Balanced Reciprocal Translocations Detected at Amniocentesis

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SUMMARY

Objective: To present perinatal findings, modes of ascertainment and parental decision in balanced reciprocal translocations detected at amniocentesis.

Materials and Methods: Between January 1987 and August 2010, 82 cases with a simple reciprocal translocation, two cases with two separate simple reciprocal translocations and three cases with a complex chromosome rearrangement (CCR) were diagnosed by amniocentesis at Mackay Memorial Hospital, Taipei, Taiwan. The 87 cases originated from 76 families; 65 families with one case and 11 families with two cases.

Results: In the 76 families, the main modes of ascertainment included advanced maternal age ($n=38$), a previous child with an unbalanced reciprocal translocation ($n=11$), recurrent miscarriage ($n=9$), abnormal maternal serum screening results ($n=9$), elective causes ($n=5$), a previous child with congenital anomalies ($n=2$) and abnormal ultrasound findings ($n=2$). In these families, there were 17 (22.4%) *de novo* cases including 14 simple translocations and three CCRs. Of 14 *de novo* cases with a simple translocation, one (7.1%) manifested a congenital malformation, which was related to an X-autosome translocation, and four (28.6%) were terminated. Of three *de novo* CCRs, two manifested congenital anomalies and one was terminated. In 87 cases, additional aneuploidy was noted in two cases including one inherited simple translocation with Turner syndrome, and one *de novo* CCR with concomitant deletions and duplication.

Conclusion: Balanced reciprocal translocations detected at amniocentesis may be associated with fetal anomalies in cases of concomitant aneuploidy, *de novo* X-autosome translocation or *de novo* CCR. Genetic counseling of a *de novo* simple reciprocal translocation at amniocentesis remains difficult because approximately one-fourth of the parents opt for termination of the pregnancy, and detailed ultrasonography and array comparative genomic hybridization are helpful for parental counseling under such circumstances. [*Taiwan J Obstet Gynecol* 2010;49(4):455–467]

Key Words: amniocentesis, balanced reciprocal translocation

Introduction

Balanced reciprocal translocations are the most frequent chromosome rearrangements in humans, occurring in 0.16–0.20% (1/625–1/500) of live births [1–3]. A simple reciprocal translocation is produced when

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there is a two-way exchange between two chromosomes in which two chromosomal segments from two chromosomes break off, translocate, and unite. In addition to simple reciprocal translocations, there are rare complex reciprocal translocations such as multiple chromosome rearrangements (MCRs) and complex chromosome rearrangements (CCRs). A MCR, or a double chromosome rearrangement, is produced when there are two separate simple translocations with double two-way exchanges. A CCR is produced when there are three or more breakpoints located on two or more chromosomes [4]. The most common type of CCR is a three-way exchange in which three chromosomal segments break off, translocate, and unite [5].

Amniocentesis may detect inherited or *de novo* balanced reciprocal translocations. In cases with inherited translocations, the parents may know their carrier status prior to amniocentesis, or may be aware of their carrier status only after detection of fetal translocations at amniocentesis. We present our experience of prenatal diagnosis of balanced reciprocal translocations detected at amniocentesis.

Materials and Methods

Between January 1987 and August 2010, balanced reciprocal translocations were diagnosed by amniocentesis in 87 cases, including 82 cases with a simple reciprocal translocation, two cases with two separate simple reciprocal translocations of an MCR, and three cases with a complex reciprocal translocation of a CCR at Mackay Memorial Hospital, Taipei, Taiwan. Various reasons for these findings included advanced maternal age, abnormal ultrasound findings, abnormal maternal serum screening results, a previous aneuploid child in the obstetric history or in the family, and a family history of congenital anomalies or chromosomal aberration, among others. Cytogenetic analyses of parental blood lymphocytes were performed in all cases. The clinical data of the 87 cases are summarized in the Table.

Results

In this study, the 87 cases of balanced reciprocal translocations originated from 76 families; 65 families with one case and 11 families (families 4, 7, 21, 33, 38, 43, 44, 47, 50, 58 and 63) with two cases. Of these 87 cases, the mean gestational age at amniocentesis was 18.43 ± 2.97 weeks (range, 14–30 weeks) and the mean maternal age at amniocentesis was 32.61 ± 4.22 years (range, 20–40 years).

Among these 87 cases, there were three CCRs (cases 35, 61 and 76) (3.4%), two MCRs (cases 16 and 69; 2.3%) and 82 (94.3%) simple reciprocal translocations. The three cases of CCRs arose *de novo*. Case 35 [t(5;8;15)(q33.3;q11.21;q26.1)] was ascertained through elective causes. The parents decided to continue the twin pregnancy, which resulted in an abnormal co-twin (case 35) with a CCR, hypoplastic left heart, mitral stenosis and neonatal death, and a normal co-twin with a normal chromosome complement and a favorable outcome. Case 61 [t(1;5;8)(p13;q14;p23.1)] was determined through advanced maternal age. The parents decided to continue the pregnancy, which resulted in a normal child. Case 76 [t(2;18;14)(q33.1;q12.2;q31.2), dup(5)(q34q34), del(7)(p21.1p21.1), del(10)(q25.3q25.3)] was ascertained through abnormal maternal serum screening results. The parents decided to terminate the pregnancy, which resulted in an abnormal fetus with multiple malformations. The two cases of MCRs were concomitant *de novo* and inherited translocations. Case 16 [t(5;12)(q33;q13)dn t(11;22)(q23.3;q11.2)mat] was determined through maternal carrier status identification because of a previous aneuploid child. The parents decided to continue the pregnancy, which resulted in a normal child. Case 69 [t(7;11)(q22;p15)dn t(9;20)(q21;p11.2)mat] was ascertained through advanced maternal age. The mother was aware of her carrier status only after the diagnosis, and the parents decided to continue the pregnancy, which resulted in a normal child.

