Down Syndrome Due to Unbalanced Homologous Acrocentric Rearrangements and its Recurrence in Subsequent Pregnancies: Prenatal Diagnosis by Amniocentesis

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SUMMARY

Objective: To present our experience of amniocentesis for the prenatal diagnosis of Down syndrome due to unbalanced homologous acrocentric rearrangements and its recurrence in subsequent pregnancies.

Case Report: From January 1987 to September 2009, six cases with rea(21q21q) Down syndrome were diagnosed among 31,194 patients who underwent amniocentesis at Mackay Memorial Hospital, Taipei, Taiwan. Cytogenetic analysis of parental blood lymphocytes was performed in each case, and polymorphic DNA markers were used to investigate the nature of the aberrant chromosome. Three of the six cases were associated with recurrence in subsequent pregnancies. The rea(21q21q) Down syndrome was associated with advanced maternal age in three cases, a previous child with rea(21q21q) Down syndrome in three cases, an abnormal maternal serum screening result in one case, and an abnormal ultrasound finding in one case. All six cases arose *de novo*. Among the six cases with molecular analysis results, all had isochromosome 21, five of which were determined to be of maternal origin.

Conclusion: We found a frequency of 0.019% for rea(21q21q) Down syndrome in patients undergoing amniocentesis. Down syndrome caused by the homologous rearrangement rea(21q21q) can be associated with recurrence. Prenatal diagnosis of rea(21q21q) Down syndrome should include extensive cytogenetic and molecular analyses of the parents and probands. [*Taiwan J Obstet Gynecol* 2009;48(4):403–407]

Key Words: amniocentesis, Down syndrome, homologous acrocentric rearrangement, i(21q), isochromosome, recurrence

Introduction

About 95% of Down syndrome cases 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, of which rea(21q21q) and rob(14q21q) are 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 by amniocentesis of recurrent Down syndrome due to unbalanced homologous acrocentric rearrangements is uncommon (Figures 1–3). Here, we report six

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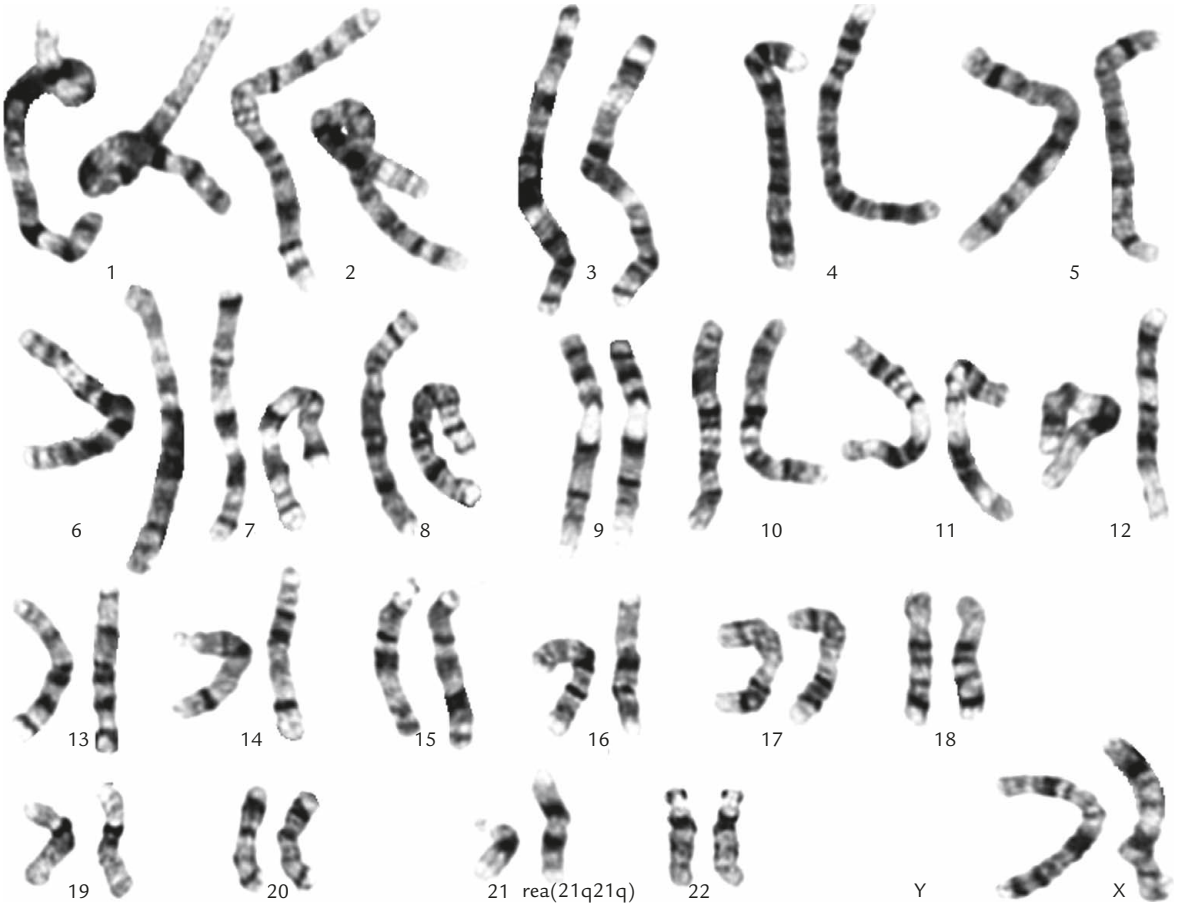

