

# Paternal pericentric inversion of chromosome 4 as a cause of recurrent pregnancy loss

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**Abstract**

**A paternal pericentric inversion of chromosome 4 was ascertained through karyotype analysis of an abortus specimen proven to be 46,XX,rec(4),dup q, inv(4)(p13q28). The relationship of paternal pericentric inversion to pregnancy loss is discussed, and a recommendation for karyotype analysis of recurrent abortion specimens is made.**

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Recurrent abortion, generally referring to the consecutive loss of two or more first trimester conceptions, afflicts approximately 2% of couples.<sup>1</sup> Though of obvious import to the individual couple so affected, the total contribution of parental chromosomal abnormalities to the aetiology of early pregnancy loss is exceedingly small, no more than 5%,<sup>2-5</sup> and possibly as low as 1 to 2%;<sup>6</sup> karyotypic analysis of 2500 spontaneous abortions detected only six (0.24%) as a result of major parental anomalies.<sup>1</sup> Pericentric inversions account for only 5 to 10% of the major chromosomal abnormalities found in couples with recurrent pregnancy loss. Hence the overall incidence of pericentric inversion as a cause of recurrent pregnancy loss is quite small (1/10 000); fewer than 20 such cases involving chromosome 4 have been reported. We describe here a couple with three consecutive first trimester losses, with the father having the karyotype 46,XY,inv(4)(p13q28).

**Case report**

A 38 year old, G4, A4 white female was seen with the onset of her fourth pregnancy. Her first conception occurred at the age of 17 and was electively terminated at 8 weeks' gestation without complication. At the age of 35, after 12 months of attempting conception, she achieved a pregnancy with a different (and current) partner. That pregnancy spontaneously aborted at 8 weeks' gestation. Over the subsequent two years she continued conception attempts ultimately conceiving and spontaneously aborting a third pregnancy at ap-

proximately 7 weeks' gestation. Her fourth conception occurred four months later, while being treated with clomiphene citrate, at the age of 38. An ultrasound examination at 7 weeks' gestation confirmed fetal cardiac activity; at 10 weeks she noted vaginal bleeding and a repeat ultrasound examination showed a non-viable pregnancy. A dilatation and curettage was performed and a karyotype was obtained on the products of conception and, subsequently, on the parents.

The maternal karyotype was 46,XX, the paternal karyotype was 46,XY,inv(4)(p13q28), and the fetal analysis showed the recombinant 46,XX,rec(4), dup q,inv(4)(p13q28)pat (fig 1). The carrier's father died at the age of 57 of lung cancer; the mother and younger brother declined karyotype analysis. A second brother proved also to be an inversion carrier; he and his wife had previously had a spontaneous first trimester loss, though a current pregnancy now at 5 months' gestation was proven karyotypically normal by amniocentesis.

**Discussion**

Though pericentric inversions have been detected in all chromosomes with varying frequency, chromosomes 2, 5, 7, 9, and 10 are statistically more prone to such rearrangements.<sup>2</sup> As many as 1/100 people exhibit such an inversion in the heterochromatic region of chromosome 9, which is felt to be simply a population variant; similar, but less frequent, inversions are found in chromosome 1 and in the Y chromosome. The majority of pericentric inversions are detected while investigating congenital malformations or mental retardation, and not because of recurrent pregnancy loss. Two recent investigations found 44 cases in 33 442 subjects, and six in 4272 subjects studied for recurrent loss.<sup>2,3</sup> A 1989 summary of several years of European, Canadian, and American prenatal diagnoses from 148 laboratories detailed 173 cases of pericentric inversions (from a total of 1833 parental abnormalities) of which only nine involved chromosome 4.<sup>8</sup> No other pericentric inversions of chromosome 4 with breakpoints identical to the current case have been reported, though two closely related

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Figure 1 Chromosome 4 in affected family.

instances have been characterised, (p12q25)<sup>9</sup> and (p12q26).<sup>10</sup>

Counselling couples carrying pericentric inversions regarding pregnancy outcome is difficult; an average figure for producing a liveborn abnormal offspring has generally been estimated to be 5 to 10%,<sup>11</sup> but, in fact, may be much higher or lower depending on the specific inversion. In a review of the familial data in 24 pericentric inversion index patients, most of which were ascertained through karyotyping because of mental retardation or congenital malformations, only 10 first trimester abortions in a total of 73 pregnancies (13.7%) were noted.<sup>7</sup> Similarly, a five generation pedigree of 24 inv(4) (p16q21) carriers showed no statistically significant difference in the abortion rate compared to the non-carrier sibs, and no recombinant offspring were produced.<sup>12</sup> Similarly, the abortion rate was not increased in two unrelated families involving inv(4)(p15q11)<sup>13</sup> and in a large kindred with inv(3)(p12q24).<sup>14</sup>

The mode of ascertainment of the proband obviously has a profound effect on the risk of recurrent pregnancy loss. If ascertained through repeated loss the abortion rate is over 90%<sup>4</sup>; if through alternate modes (that is, advanced maternal age, mental retardation, congenital anomalies, routine screening) there appears to be no significantly increased risk. In fact, ascertainment through repeated pregnancy loss occurs in the minority of cases; in a series of 55 pericentric inversion cases, only four (7.2%) were detected secondary to recurrent pregnancy loss.<sup>15</sup> Our method of ascertainment through analysis of the abortion specimen is exceptional.

