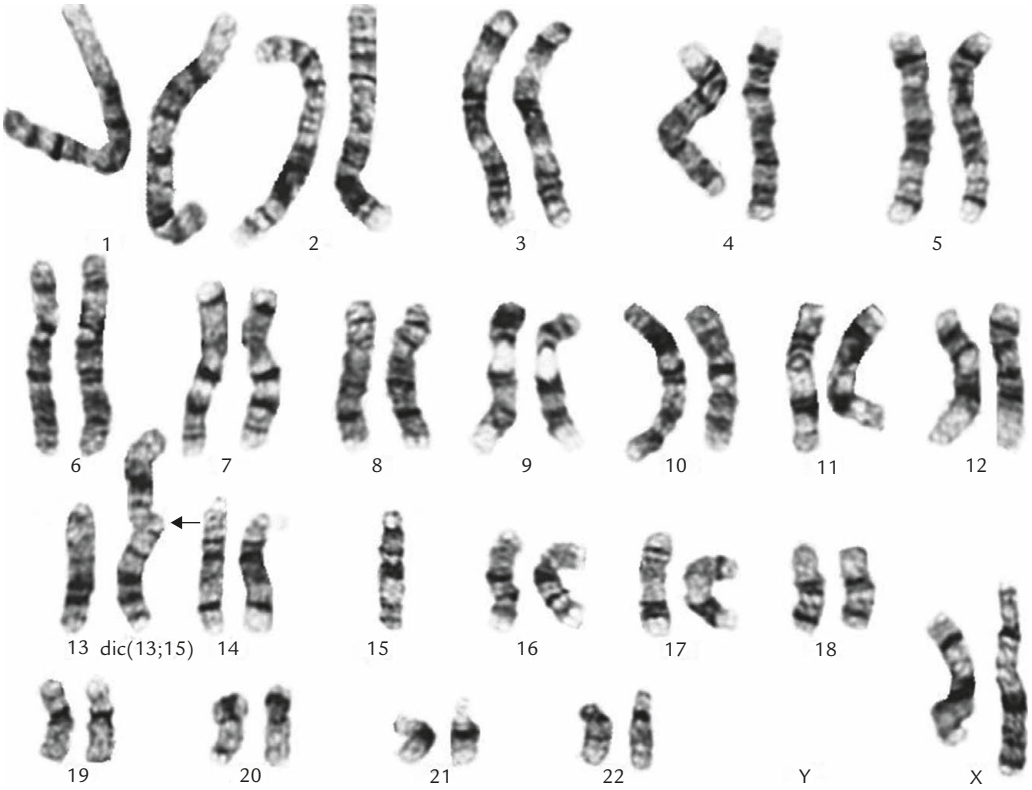

Figure 5. A case of balanced heterologous Robertsonian translocation rob(13q15q) carrier with a dicentric chromosome and a 45,XX,dic(13;15)(p11.2;p11.2) karyotype. There is one free chromosome 13, one free chromosome 15, and one dicentric chromosome dic(13;15) (arrow) containing one translocated chromosome 13 (13p11.2 → qter) and one translocated chromosome 15 (15p11.2 → qter).

