증 례

Repetitive Pregnancy Loss in inv(22)(p13q12) Carrier

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Pericentric inversion is not rare in humans and is usually benign. However, pericentric inversion can lead to production of an unbalanced recombinant and might be a cause of repetitive pregnancy loss. Pericentric inversion of chromosome 22 is rare and only a few cases have been reported. We report a case of inv(22)(p13q12) carrier who had history of repetitive pregnancy loss including three spontaneous abortions and one fetal hydrops in which the chromosomal complement was rec(22)dup(22q) inv(22)(p13q12)mat. The maternal inv(22) and fetal rec(22) were confirmed by fluorescence in situ hybridization using region-specific probes (TUPLE1 on 22q11.2 and ARSA on 22q13). Because the identification of inv(22) or rec(22) in conventional karyotyping might be easily overlooked, great attention and additional molecular tests are required for accurate diagnosis of inv(22) and rec(22).

Key Words: Recombinant, inv(2), Partial trisomy 22, Repetitive pregnancy loss

Introduction

The pericentric inversions are estimated to occur in frequency of 0.12-0.7%, and most commonly discovered in chromosome 1, 9, 16 and Y[1)]. Pericentric inversions are usually benign and do not cause any phenotypic effects. However, those inversions can cause an abnormal pregnancy or abnormal offspring by production of recombinant unbalanced gametes[1-8)]. The present report describes a case of pericentric inversion 22 in a female experiencing repetitive pregnancy loss and fetal hydrops, which may have been caused by unbalanced recombinant derived from maternal inv(22)(p13q22).

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Case Report

A 37-year-old female underwent an amniocentesis at 15 weeks gestation due to fetal hydrops that was detected in an ultrasonograph examination. This was the fifth pregnancy for her. The patient had previously experienced three times spontaneous abortions at an early gestational age. After abortions, karyotyping analysis had been performed for patient and her husband. Findings had been unremarkable. Subsequently, another pregnancy ended in the successful delivery of a healthy and full-term baby. That baby was healthy (body weight 3,520 g, height 50 cm, and body circumference 35 cm) and didn't show any abnormal findings. This time pregnancy, amniotic karyotyping analysis revealed an abnormally large p arm of chromosome 22 (22p+), which was suspected to be a derivative chromosome (Fig. 1A). Based on this finding, the previous parental karyotyping data was reviewed again. The review uncovered a chromosome 22 abnormality that was suspected to be a inversion 22 in the maternal karyotype

(Fig. 1B). Fluorescence in situ hybridization (FISH) analysis was performed to confirm inv(22). The analysis utilized DiGeorge/VCFS region-specific probes (Vysis, Downers, USA) which consist of a *TUPLE1* (22q11.2) probe labeled with SpectrumOrange and an ARSA (22q13) probe labeled with SpectrumGreen. One orange and one green signal were evident on normal chromosome 22, whereas one orange and two green signals were found on abnormal chromosome 22 in fetal metaphase cells (Fig. 2A). In the maternal FISH analysis, one orange signal and one green signal were found on both chromosome 22, but each signal was located on each arm of inverted chromosome 22, compared to the location of all signals on only one arm of normal chromosome 22 (Fig. 2B). Therefore, the karyotype of fetus was established as 46,XX,rec(22)dup(22q)inv(22)(p13q12)mat and a maternal karyotype as 46,XX, inv(22)(p13q12).

Discussion

In our knowledge, only eight cases about inv(22) have been reported in the literature[1-8]. Most of the cases were of liveborn patients who displayed a partial trisomy of 22q due to rec(22) derived from a parental inv(22) carrier. The eight cases shared a similar phenotype such as mental retardation, growth retardation, cleft lip/palate, micrognathia and microcephaly, which have been found in other types of partial trisomy 22 syndrome. In one case, partial monosomy of 22q was derived from a familial inv(22)(p11q12)[4]. That patient also revealed some abnormalities, such as mental retardation and dysmorphic phenotypes. In some of the eight cases, the inv(22) carrier parents experienced abnormal pregnancy histories that included repetitive pregnancy loss; whether this is consistent with all the cases is unknown, since not all the reports described the pregnancy history. In our case, the patient experienced repetitive pregnancy loss at early gestational ages and a fetal hydrops. Although the karyotyping analysis was not performed following the unsuccessful pregnancies, partial trisomy 22q or partial monosomy 22q due to recombination might be the main cause of pregnancy loss.