Figure 1. Typical karyotype of rea(21q21q) Down syndrome.

cases of rea(21q21q) Down syndrome diagnosed among 31,194 patients who underwent amniocentesis at Mackay Memorial Hospital, Taipei, Taiwan, during the period between January 1987 and September 2009. Reasons for amniocentesis included advanced maternal age, abnormal ultrasound findings, abnormal maternal serum screening results, a previous child with congenital anomalies, and a family history of chromosome aberrations.

Case Report

Case 1

This was the fourth pregnancy of a 35-year-old, gravida 4, para 2, woman. Amniocentesis was performed at 17 weeks' gestation because of advanced maternal age and a previous child with rea(21q21q) Down syndrome. The woman had experienced one previous abortion. She had a 5-year-old daughter affected with homologous Robertsonian translocation Down syndrome and a 3-year-old normal daughter with a 46,XX karyotype. Polymorphic DNA marker analysis of the affected daughter showed that the rea(21q21q) was isochromosome 21 and was of maternal origin (Figure 2). The karyotype was 46,XX,i(21)(q10). Parental karyotypes derived from blood lymphocytes were normal. Amniocentesis during the current pregnancy revealed recurrent rea(21q21q) Down syndrome. Polymorphic DNA marker analysis showed that the rea(21q21q) was isochromosome 21 and was of maternal origin (Figure 2). The karyotype was 46,XY,i(21)(q10). The pregnancy was subsequently terminated. The karyotype of cord blood lymphocytes was 46,XY,i(21)(q10). Her fifth pregnancy resulted in a normal male baby with a 46,XY karyotype.

Case 2

This was the second pregnancy of a 36-year-old, gravida 2, para 1, woman. Amniocentesis was performed at 16 weeks' gestation because of advanced maternal age and a previous child with rea(21q21q) Down syndrome. She had a 2-year-old daughter affected with rea(21q21q) Down syndrome. Polymorphic DNA marker analysis showed that the rea(21q21q) was isochromosome 21 and was of maternal origin (Figure 3). The karyotype was 46,XX,i(21)(q10). The parental karyotypes derived from blood lymphocytes were normal.

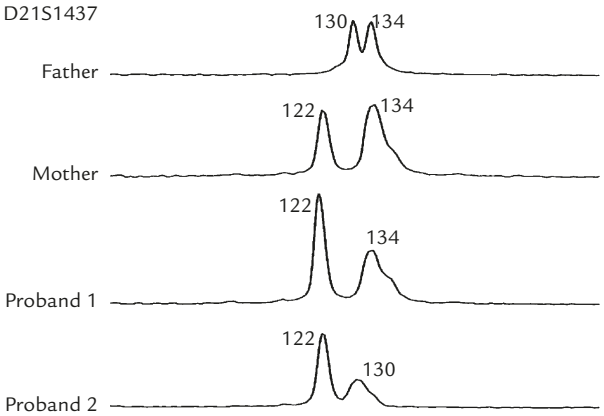

Figure 2. Representative electrophoretograms of the family members of Case 1 with recurrent rea(21q21q) Down syndrome showing isochromosome 21 Down syndrome of maternal origin in the affected daughter (Proband 1) and in the affected fetal son (Proband 2). Using the microsatellite marker D21S1437, one maternally originated 122-bp allele and one paternally originated 134-bp allele are seen in Proband 1, and one maternally originated 122-bp allele and one paternally originated 130-bp allele are seen in Proband 2. The two peaks (maternal to paternal ratio, 122:134) of unequal fluorescence activity with a ratio of 2:1 in Proband 1 and two peaks (maternal to paternal ratio, 122:130) of unequal fluorescence activity with a ratio of 2:1 in Proband 2 indicate a maternal origin for isochromosome 21.