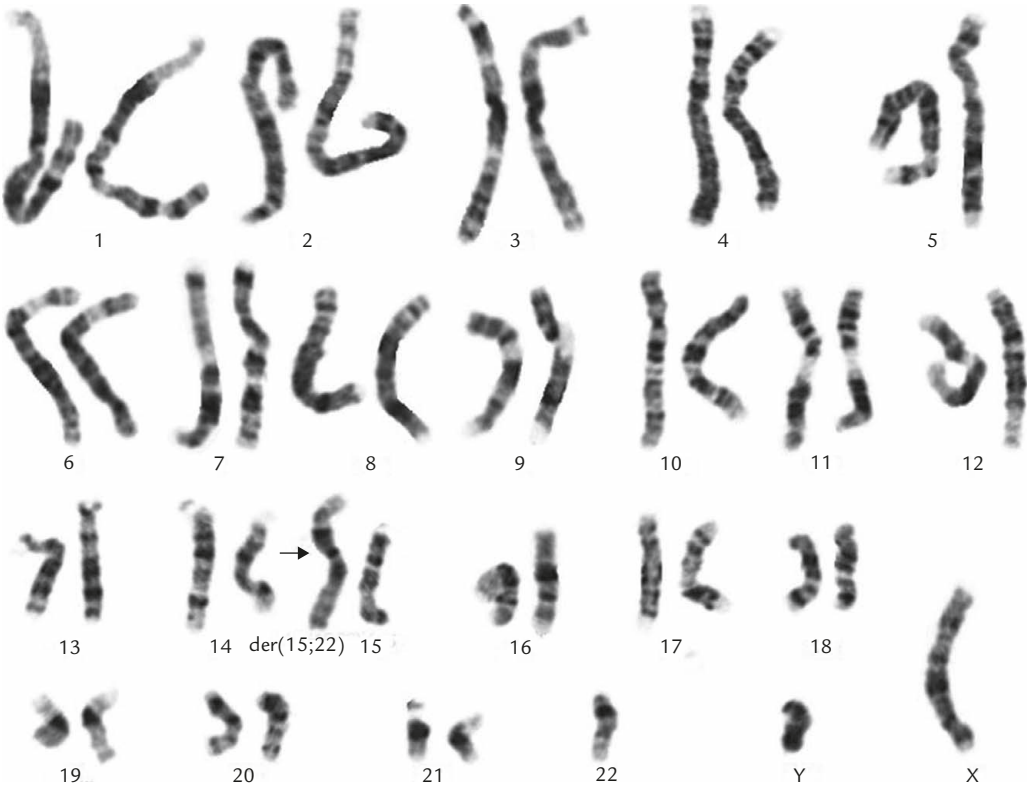

Figure 6. A case of balanced heterologous Robertsonian translocation rob(15q22q) carrier with a 45,XY,der(15;22)(q10;q10) karyotype. There is one free chromosome 15, one free chromosome 22, and one derivative chromosome der(15;22) (arrow) containing one translocated chromosome 15q and one translocated chromosome 22q.

