

# A Prenatal Case of Paracentric Inversion of Chromosome 18, inv(18)(q21.1q22)

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Paracentric inversion of chromosome 18 is a rare cytogenetic abnormality. The vast majority of paracentric inversions are harmless and the offspring of paracentric inversion carriers have only slightly elevated risks for unbalanced karyotypes. However, various clinical phenotypes are seen due to breakpoint variation or recombination. We report a prenatally detected case of familial paracentric inversion of chromosome 18, inv(18)(q21.1q22), with normal clinical features.

**Key words:** Paracentric inversion, Chromosome 18

## Introductions

The presence of a chromosome inversion usually does not increase the risk of phenotypic abnormality resulting in the birth of an abnormal child. However, meiotic crossing over in the inverted segment may cause chromosomally unbalanced gametes.<sup>1)</sup> The risk of chromosome imbalance depends on the chances of pairing and crossing over occurring within the inverted segment, which is proportional to the length of the inverted segment.<sup>2,3)</sup> In rare cases, chromosomally unbalanced gametes from certain paracentric inversion heterozygotes may result in a recognized pregnancy that ends in spontaneous abortion or an abnormal child.<sup>4)</sup>

Diagnosing unbalanced recombinant chromosome can be difficult due to the variety of unpredictable unbalanced chromosome products that can result from paracentric inversion. Carriers of paracentric inversions have a low risk for having

an abnormal child. Madan K et al reported out of 50 cases of paracentric inversion, 34 were familial with one or more phenotypically normal carriers in the family.<sup>1)</sup> Most paracentric inversions are likely to be harmless, but due to breakpoint variation or recombination, various clinical phenotypes are seen.<sup>5-7)</sup> Paracentric inversions can cause infertility, recurrent spontaneous abortion,<sup>8,9)</sup> or abnormal children which includes mental retardation or microcephaly.<sup>10)</sup>

We report a prenatally detected case of familial chromosome 18 paracentric inversion with normal clinical features (Fig. 1).

## Case Report

A 38-year-old multigravida pregnant woman was referred to our department from a local clinic at 18.6 weeks gestation for

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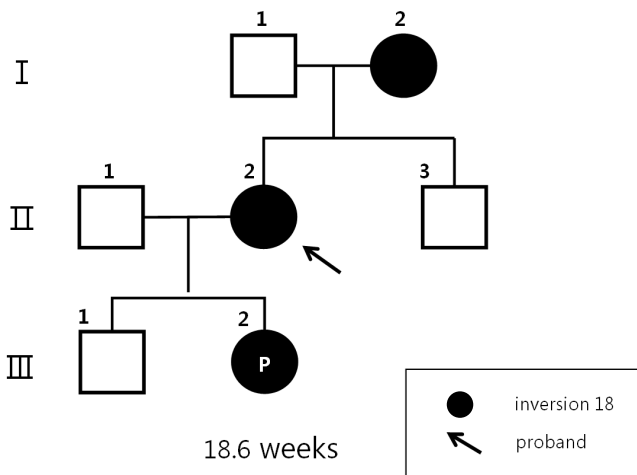
an abnormal fetal karyotype. The karyotype 46,XX,add(18) was found during antenatal diagnosis with amniocentesis performed at a local clinic and was due to advanced maternal age. Amniocentesis, cytogenetic evaluation of the family, and high resolution ultrasonography of the fetus were planned.

The amniocentesis was performed and the chromosome analysis documented a paracentric inversion of chromosome 18 with breakpoints at q21.1 and q22: 46,XX,inv(18)(q21.1q22) at the 550-band levels. The mother, father, maternal grandmother, and

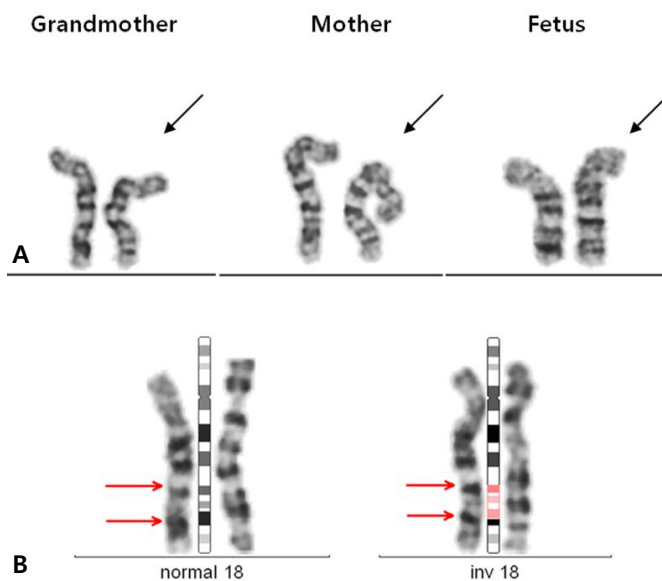
maternal grandfather underwent high-resolution chromosomal analysis using peripheral blood at the 700-850-band levels by GTL-band and RBG-band. Chromosome studies showed that the inversion was also found in the mother and maternal grandmother of the fetus as 46,XX,inv(18)(q21.1q22.1) (Fig. 2) and they were phenotypically normal. The father and grandfather showed a normal karyotype.