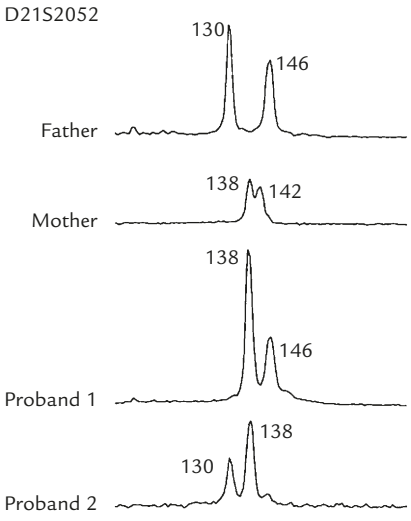

Figure 3. Representative electrophoretograms of the family members of Case 2 with recurrent rea(21q21q) Down syndrome showing isochromosome 21 Down syndrome of maternal origin in the affected daughter (Proband 1) and in the affected fetal daughter (Proband 2). Using the microsatellite marker D21S2052, one maternally originated 138-bp allele and one paternally originated 146-bp allele are seen in Proband 1, and one paternally originated 130-bp allele and one maternally originated 138-bp allele are seen in Proband 2. The two peaks (maternal to paternal ratio, 138:146) of unequal fluorescence activity with a ratio of 2:1 in Proband 1 and two peaks (paternal to maternal ratio, 130:138) of unequal fluorescence activity with a ratio of 1:2 in Proband 2 indicate a maternal origin for isochromosome 21.

Amniocentesis during this pregnancy revealed recurrent rea(21q21q) Down syndrome. The pregnancy was subsequently terminated. The karyotype of skin fibroblasts was 46,XX,i(21)(q10).

Case 3

This was the first pregnancy of a 25-year-old, gravida 1, para 0, woman. Amniocentesis was performed at 19 weeks' gestation because of an increased maternal serum Down screening risk of 1/115. Amniocentesis revealed rea(21q21q) Down syndrome. The parental karyotypes derived from blood lymphocytes were normal. Polymorphic DNA marker analysis showed that the rea(21q21q) was isochromosome 21 and was of maternal origin. The karyotype was 46,XX,i(21)(q10). The pregnancy was subsequently terminated. The karyotype of cord blood lymphocytes was 46,XX,i(21)(q10). Her second pregnancy resulted in a normal male co-twin with a 46,XY karyotype and a normal female co-twin with a 46,XX karyotype.

Case 4

This was the first pregnancy of a 30-year-old, gravida 1, para 0, woman. Amniocentesis was performed at 18 weeks' gestation because of increased nuchal thickness. Amniocentesis revealed rea(21q21q) Down syndrome. The parental karyotypes derived from blood lymphocytes were normal. Polymorphic DNA marker analysis showed that the rea(21q21q) was isochromosome 21 and was of maternal origin. The karyotype was 46,XX,i(21)(q10). The pregnancy was subsequently terminated. The karyotype of cord blood lymphocytes was 46,XX,i(21)(q10).

Case 5

This was the first pregnancy of a 34-year-old, gravida 1, para 0, woman. Amniocentesis was performed at 19 weeks' gestation because of advanced maternal age. Amniocentesis revealed rea(21q21q) Down syndrome. The parental karyotypes derived from blood lymphocytes were normal. Polymorphic DNA marker analysis showed that the rea(21q21q) was isochromosome 21 and was of maternal origin. The karyotype was 46,XX,i(21)(q10). The pregnancy was subsequently terminated.

Case 6

This was the second pregnancy of a 26-year-old, gravida 2, para 1, woman. Amniocentesis was performed at 15 weeks' gestation because of a previous fetus with rea(21q21q) Down syndrome. The fetus of her first pregnancy had rea(21q21q) Down syndrome with a 46,XX,+21, der(21;21)(q10;q10) karyotype, which was diagnosed by amniocentesis 2 years prior to the

current pregnancy because of a maternal Down syndrome serum screening risk of 1/111. At that time, the parental karyotypes derived from blood lymphocytes were normal. The pregnancy was subsequently terminated. Amniocentesis during the current pregnancy revealed recurrent rea(21q21q) Down syndrome. Polymorphic DNA marker analysis showed that the rea(21q21q) was isochromosome 21. The parental origin was not determined, because parental DNA was not obtained. The karyotype was 46,*XY*,i(21)(q10). The pregnancy was subsequently terminated. Her third pregnancy resulted in a normal female baby with a 46,*XX* karyotype, following preimplantation genetic diagnosis and amniocentesis.