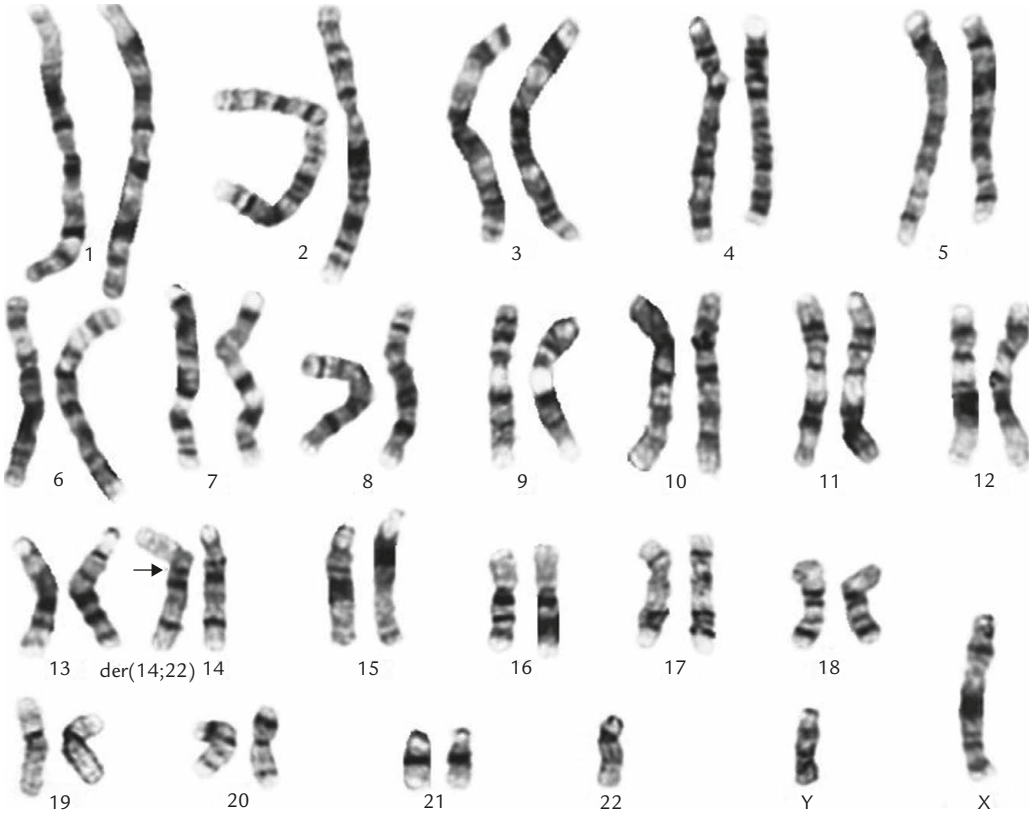

Figure 7. A case of mosaic balanced heterologous Robertsonian translocation rob(14q22q) carrier with a 45,XY,der(14;22)(q10;q10)/46,XY karyotype. The 45,XY,der(14;22)(q10;q10) karyotype shows one free chromosome 14, one free chromosome 22, and one derivative chromosome der(14;22) (arrow) containing one translocated chromosome 14q and one translocated chromosome 22q.

[13] investigated 22 cases of balanced Robertsonian translocations and found no UPD. Silverstein et al [14] studied 42 fetuses with non-homologous Robertsonian translocations and found one fetus with rob(13q14q) and maternal isodisomy of chromosome 14. They summarized an additional 273 cases from Berend et al [15], Gualandi et al [12] and Jay et al [13], and concluded that the risk of UPD was 0.63% (2/315; 95% confidence interval, 0.2–2.3%) in prenatally diagnosed non-homologous Robertsonian translocations. Sensi et al [16] studied 160 fetuses with non-homologous Robertsonian translocations and found one case of upd(14)mat with a 45,XX,der(14;22)(q10;q10)mat karyotype. They summarized an additional 243 cases from Eggermann et al [17], Berend et al [15], Silverstein et al [14] and their additional cases, and concluded that the risk of UPD was 0.74% (3/403; 95% confidence interval, 0.17–2.34%) in prenatally diagnosed non-homologous Robertsonian translocations. In a study of 65 fetuses carrying familial and *de novo* non-homologous Robertsonian translocations involving chromosomes 14 and/or 15, and 18 fetuses who were conceived by a Robertsonian translocation carrier parent and had a normal karyotype, Ruggeri et al [18] found one case of upd(14)mat with *de novo* rob(14q21q).

We found a *de novo* case of trisomy 13 with an i(13q) of maternal origin (Case 1). This case had no recurrence of trisomy 13 in two subsequent pregnancies. Hassold et al [19] reported one *de novo* case of rea(13q13q) trisomy 13 with an i(13q) of paternal origin. Shaffer et al [20] studied four *de novo* cases of rea(13q13q) trisomy 13 and found that all were dicentric, two were i(13q) of maternal origin, one was i(13q) of paternal origin, and one was rob(13q13q) of maternal origin. Robinson et al [21] reported two *de novo* cases of rea(13q13q) trisomy 13, both of which were i(13q) of maternal origin. Bugge et al [3] studied six *de novo* cases of rea(13q13q) of trisomy 13, and found one i(13q) case of maternal origin, four i(13q) cases of paternal origin, and one rob(13q13q) case of maternal origin. Of the 14 cases of *de novo* rea(13q13q) reported in the literature, two were rob(13q13q) of maternal origin, six were i(13q) of maternal origin, and six were i(13q) of paternal origin. In view of the equal number (6:6) of maternal- and paternal-derived cases of i(13q), Bugge et al [3] suggested that the majority of cases of trisomy 13 due to rea(13q13q) were i(13q) caused by postzygotic events. As for the two rob(13q13q) trisomy 13 cases, the maternal origin of rob(13q13q) may have arisen during oogenesis.