Two cases (cases 49 and 76) were associated with additional chromosomal aberration. Case 49 was associated with Turner syndrome and cystic hygroma. Case 76 was associated with multiple deletions, a duplication and dysmorphisms. Of the 87 cases with balanced reciprocal translocations, three (cases 35, 45 and 49; 3.4%) were associated with abnormal ultrasound findings and four (35, 45, 49 and 76; 4.6%) were associated with congenital anomalies.

Among the 76 families, the main modes of ascertainment included advanced maternal age (n = 38), parental carrier status identified through a previous aneuploid child with an unbalanced reciprocal translocation in the obstetric history or in the family (n = 11), parental carrier status identified through recurrent miscarriage (n = 9), abnormal maternal serum screening results (n = 9), elective causes (n = 5), a previous child with structural anomalies or common aneuploidy (n = 2), and abnormal ultrasound findings (n = 2). Of these families, two (families 16 and 69; 2.6%) were associated with concomitant *de novo* and inherited translocations, 15 (families 3, 6, 13, 14, 31, 35, 37, 41, 45, 53, 57, 61, 65, 68 and 76; 19.7%) were associated with only *de novo* translocations, and 59 (77.6%) were associated with

Table. Clinical data for cases with balanced reciprocal translocations diagnosed by amniocentesis

Family/ Case	Indication for amniocentesis	Maternal age (yr)	Gestational age at amniocentesis (wk)	Fetal karyotype	Inheritance of translocation	Carrier status	Parental decision and perinatal findings in the *de novo* case and the anomalous case
1	AMA	39	19	46,XY,t(5;11)(p15.1;q14.2)pat	Paternal	UK	
2	Elective cause	29	18	46,XX,t(5;10)(q33.1;q24.1)mat	Maternal	UK	
3	AMA	38	18	46,XY,t(3;6)(q26.2;p21.2)dn (Figure 1)	*De novo*	UK	Continuing pregnancy, normal ultrasound findings, normal aCGH result
4-1	Maternal carrier status†	27	17	46,XX,t(12;13)(q24.3;q34)mat	Maternal	K	
4-2	The same mother as 4-1	28	18	46,XY,t(12;13)(q24.3;q34)mat	The same as 4-1	K	
5	Maternal carrier status†	32	24	46,XY,t(10;11)(q23;q25)mat	Maternal	K	
6	Elective cause	33	16	46,XX,t(7;10)(q31.2;q24.1)dn	*De novo*	UK	Termination, no ultrasound abnormalities
7-1	AMA	35	19	46,XY,t(1;2)(p22;q31)mat	Maternal	UK	
7-2	The same mother as 7-1	37	17	46,XX,t(1;2)(p22;q31)mat	The same as 7-1	K	
8	AMA	34	17	46,XX,t(8;14)(p10;q10)pat	Paternal	UK	
9	AMA	38	18	46,XX,t(6;14)(q27;q22)mat	Maternal	UK	
10	AMA	36	18	46,XY,t(Y;15)(q12;p13)pat	Paternal	UK	
11	Abnormal maternal serum screening result (Down risk=1/197)	33	19	46,XY,t(8;12)(p21.1;q22)mat	Maternal	UK	
12	AMA	36	17	46,XX,t(9;15)(q22;q11.2)mat	Maternal	UK	
13	AMA	37	18	46,XY,t(4;14)(q32;q32.1)dn	*De novo*	UK	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth
14	Elective cause	32	19	46,XY,t(8;10)(q12.2;q26.3)dn	*De novo*	UK	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth
15	AMA	34	17	46,XY,t(11;22)(q23.3;q11.2)pat	Paternal	UK	
16	Maternal carrier status†	31	17	46,XY,t(5;12)(q33;q13)dn t(11;22)(q23.3;q11.2)mat (Figure 4)	*De novo* Maternal	K	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth
17	AMA	34	17	46,XY,t(7;11)(p14;q13)mat	Maternal	UK	
18	AMA	36	18	47,XY,t(17;18)(q11.1;q11.2), +mar mat	Maternal	UK	
19	Paternal carrier status‡	31	17	46,XY,t(4;5)(q31.3;q22)pat	Paternal	K	
20	Paternal carrier status‡	29	17	46,XY,t(1;5)(p36.13;q31.1) pat,9qh+ pat	Paternal	K	