Interestingly, about five of the eight previous inv(22) cases were Hispanics from Mexico. This has led to a suggestion of a "founder effect" and the possibility that rec(22) derived from inv(22) might be a hidden cause of mental retardation in Hispanic people[3]. The latter study also suggested that the cause of underestimation of rec(22) is due to the difficulties in detecting rec(22) through conventional karyotyping analysis. Detection of rec(22) is somewhat difficult due to small size and morphologic similarities with normal variant 22 having

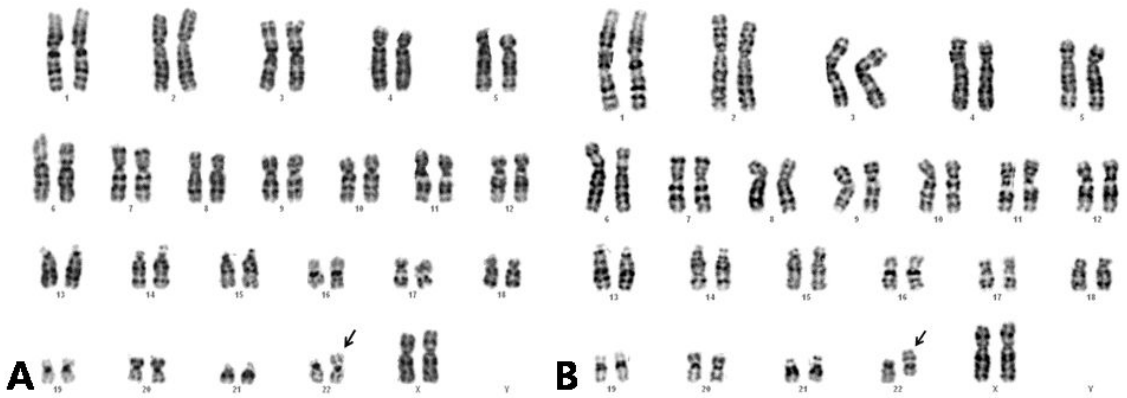

Fig. 1. Karyotyping of fetus (A) and mother (B). Arrowed chromosome 22 in each karyogram represents a rec(22)dup(22q)inv(22)(p12q12) and a inv(22)(p13q12) in fetus and mother, respectively.

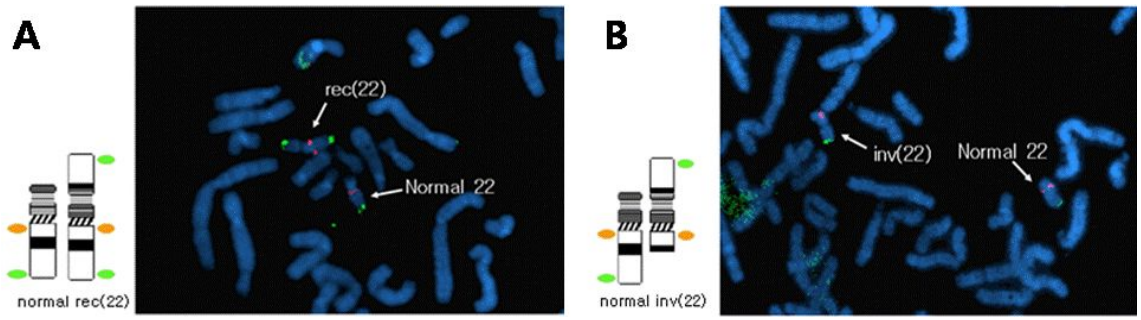

Fig. 2. FISH analysis. The *TUPLE1* (22q11.2) with spectrumOrange and *ARSA* (22q13) with spectrumGreen probes were labeled. (A) Two green signals on both side of centromere and one orange signal on one side are found on fetal rec(22) chromosome. (B) One orange and one green signal on each side of centromere are found in mother's inv(22) chromosome.

a large satellite. Identification of inv(22) is similarly difficult. Chromosome 22 is very small in size and bright color in conventional staining method, so it is easy to be overlooked. Although the present patient did successfully give birth to a healthy baby, there was a possibility that the patient experienced another spontaneous abortion without notice because of the missed diagnosis. Therefore, care should be taken in detection of small chromosomal changes like 22 and the possibility of inv(22) as well as rec(22) should be recognized in the examination of infertility cases or prenatal tests. Moreover, additional molecular tests like FISH might be helpful for confirmation of suspected cases.

The present study reports a case of inv(22)(p13q12) carrier who experienced repetitive pregnancy loss and fetal hydrops due to rec(22)dup(22q)inv(22)(p13q12) mat. Careful attention should be paid during examination of chromosome 22 to the probability of inv(22) or rec(22), because detection of such abnormalities can be easily overlooked due to small size and confusing morphology.

국문초록

완간역위는 드물지 않게 관찰되는 이상이며, 일반적으로 표현형 이상을 일으키지 않으나, 불균형 생식자를 생성하여 반복적인 임신 상실의 원인이 될 수 있다. 22번 염색체의 완간역위는 매우 드물며, 지금까지 몇 례만이 보고되어 있다. 저자들은 반복 임신 상실을 보인 inv(22)(p13q12) 보인자 1례를 보고하고자 한다. 환자는 3번의 초기 임신 상실력이 있었고, 이번 임신에서 rec(22)dup(22q)inv(22)(p13q12) mat 염색체 이상으로 인한 태아수종을 경험하였다. 모체의 22번 완간역위와 이로 인한 태아의 재조합 이상은 위치특이 탐색자(*TUPLE1* on 22q11.2, *ARSA* on 22q13)를 이용한 형광제자리부합법으로 증명하였다. 22번 완간역위와 재조합 22번 염색체는 염색체 검사상 쉽게 간과될 수 있는 이상의 하나로, 정확한 진단을 위해서는 추가 분자유전학적 검사를 비롯해 세심한 주의가 필요하다.

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