Discussion

Chen et al [2] previously reported a frequency of chromosome aberrations of 2.53% among 166,419 amniocenteses, and about 30% of the detected aneuploidies were Down syndrome. In this report, we found a frequency of 0.019% for rea(21q21q) Down syndrome among patients who underwent amniocentesis. We determined that rea(21q21q) Down syndrome could be associated with advanced maternal age (Cases 1, 2 and 5), a previous child with rea(21q21q) Down syndrome (Cases 1, 2 and 6), an abnormal maternal serum screening result (Case 3) or an abnormal ultrasound finding (Case 4), and that the homologous rearrangement rea(21q21q) Down syndrome could be associated with recurrence.

Homologous rearrangement rea(21q21q) Down syndrome includes isochromosome 21 i(21q) Down syndrome and homologous Robertsonian translocation rob(21q21q) Down syndrome. More than 95% of rea(21q21q) Down syndrome cases arise *de novo* [3]. In isochromosome 21 Down syndrome, i(21q) is derived from a single chromosome 21; whereas in homologous Robertsonian translocation Down syndrome, rob (21q21q) is derived from two different homologous chromosome 21 [3,4]. Conventional cytogenetic analysis is unable to distinguish between rob(21q21q) and i(21q), and molecular technology using polymorphic DNA markers is required to make this distinction.

The majority of cases with rea(21q21q) Down syndrome reported to date have been of i(21q) Down syndrome [3–6]. In a meta-analysis of 34 cases of rea (21q21q) Down syndrome based on three reports [3,5,6], Kovaleva and Shaffer [7] found that 30 cases (88.2%) were i(21q) Down syndrome, and four (11.8%) were rob(21q21q) Down syndrome. The incidence of maternally derived i(21q) has been noted to be similar to that of paternally derived i(21q) [3,5,8,9]. Most cases with i(21q) showed no recombination, consistent with a postzygotic mitotic event [4,10,11], whereas only a few showed recombination consistent with a meiotic event [3,9].

All six of the current cases arose *de novo*. These six cases underwent molecular analysis and demonstrated isochromosome 21, five of which were determined to be of maternal origin. These cases were likely to be the results of mitotic events. The recurrence of rea(21q21q) Down syndrome in Cases 1, 2 and 6 is of interest. Recurrence of rea(21q21q) Down syndrome has been shown to be associated with low-level parental mosaicism or gonadal mosaicism. Kovaleva and Shaffer [7] found that parents of rea(21q21q) Down syndrome offspring more often demonstrated mosaicism. They found a sevenfold increase in the number of mosaic cases in parents of rea(21q21q) Down syndrome offspring compared with parents of non-rea(21q21q) offspring. Kovaleva and Shaffer [7] suggested that extensive parental analysis for mosaicism should be undertaken in cases of recurrent rea(21q21q) Down syndrome. The recurrence rate for *de novo* rea(21q21q) Down syndrome has been reported to be low. In a study of 112 families with a child with *de novo* 21q21q translocation Down syndrome, Steinberg et al [12] found that none of the parents had a second child with Down syndrome, and three of 112 sets of parents had low-grade mosaicism for a 21q21q translocation. However, three of the six cases (50%) in our study were associated with recurrence. In the families with recurrent *de novo* rea(21q21q) Down syndrome, several reports have demonstrated mosaicism for rea(21q21q) in the skin or ovary of one parent but normal karyotypes in the parental blood lymphocytes [13–17] and very low levels of rea(21q21q) mosaicism in the blood lymphocytes of one parent [18]. Parental cytogenetic studies of tissues, as well as blood, could therefore be helpful for detecting low percentage mosaicism in the parents of families with recurrent Down syndrome. Preimplantation genetic screening using fluorescence *in situ* hybridization or comparative genomic hybridization for the analysis of chromosomes in preimplantation embryos may provide parents with the chance of starting a pregnancy knowing that the baby will be free of Down syndrome. The recurrence of familial rea(21q21q) Down syndrome in pregnancies of couples in whom one of the partners is a carrier of balanced rea(21q21q) is 100%. In such cases, genetic counseling should include advice to refrain from further pregnancies, the use of artificial insemination with normal donor sperm (in case of a male carrier), or the use of normal donor ova (in case of a female carrier).

Acknowledgments

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