Table. *(Continued)*

Family/ Case	Indication for amniocentesis	Maternal age (yr)	Gestational age at amniocentesis (wk)	Fetal karyotype	Inheritance of translocation	Carrier status	Parental decision and perinatal findings in the *de novo* case and the anomalous case
21-1	Maternal carrier status†	32	18	46,XY,t(10;18)(q11.2;p11.2)mat	Maternal	K	
21-2	The same mother as 21-1	34	18	46,XY,t(10;18)(q11.2;p11.2)mat	The same as 21-1	K	
22	AMA	35	19	46,XX,t(3;11)(q29;q23.1)mat	Maternal	UK	
23	Paternal carrier status‡	32	17	46,XX,t(1;2)(q43;q32.1)pat	Paternal	K	
24	Maternal carrier status*†, AMA	34	17	46,XX,t(9;12)(p11.2;p13.3)mat	Maternal	K	
25	AMA	37	18	46,XY,t(2;7)(p25.1;q31.2)mat	Maternal	UK	
26	AMA	40	18	46,XY,t(1;4)(p22.3;q31.3)pat	Paternal	UK	
27	Paternal carrier status†	27	16	46,XX,t(3;11)(p21;q23)pat	Paternal	K	
28	AMA	36	20	46,XY,t(5;11)(q13;q25)mat	Maternal	UK	
29	AMA	36	17	46,XX,t(1;10)(p10;p10)mat	Maternal	UK	
30	Maternal carrier status‡	28	19	46,XX,t(3;6)(q22;q25.3)mat	Maternal	K	
31	Elective cause	32	21	46,XX,t(4;10)(p10;p10)dn	*De novo*	UK	Termination, no ultrasound abnormalities
32	AMA	37	19	46,XY,t(1;13)(p13;q14)mat	Maternal	UK	
33-1	Maternal carrier status†	30	18	46,XY,t(3;11)(q21;q23)mat	Maternal	K	
33-2	The same mother as 33-1	31	18	46,XY,t(3;11)(q21;q23)mat	The same as 33-1	K	
34	Previous child with anencephaly	27	16	46,XX,t(10;13)(q26;q14.1)pat	Paternal	UK	
35	Elective cause	33	18	46,XX,t(5;8;15)(q33.3;q11.21; q26.1)dn, 1qh+ mat (Figure 5)	*De novo*	UK	Continuing pregnancy, abnormal ultrasound findings of congenital heart defects, preterm delivery, hypoplastic left heart, severe mitral stenosis at birth, neonatal death
36	AMA	34	17	46,XX,t(5;18)(q15;q11.2)pat	Paternal	UK	
37	AMA	35	16	46,XY,t(11;22)(q23.3;q11.2)dn	*De novo*	UK	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth
38-1	Paternal carrier status†	20	17	46,XY,t(10;22)(q24.1;p11.2)pat	Paternal	K	
38-2	The same mother as 38-1	21	18	46,XY,t(10;22)(q24.1;p11.2)pat	The same as 38-1	K	
39	Abnormal maternal serum screening result (Down risk=1/88)	27	17	46,XY,t(1;2)(p22;p23)pat	Paternal	UK	

40	Abnormal maternal serum screening result (Down risk = 1/20)	24	16	46,XX,t(2;17)(q11;q22)mat	Maternal	UK	
41	AMA	34	27	46,XX,t(3;9)(q13.3;q34.1)dn	*De novo*	UK	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth
42	Previous child with Down syndrome	31	20	46,XY,t(4;7)(p10;q10)pat	Paternal	UK	
43-1	Maternal carrier status†	30	18	46,XX,t(4;15)(p16;p11.1)mat	Maternal	K	
43-2	The same mother as 43-1	31	23	46,XX,t(4;15)(p16;p11.1)mat	The same as 43-1	K	
44-1	Paternal carrier status‡	31	25	46,XX,t(16;19)(p10;p10)pat	Paternal	K	
44-2	The same mother as 44-1	33	15	46,XY,t(16;19)(p10;p10)pat	The same as 44-1	K	
45	Hydrocephalus	28	26	46,X,t(X;7)(p11.2;q36)dn (Figure 2)	*De novo*	UK	Termination, abnormal ultrasound findings of hydrocephalus, macrocephaly at birth
46	AMA	35	24	46,XX,t(9;17)(q34.3;q21)mat	Maternal	UK	
47-1	AMA	35	17	46,XX,t(3;10)(p10;p10)pat	Paternal	UK	
47-2	The same mother as 47-1	37	17	46,XY,t(3;10)(p10;p10)pat	The same as 47-1	K	
48	AMA	35	16	46,XY,t(10;18)(p11.2;q21.1)mat	Maternal	UK	
49	Cystic hygroma	21	14	45,X,t(2;3)(q13;q26.2)mat (Figure 3)	Maternal	UK	Termination, abnormal ultrasound findings of cystic hygroma, hydrops fetalis at birth
50-1	AMA	38	16	46,XY,t(2;6)(q13;q24)mat	Maternal	UK	
50-2	The same mother as 50-1	39	16	46,XX,t(2;6)(q13;q24)mat	The same as 50-1	K	
51	Abnormal maternal serum screening result	26	18	46,XY,t(11;15)(p11.5;q26.1)pat	Paternal	UK	
52	AMA	37	18	46,XY,t(6;11)(p21.2;p15.5)pat	Paternal	UK	
53	AMA	34	17	46,XX,t(9;21)(p24;q22.1)dn	*De novo*	UK	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth
54	AMA	36	15	46,XX,t(8;17)(p22;q24)pat	Paternal	UK	
55	AMA	34	18	46,XY,t(10;13)(q22.3;q12.3)pat	Paternal	UK	
56	AMA	34	16	46,XY,t(9;12)(q22.2;q22.3)mat	Maternal	UK	
57	AMA	36	16	46,XX,t(4;11)(p27;q21)dn	*De novo*	UK	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth
58-1	Paternal carrier status‡	33	17	46,XX,t(1;9)(p36.2;p22)pat	Paternal	K	
58-2	The same mother as 58-1	34	17	46,XX,t(1;9)(p36.2;p22)pat	The same as 58-1	K	
59	Abnormal maternal serum screening result (Down risk = 1/47)	27	19	46,XX,t(3;12)(p10;q10)mat	Maternal	UK	
60	Maternal carrier status†	33	16	46,XX,t(3;5)(p21;q34)mat	Maternal	K	