In our study, we detected only one unbalanced rearrangement (Case 2 with translocation trisomy 13) among 19 fetuses from 16 families with an inherited Robertsonian translocation. In a study of 230 cases of amniocentesis performed because of rob(13q14q) carrier mothers (157 cases) or rob(13q14q) fathers (73 cases), Boué and Gallano [22] found no unbalanced results. In a study of 204 cases who underwent prenatal diagnosis because of the presence of parental carriers of a balanced rob(13q14q) translocation, Daniel et al [23] found one case of translocation trisomy 13 among 136 carrier mothers and two cases of translocation trisomy 13 among 68 carrier fathers. In their study, the rate of translocation trisomy 13 to female or male carriers of Robertsonian (13;14) translocation was 1–2%. Robinson et al [21] reported an interesting translocation trisomy 13 case in which the extra chromosome 13 was derived from a maternal meiotic event and the derivative chromosome rob(13q14q) was inherited from the father. Since there is no significantly increased risk of unbalanced offspring for a rob(13q14q) carrier and because most trisomies are maternal in origin, Robinson et al [21] believed this interesting case was not surprising. In a study of 15 cases of amniocentesis performed because of rob(13q15q) carrier parents, Boué and Gallano [22] found no unbalanced results, and Daniel et al [23] also found no unbalanced results in a study of 16 cases of amniocentesis performed because of rob(13q15q) carrier parents. In a study of 31 cases of amniocentesis performed because of rob(13q21q) carrier mothers (20 cases) or rob(13q21q) carrier fathers (11 cases), Boué and Gallano [22] found two translocation trisomy 21 fetuses, all in carrier mothers. In a study of 23 cases of amniocentesis performed because of rob(13q21q) carrier mothers (14 cases) or rob(13q21q) carrier fathers (nine cases), Daniel et al [23] found two translocation trisomy 21 fetuses, also all in carrier mothers. They suggested that there was a 10–15% rate of unbalanced translocation trisomy 21 progeny for female carriers of Robertsonian (D group chromosome;21) translocations, while the rate was 2–5% for males. However, the risk of having a child with translocation trisomy 13 or UPD for rob(13q14q), rob(13q15q), rob(13q21q) and rob(13q22q) carriers is low. For rob(13q14q), rob(13q15q), rob(13q21q) and rob (13q22q) carriers, Gardner and Sutherland [5] suggested a risk of ≤ 1% for translocation trisomy 13 and < 0.5% risk for UPD14 and/or UPD15.

Both of our two cases with trisomy 13 caused by unbalanced acrocentric rearrangements manifested HPE on prenatal ultrasound. The phenotypic features of unbalanced translocation trisomy 13 or rea(13q13q) trisomy 13 are basically the same as those of free trisomy 13. Fetuses with translocation trisomy 13 or rea(13q13q) trisomy 13 may predominantly present with HPE on prenatal ultrasound, since HPE is associated with as many as 70% of trisomy 13 cases [24–26]. Prenatal sonographic detection of HPE should prompt cytogenetic investigations that may lead to the identification of an unexpected parental Robertsonian translocation involving chromosome 13.

In conclusion, we have presented the results of prenatal diagnostic examinations for unbalanced and balanced acrocentric rearrangements involving chromosomes other than chromosome 21, using amniocentesis, parental cytogenetic analysis, and UPD investigation. We suggest that prenatal diagnosis of acrocentric rearrangements should include cytogenetic analysis of the parents and UPD testing for cases involving chromosomes 14 and 15.

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