We were unable to perform the molecular cytogenetic analysis of the mother's brother and we could not confirm the karyotype. The high-resolution ultrasonography performed at 20.7 weeks showed normal findings. Medical geneticists provided genetic counseling to the family. The family was informed of the characteristics, prognosis, and management of paracentric inversions, and that they usually show good prognosis except for those with secondary rearrangements with deletions at the inversion site.

The baby was born at 37.8 weeks by lower segment cesarean section due to a previous cesarean section. The newborn was female and had a birth weight of 2,800 g. The baby showed good activities and crying. She had a normal appearance and nonspecific findings in the physical and neurologic examinations.



**Fig. 1.** Pedigree of the patient. All carriers had a normal phenotype. The karyotype of each family member was as follows: I-2: 46,XX,inv(18)(q21.1q22.1); II-2: 46,XX,inv(18)(q21.1q22.1); III-2: 46,XX,inv(18)(q21.1q22). The arrow shows the pregnant woman.



**Fig. 2.** (A) GTL-(G-bands by trypsin using Leishman) banded partial karyotypes for chromosome 18 of the grandmother, mother and fetus with paracentric inversion of 18q (right arrowed). (B) Left of the ideogram (middle) is GTL-banding and to the right is RBG-(R-bands by BrdU using Giemsa) banding show the breakpoints, inv(18)(q21.1q22.1) of maternal chromosome 18 at the 850-band levels of high resolution.

### Discussion

An inversion is a chromosome rearrangement in which a chromosome segment is reversed end to end. Inversions occur when a single chromosome undergoes breakage and rearrangement within itself. Inversions are of two types: paracentric and pericentric. Paracentric inversions do not include the centromere in the inverted segment and both breaks occur in one arm of the chromosome. Pericentric inversions include the centromere and there is a break point in each arm.

Among cytogenetic structural abnormalities, the incidence of paracentric inversion is 0.25%.<sup>11</sup> A French study in 1986 found a tenfold lower incidence of paracentric inversions than pericentric inversions.<sup>12</sup>

As long as the rearrangement is balanced with no extra or missing genetic information, inversions usually do not cause phenotypic abnormalities in carriers. However, in individuals heterozygous for an inversion, there is an increased risk of producing abnormal chromatids. This leads to lowered fertility due to the production of unbalanced gametes.

Various reviews of 184 cases by Madan k. have confirmed that the risk of producing unbalanced gametes is very low.<sup>13</sup> Conversely, a large review of 446 cases of paracentric inversions by Pettenati et al. gave the risk of viable recombinants as 3.8%.<sup>11</sup> Such conflicting

information causes a dilemma for genetic counselors.

Although most paracentric inversion heterozygotes have a low risk of viable recombinants, prenatal diagnosis should be considered in particular cases. One example is with chromosome 18q paracentric inversion, for which a variety of small and large imbalances are compatible with live birth.<sup>14)</sup>

In 1979, Wilson et al reported that loss of the specific critical region 18q21.3 is required to express the 18q-syndrome.<sup>15)</sup> However, some authors have shown the relationship with another breakpoint as 18q22.3.<sup>16, 17)</sup> In general, the familial type of cytogenetic variation does not increase the risk of unbalanced karyotypes. However, there is a report of chromosome 18q paracentric inversion involving mental retardation and hearing loss in a mother and her daughter.<sup>18)</sup>

In our case, the breakpoints were q21.1 and q22. The mother, maternal grandmother, and baby showed normal phenotypes. We attempted high-resolution cytogenetic analyses by GTL-band at the 550-band levels for fetus and by GTL-band and RBG-band at the 700-850-band levels for parents and grandparents according to the laboratory internal guidelines. However, there would be the possibilities of the gene disruptions near regions of the breakpoint. Unfortunately we were unable to perform the molecular cytogenetic analysis at the gene level. Therefore, the baby should have long term follow up with physical activity and neurodevelopment.

Families that may be carriers of inversions should be offered genetic counseling and genetic testing to become informed about various results and prognoses. More data on the reproductive outcomes and risk for abnormal offspring among their carriers are a necessary basis for genetic counseling.

This report underlines the importance of careful antenatal diagnosis and genetic counseling for parental and fetal paracentric inversion.

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