Table. *(Continued)*

Family/ Case	Indication for amniocentesis	Maternal age (yr)	Gestational age at amniocentesis (wk)	Fetal karyotype	Inheritance of translocation	Carrier status	Parental decision and perinatal findings in the *de novo* case and the anomalous case
61	AMA	35	20	46,XY,t(1;5;8)(p13;q14;p23.1)dn	*De novo*	UK	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth and at 16 years old
62	Paternal carrier status‡	33	15	46,XX,t(10;13)(p11.2;q14)pat	Paternal	K	
63-1	Maternal carrier status‡	26	20	46,XX,t(6;11)(q25;q13.5)mat	Maternal	K	
63-2	The same mother as 63-1	31	16	46,XX,t(6;11)(q25;q13.5)mat	The same as 63-1	K	
64	Paternal carrier status†	32	16	46,XX,t(8;13)(q13;q32)pat	Paternal	K	
65	Abnormal maternal serum screening result (low MSAFP level)	28	28	46,XX,t(1;12)(p34.1;q13.1)dn	*De novo*	UK	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth
66	AMA	36	19	46,XY,t(5;20)(q15;q13)pat	Paternal	UK	
67	AMA	34	18	46,XY,t(16;17)(p10;q10)pat	Paternal	UK	
68	AMA	35	15	46,XY,t(6;20)(p22.2;p12)dn	*De novo*	UK	Termination, no ultrasound abnormalities
69	AMA	40	22	46,XY,t(7;11)(q22;p15)dn t(9;20)(q21;p11.2)mat	*De novo* Maternal	UK UK	Continuing pregnancy, normal ultrasound findings, term delivery, normal at birth
70	AMA	35	18	46,XY,t(1;18)(q24;q22)pat	Paternal	UK	
71	AMA*, previous anomalous child of unknown cause	35	19	46,XX,t(3;6)(p15;q21)mat	Maternal	UK	
72	AMA	36	18	46,XX,t(13;16)(q12;q12.1)pat	Paternal	UK	
73	Abnormal maternal serum screening result (low MSAFP level)	26	25	46,XX,t(11;22)(q23;q13.1)mat	Maternal	UK	
74	Paternal carrier status‡	32	30	46,XX,t(4;5)(q35;q31)pat	Paternal	K	
75	Abnormal maternal serum screening result (low MSAFP level)	31	22	46,XX,t(1;5)(q23;q15)pat	Paternal	UK	
76	Abnormal maternal serum screening result (Down risk=1/132)	29	18	46,XY,t(2;18;14)(q33.1;q12.2;q31.2)dn, dup(5)(q34q34), del(7)(p21.1p21.1), del(10)(q25.3q25.3)	*De novo*	UK	Termination, normal ultrasound findings, facial dysmorphism, clinodactyly of both hands and hypoplasia of the left great toe at birth Reference: Chen et al [27]

**Main mode of ascertainment; †translocation carrier status identified because of a previous aneuploid child with an unbalanced translocation in the obstetric history or in the family history; ‡translocation carrier status was identified because of recurrent miscarriage. AMA=advanced maternal age; UK=unknown at amniocentesis; K=known at amniocentesis; aCGH=array comparative genomic hybridization; MSAFP=maternal serum α-fetoprotein.*

only inherited translocations. In the 17 families of *de novo* translocations, the main modes of ascertainment included advanced maternal age ($n=9$), elective causes ($n=4$), abnormal maternal serum screening results ($n=2$), abnormal ultrasound findings ($n=1$), and parental carrier status identified through a previous aneuploid child in the obstetric history or in the family ($n=1$). In the 61 families of inherited translocations, the main modes of ascertainment included advanced maternal age ($n=30$), parental carrier status identified through a previous aneuploid child with an unbalanced translocation in the obstetric history or in the family ($n=11$), parental carrier status identified through recurrent miscarriage ($n=9$), abnormal maternal serum screening results ($n=7$), a previous child with structural anomalies or common aneuploidy ($n=2$), elective causes ($n=1$) and abnormal ultrasound findings ($n=1$).

Among these 61 families of inherited balanced translocations, 20 (32.8%) had a known parental carrier status prior to the first amniocentesis due to a previous aneuploid child in the obstetric history or in the family ($n=11$), or parental carrier status identified through recurrent miscarriage ($n=9$), The other 41 (67.2%) families were aware of their parental carrier status only after detection of fetal balanced reciprocal translocation by amniocentesis for various reasons such as advanced maternal age ($n=30$), abnormal maternal serum screening results ($n=7$), a previous child with structural anomalies or common aneuploidy ($n=2$), elective causes ($n=1$) and abnormal ultrasound findings ($n=1$). For progeny with an alternate 2:2 segregating reciprocal translocation in 61 couples of 61 inherited families, the parental female carrier/male carrier ratio was 32/29.

Of the 17 *de novo* cases, five (cases 6, 31, 45, 68 and 76; 29.4%) were terminated, 12 (70.6%) were carried to term, and three (cases 35, 45 and 76; 17.6%) manifested congenital malformations. Of the 14 *de novo* cases with a simple balanced reciprocal translocation, only one case (case 45; 7.1%) manifested a congenital anomaly [t(X;7)(p11.2;q36)], which was associated with congenital hydrocephalus and an X-autosome translocation. In four (cases 6, 31, 45 and 68; 28.6%) of these 14 cases with three (cases 6, 31 and 68) without ultrasound abnormalities, the parents opted to terminate the pregnancy following genetic counseling, and in 10 (71.4%) cases, the parents opted to continue the pregnancy following genetic counseling. Of the three (cases 35, 61 and 76) *de novo* cases with a CCR, two (cases 35 and 76) were associated with congenital anomalies and one (case 76), which had additional chromosomal aberration, was terminated. Of the two (cases 16 and 69) cases with an MCR and concomitant *de novo* and inherited translocations, both were carried to term with a normal outcome.