The risk of abnormal pregnancy outcome in a pericentric inversion carrier is a consequence of the formation of gametes with partial dupli-

cation and partial deletion, which in turn result from a crossover occurring within the inverted segment during meiosis. The large inverted segment usually forms a loop to pair with its (non-inverted) homologue during meiosis; if crossover occurs within the inversion, "aneusomie de recombinaison"<sup>16</sup> results in two unbalanced gametes, one with a duplication of the inverted long arm material and a deletion of the short arm chromatin, and the other with duplication of the short arm material and a deletion of the long arm chromatin (fig 2). Chiasma formation is dependent both on the specific chromosome involved as well as on the length of the inversion. For the normal chromosome 4 the average chiasma frequency has been estimated at 2.8<sup>17</sup>; it may be significantly different when an inversion is present.

The larger the inversion the greater the chance of crossover, but the amount of chromatin deleted will be decreased, thereby giving rise to less severely unbalanced gametes and an increased chance of a liveborn, unbalanced offspring. Alternatively, as the inversion becomes smaller there is less chance of chiasma formation, both because of decreased length, but also because of the known diminished incidence of chiasma formation near the centromere. Consequently, large inversions lead to increased crossing over and less deletion (more duplication) and an increased risk of abnormal liveborn offspring whereas smaller inversions provide a lower incidence of chiasma formation but, when formed, gametes which are much more unbalanced; all of which translates into very early non-viable conceptions or karyotypically normal gestations such that no reproductive aberrations are noticed.

Until recently, chromosomal analysis of first trimester spontaneous abortions or products of conception has not been uniformly recom-

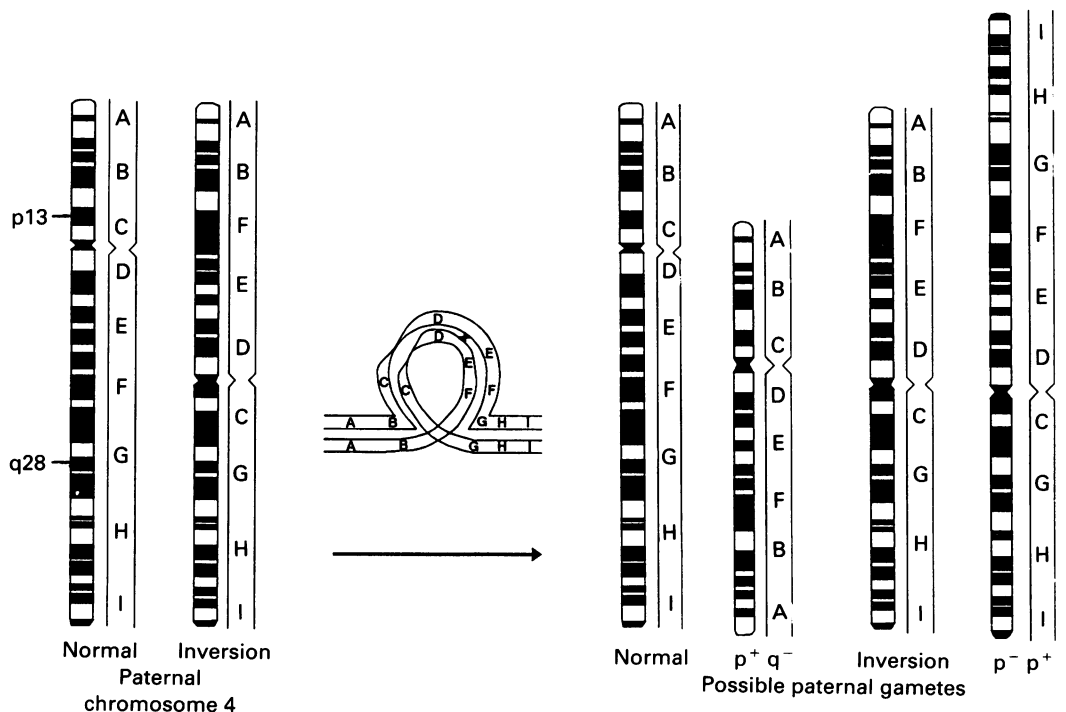


Figure 2 Chromosome 4 in possible paternal gametes.

mended,<sup>18</sup> primarily because tissue culture in such cases had a high failure rate, and because contamination with maternal cells frequently distorted the results. Recent advancements in chorionic villus culture has provided dramatic improvements resulting in 99 to 100% success rates for karyotyping abortus specimens,<sup>19,20</sup> and it would now seem economically expedient to make a concerted effort to karyotype all products of conception resulting from a second successive first trimester loss. The knowledge gained can have a major impact on the further evaluation of the couple by indicating a parental abnormality (as in the current case) or, much more frequently, confirming a lethal trisomy or monosomy X unrelated to, and not requiring delineation of, maternal or paternal karyotype or other maternal disorders. Such information is invaluable for parental counselling and for emotional support.

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