Discussion

In this study, the majority of balanced reciprocal translocations detected at amniocentesis were ascertained through advanced maternal age (50%, 38/76), a previous child with an unbalanced reciprocal translocation in the obstetric history or in the family (14.5%, 11/76), recurrent miscarriage (11.8%, 9/76) and abnormal maternal serum screening results (11.8%, 9/76). Our study shows that inherited balanced reciprocal translocations detected at amniocentesis are determined through recurrent miscarriage as often as through a previous child with an unbalanced translocation (11.8% *vs*. 14.5%). In contrast, inherited unbalanced structural chromosomal abnormalities at prenatal diagnosis are rarely ascertained through recurrent miscarriage [6]. Various reports have shown that carrier couples ascertained through a previous child with an unbalanced karyotype are at a higher risk of unbalanced viable offspring than those ascertained through recurrent miscarriage [7–10]. Since the main indications for amniocentesis in the Taiwanese population are advanced maternal age (~50%) and abnormal maternal serum screening results (~25%) [11–13], and balanced reciprocal translocations are among the most frequent chromosome rearrangements in humans, it is reasonable that the majority of balanced reciprocal translocations detected at amniocentesis in our study were ascertained through advanced maternal age and abnormal maternal serum screening results, in addition to a previous aneuploid child and recurrent miscarriage.

Prenatal diagnosis of a balanced reciprocal translocation may incidentally detect a balanced translocation in the family. In this study, among the 61 families with an inherited reciprocal translocation detected at amniocentesis, 67.2% (41/61) were aware of their parental carrier status only after detection of fetal chromosomal aberration by amniocentesis. The carriers of a balanced reciprocal translocation are usually phenotypically normal because of a balanced complement of the genes. A balanced reciprocal translocation can produce 32 different gametes, only two of which would result in a normal complement or a balanced rearrangement by the 2:2 alternate rearrangement [14]. Our study shows that in the alternate 2:2 segregating reciprocal translocation, the parental male carriers have the same possibility of balanced progeny as the female carriers, indicating that there is little effect of alternate 2:2 segregation on the fertility of the male carriers.

Our results show that balanced reciprocal translocations detected at amniocentesis are rarely associated with abnormal ultrasound findings. This is in contrast to unbalanced reciprocal translocations, which are frequently associated with abnormal ultrasound abnormalities. In our study, among 87 prenatally detected unbalanced reciprocal translocations, only 3.4% (3/87) presented abnormal ultrasound findings, 4.6% (4/87) manifested congenital anomalies, and the anomalous cases were limited to those with concomitant aneuploidy, *de novo* X-autosome translocation and *de novo* CCR.

Female carriers with a balanced X-autosome translocation are generally phenotypically normal. However, when there is predominant inactivation of the derivative X chromosome or disruption of the genes at the breakpoints, abnormal phenotypes may occur. In our study, we observed a female fetus (case 45) with a *de novo* X-autosome translocation of t(X;7)(p11.2;q36) and congenital hydrocephalus. The abnormal phenotype of this case could be due to disruption of the genes at the breakpoints on chromosomes Xp and/or 7q, or partial functional disomy Xp (Xp11.2→pter) and partial monosomy 7q (7q36→qter) following predominant inactivation of the derivative X chromosome. Partial functional disomy of Xp as a result of a balanced X-autosome translocation is reportedly associated with phenotypic abnormalities in females with a balanced X-autosome translocation [15–18]. Disruption of the genes at the breakpoints can also cause abnormal phenotypes. For example, Lossi et al [19] reported abnormal expression of the *KLF8* gene due to disruption of the gene at the X chromosome breakpoint in a female patient with a balanced X-autosome translocation of t(X;21)(p11.2;q22.3) and non-syndromic mental retardation. Partial monosomy 7q36→qter may cause severe central nervous system abnormalities. Genes at distal 7q such as *SHH* at 7q36 [20], *En2* at 7q36 [21] and *HTR5A* at 7q36.1 [22] are important for brain development. Male carriers with a balanced X-autosome translocation are likely to suffer from azoospermia because of a disturbance in spermatogenesis and a failure of most spermatocytes to enter into meiosis [23–26]. All *de novo* balanced X-autosome translocations are of paternal origin and once a balanced X-autosome translocation with phenotypic normality is established in the family, the transmission will be matrilineal since male infertility makes being patrilineal impossible [5].

In this study, two of three fetuses with a *de novo* apparently balanced CCR were associated with phenotypic abnormalities. In a review of 18 cases of prenatally ascertained *de novo* apparently balanced CCRs and MCRs, Chen et al [27] reported that 55.6% (10/18) manifested phenotypic abnormalities. It has been reported that *de novo* apparently balanced CCRs probably have a high risk for abnormal phenotypes, and the risk increases with the numbers of breakpoints [28,29]. The CCRs may cause reproductive failure, multiple miscarriage, stillbirths, mental retardation, dysmorphism and congenital malformations, and such CCRs may involve an unexpected level of complexity with imbalance at or near the breakpoints or in other chromosomes. Currently, precise definitions of CCRs can be made, and their complexity can be elucidated by means of molecular cytogenetic technologies such as fluorescence *in situ* hybridization and array comparative genomic hybridization (aCGH) [30–37]. Most *de novo* CCRs are of paternal origin [38,39], and most familial CCRs are of maternal origin and usually have three to four breakpoints [29,39]. CCRs arise during spermatogenesis and are preferentially transmitted through oogenesis in families [39].

Structural chromosome rearrangements are usually familial (80%), but they may arise *de novo* [3]. Olson and Magenis [40] reported that 84.4% (27/32) of cases with a *de novo* structural chromosome rearrangement were paternal in origin. Seventeen of 76 families (22.4%) in our study were associated with *de novo* balanced reciprocal translocations including three *de novo* CCRs and 14 *de novo* simple balanced reciprocal translocations. In our study, 7.1% (1/14) of *de novo* simple balanced reciprocal translocations manifested a congenital anomaly, and the anomalous case was related to an X-autosome translocation. Warburton [41] reported that the risk of a serious congenital anomaly was 6.1% (10/163) for prenatally detected *de novo* balanced reciprocal translocations. The abnormal cases in their report also included a case with X-autosome translocation of 46,X,t(X;4)(p21;q35). Warburton [41] reported a termination rate of 24% for *de novo* balanced reciprocal translocations detected at prenatal diagnosis. In our study, 28.6% (4/14) of the cases with a *de novo* simple balanced reciprocal translocation were terminated owing to the parents' decision following counseling for the risk of abnormalities with a *de novo* rearrangement. Gardner and Sutherland [5] suggested that in prenatally detected *de novo* simple balanced reciprocal translocations, the risk for abnormalities may comprise 3% for the background risk, 3% for the chromosome defect risk and an additional 1% for the overall risk for both major malformations and functional deficits.

In summary, we have presented perinatal findings, the modes of ascertainment and the parental decision of balanced reciprocal translocations detected at amniocentesis. Balanced reciprocal translocations detected at amniocentesis may be associated with fetal anomalies in cases of concomitant common aneuploidy, *de novo*

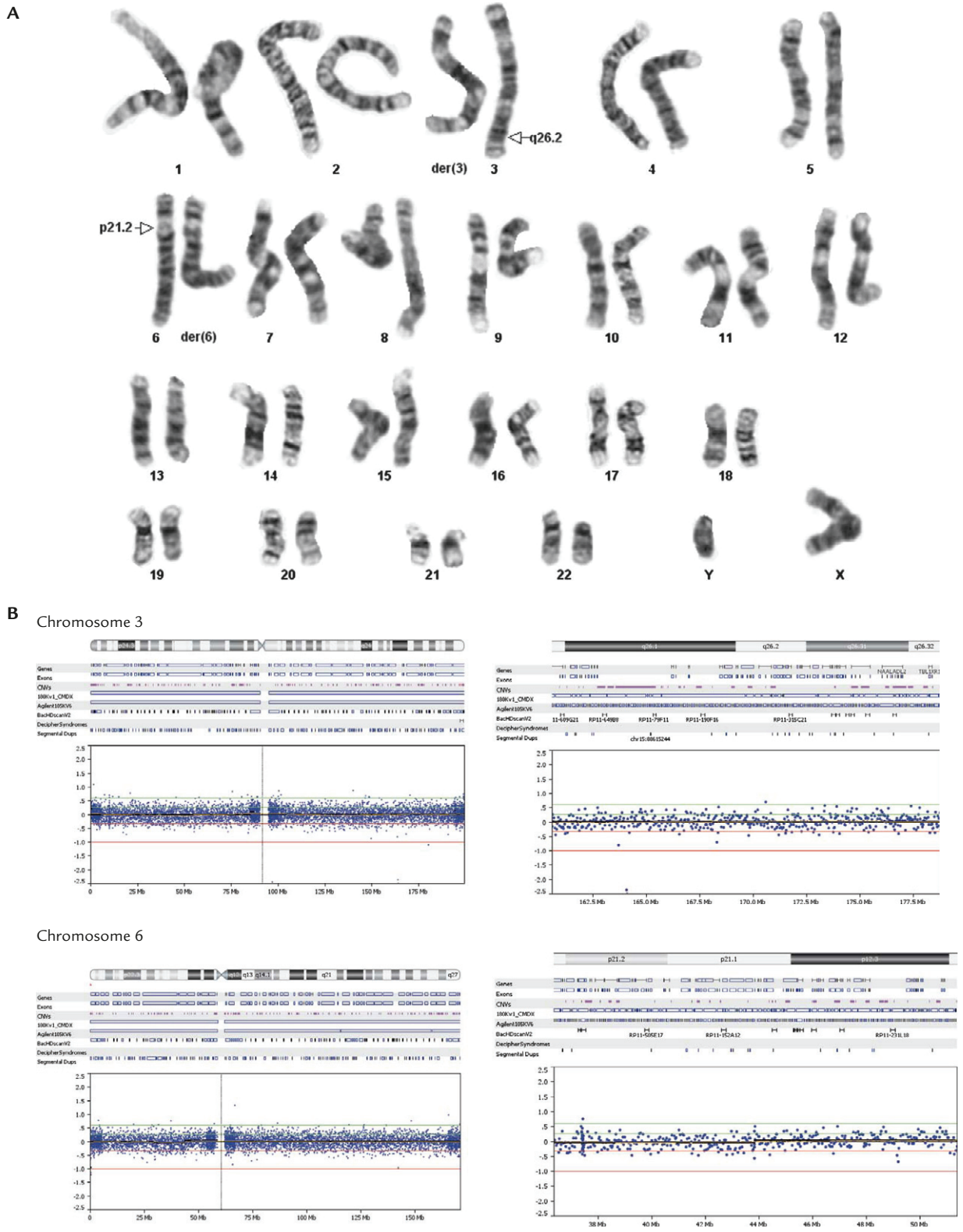

Figure 1. A case (case 3) with a *de novo* balanced simple reciprocal translocation. (A) A karyotype of 46,XY,t(3;6)(q26.2; p21.2)dn. The arrows indicate the breakpoints. dn = *de novo*. (B) Oligonucleotide-based array comparative genomic hybridization using Oligo HD Scan (CMDX, Irvine, CA, USA) shows no loss or increase in the dosage of genetic probes specific for chromosomes 3 and 6.

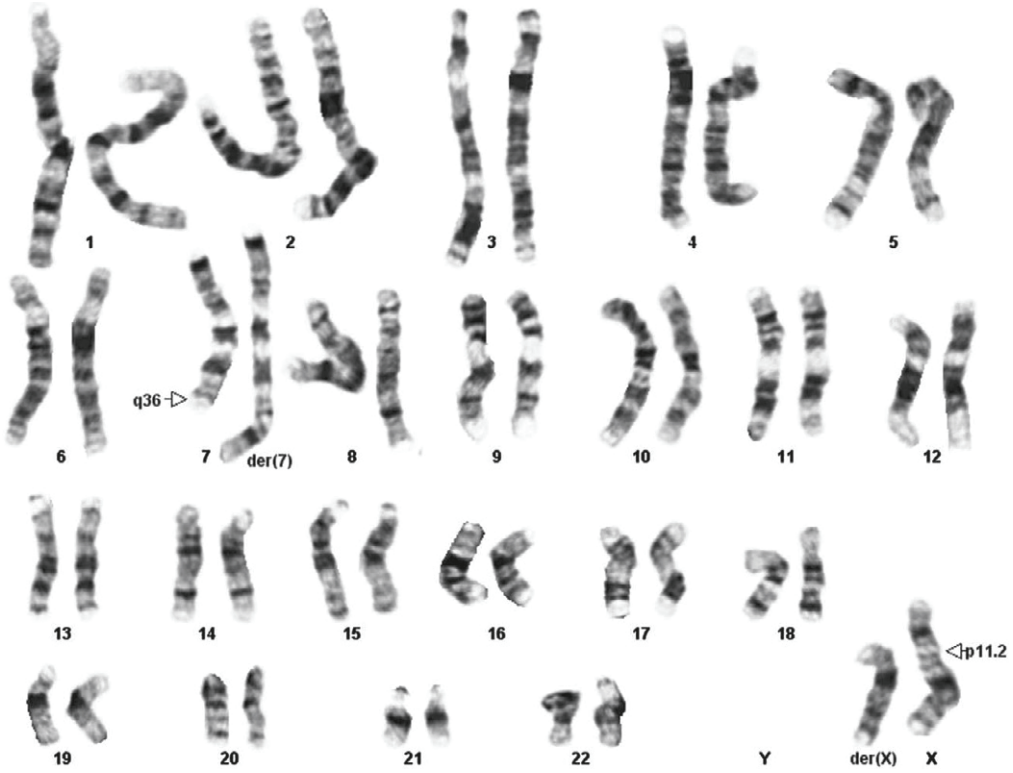

Figure 2. A case (case 45) with a *de novo* X-autosome translocation, hydrocephalus and a karyotype of 46,X,t(X;7)(p11.2;q36)dn. The arrows indicate the breakpoints.

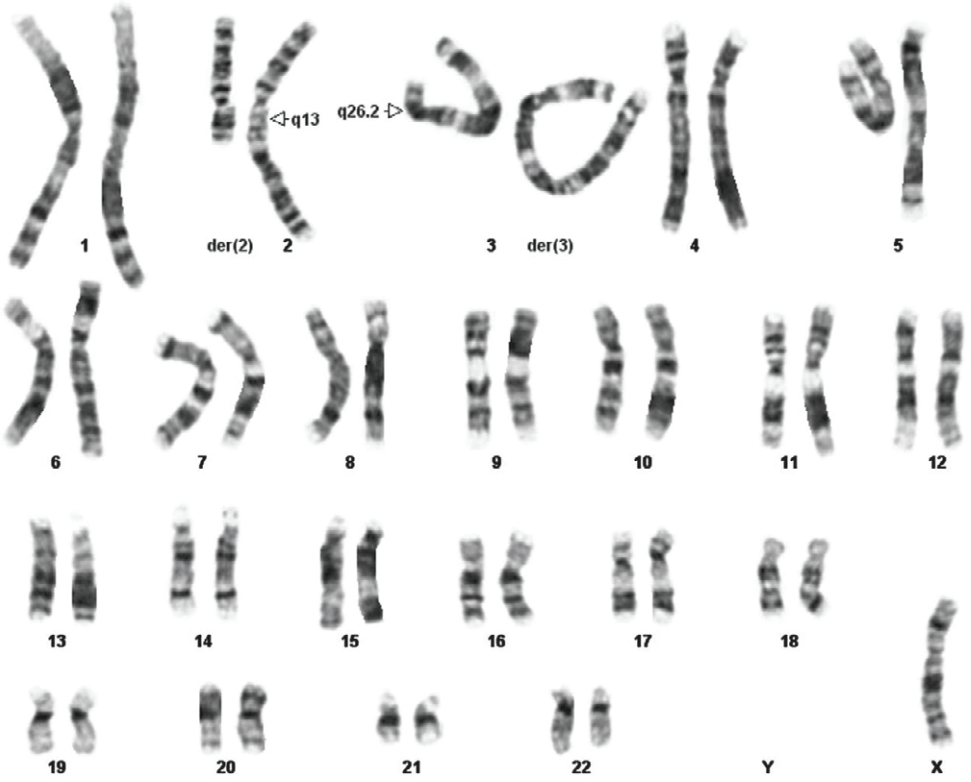

Figure 3. A case (case 49) with concomitant Turner syndrome, an inherited simple reciprocal translocation, cystic hygroma and a karyotype of 45,X,t(2;3)(q13;q26.2)mat. The arrows indicate the breakpoints. mat = maternal.

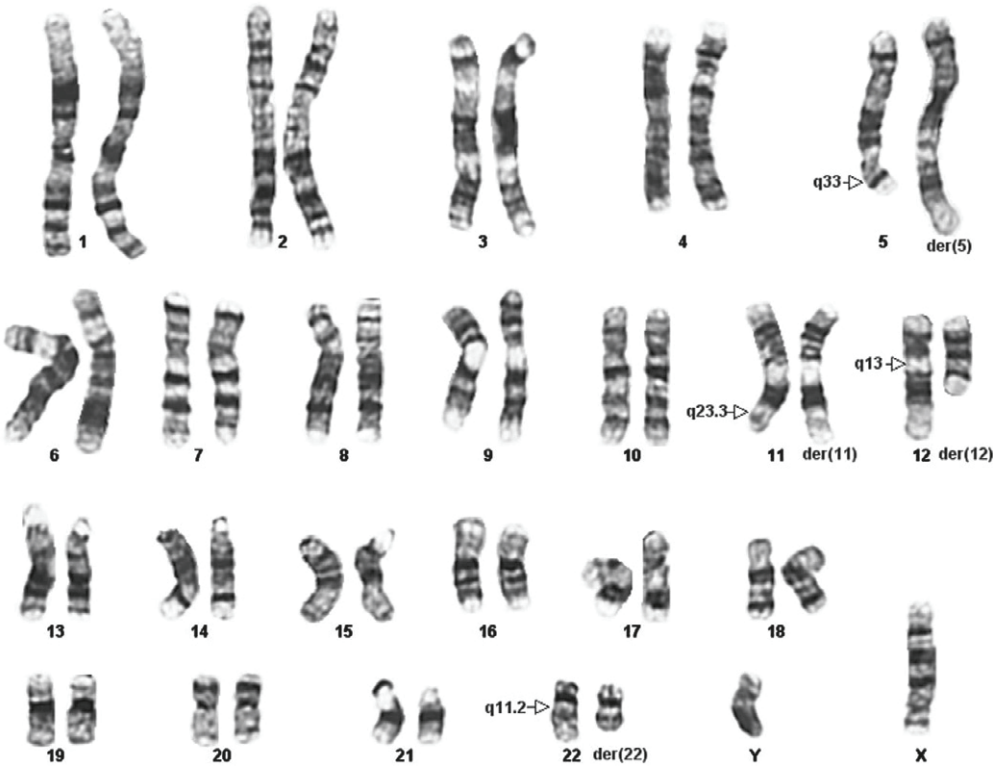

Figure 4. A case (case 16) with a multiple chromosome rearrangement consisting of two separate simple reciprocal translocations (*de novo* and inherited) and a karyotype of 46,*XY*,t(5;12)(q33;q13)dn t(11;22)(q23.3;q11.2)mat. The arrows indicate the breakpoints.

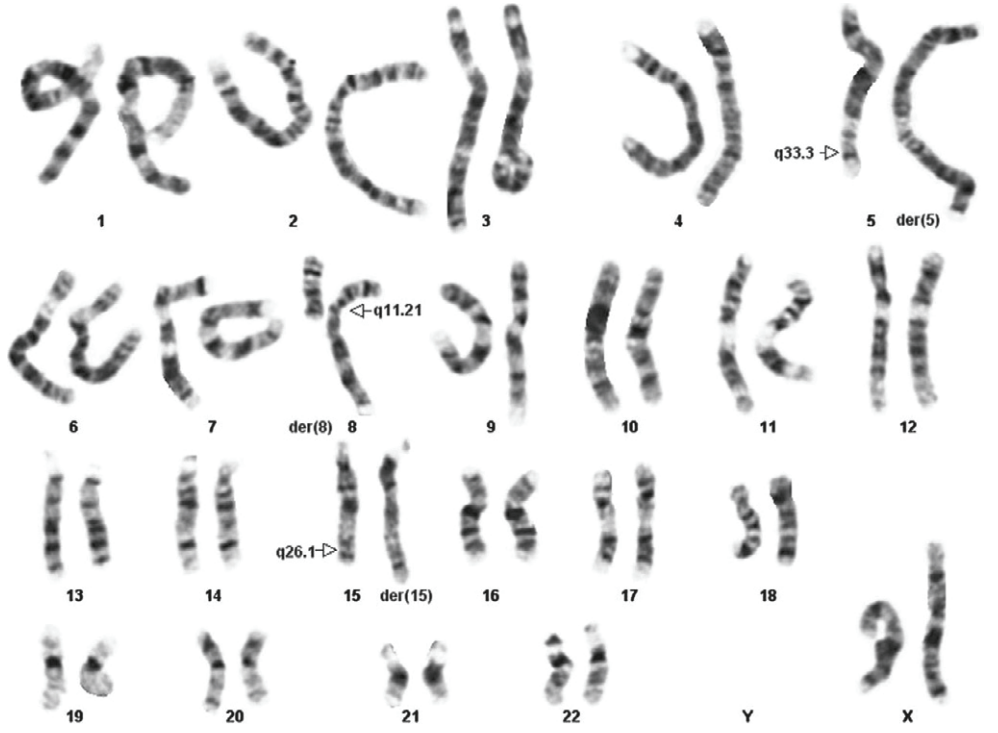

Figure 5. A case (case 35) with a *de novo* complex chromosome rearrangement with three breakpoints and a karyotype of 46,XX,t(5;8;15)(q33.3;q11.21;q26.1)dn, 1qh+ mat. The arrows indicate the breakpoints.

X-autosome translocation, or *de novo* CCR. Genetic counseling for a *de novo* simple reciprocal translocation at amniocentesis remains difficult because approximately one fourth of the parents opt for termination of the pregnancy, and detailed ultrasonography and aCGH are helpful for parental counseling under such circumstances.

Acknowledgments

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