

Paracentric inversions in man

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SUMMARY We have reviewed 50 cases of paracentric inversions. Of these 34 were familial with 62 phenotypically normal carrier relatives. Twenty of the 50 were discovered fortuitously. There were two reports of children with easily recognised unbalanced karyotypes resulting from a paracentric inversion in one of the parents. The vast majority of paracentric inversions are harmless. The risk of abnormal children for paracentric inversion heterozygotes is low but increases with the finding of recurrent abortions or abnormal children or both in other carriers in the family. We emphasise the need for caution in interpreting the results of antenatal diagnosis because of (1) the variety of unexpected unbalanced chromosome types that can result from a paracentric inversion, and (2) the difficulty in recognising, with confidence, minute differences (for the detection of which very high resolution banding is required) between apparently similar parental and fetal inversions.

Paracentric inversions were undetectable in somatic chromosomes before the advent of the chromosome banding techniques. During the last few years paracentric inversions have been reported with increasing frequency. To date we have found 32 published reports. In this article we review these reports together with 18 new cases of our own.

Case reports

CASE 1

A paracentric inversion of chromosome 1 and a pericentric inversion of chromosome 7 were found in a floppy baby with cerebral palsy, karyotype 46,XX,inv(1)(q25q42),inv(7)(p12q31·2). Both inversions were found in the father and the sister who was investigated antenatally and who was a normal baby at term. Two brothers and a paternal aunt had normal chromosomes.

CASE 2

A karyotype 46,XY,inv(3)(p11p21) was found in a fetus during antenatal diagnosis carried out because of raised levels of serum alphafetoprotein in the mother. The inversion was also found in the mother and maternal grandfather.

CASE 3

A karyotype 46,XX,inv(5)(p13p15) was found in a pregnant female referred to one of us (RHL) because of the presence of this inversion in many of her relatives. The initial ascertainment was through a female relative who had had five miscarriages. The paracentric inversion was present in nine members in three generations of the family. Apart from the abortions of the index patient there were no abortions or abnormal children in the family (A McDermott, 1983 personal communication).

CASE 4

A 10 year old male with undescended testes had a karyotype 46,XY,inv(7)(q11q22). The inversion was

also found in the mother, a half brother, a half sister, and maternal uncle of the patient. One half brother and three children of the maternal uncle had normal chromosomes. There were no known abnormalities in the family.

CASE 5

A karyotype 46,XY,inv(7)(q21q32) was found in a fetus during antenatal diagnosis for maternal age (39 years). The inversion was also found in the mother.

CASE 6

A karyotype 47,XXY,inv(7)(q22q31) was found in a male referred for Klinefelter's syndrome. The inversion was also found in the father.

CASE 7

A karyotype 46,XX,inv(8)(q21·2q22) was found during antenatal diagnosis carried out because of a previous child with a neural tube defect. The father was a carrier of the same inversion.

CASE 8

A karyotype 46,XX,inv(8)(q22q24) was found in a female referred for infertility, oligomenorrhoea, hirsutism, and scanty pubic hair. It was not possible to investigate the family.

CASE 9

A karyotype 46,XY,inv(9)(q32q34) was found during antenatal diagnosis carried out because of Down's syndrome in the father's aunt. The inversion was also found in the mother of the fetus.

CASE 10

A karyotype 47,XXY,inv(11)(q21q23) was found in a patient referred for Klinefelter's syndrome. His mother had a normal karyotype. His father was dead and relatives of the father were not available for investigation.

CASE 11

A karyotype 46,XX,inv(11)(q21q23) was found in a female patient referred for habitual abortions after artificial insemination. Both her parents were dead and her only sib had a normal male karyotype.

CASE 12

A karyotype 46,XY,inv(11)(q21q23) was found in a male referred for azoospermia and raised gonadotrophins. The inversion was also found in the mother.

CASE 13

A karyotype 46,XY,inv(12)(q15q24) was found in a healthy voluntary donor for artificial insemination.

Chromosomes of the parents could not be investigated. He was second of a sibship of five. Both parents were from large sibships. There was no record of miscarriages or abnormalities.

CASE 14

A karyotype 46,XY,inv(13)(q14·1q22) was found during antenatal diagnosis carried out because of a previous child with anencephaly. The paracentric inversion appeared to have arisen de novo. The pregnancy ended in the birth of a normal boy.

CASE 15

A karyotype 46,XY,inv(14)(q24·1q32·1) was found during antenatal diagnosis performed because of raised serum alphafetoprotein levels in the mother. The same paracentric inversion was found in the father. The mother was a carrier of a balanced reciprocal translocation t(11;13)(q22·2;q22·1).

CASE 16

A karyotype 46,XY,inv(15)(q13q24) was found during antenatal diagnosis performed because of advanced maternal age (38 years). The inversion was also found in the mother, sister, and maternal aunt of the fetus.

CASE 17

A karyotype 46,XY,inv(16)(q11q13) was found in a boy referred because he was very small for his age. The inversion appeared to have arisen de novo.

CASE 18

A karyotype 47,XX,inv(21)(q21q22),+21 was found in a girl with Down's syndrome. The same inversion was found in her mother and brother.

The inversion inv(11)(q21q23) found in cases 10, 11, and 12 was identical. All these three cases were found in different parts of North Holland. However, no relationship was found going back seven generations in the three families.

The findings from these 18 patients are summarised in table 1.

Discussion

Since the first detection in *Drosophila* by Sturtevant¹ in 1921 from genetic linkage studies, inversions have been found in a wide variety of species. They are a frequent type of chromosomal aberration in natural animal and plant populations.^{2,3} In general, presence of a chromosome inversion does not of itself give rise to phenotypic abnormality, but meiotic crossing over in the inverted segment may generate chromosomally unbalanced gametes.

TABLE 1 Findings in 18 patients with paracentric inversions.

Case	Sex	Paracentric inversion	Reason for referral	Inversion carriers in family
1	F	1(q25q42)	Floppy baby, cerebral palsy	Father, sister (2)
2	M	3(p11p21)	AD for increased serum AFP	Mother, grandfather (2)
3	F	5(p13p15)	Relative with habitual abortion	5F and 4M (9)
4	M	7(q11q22)	Undescended testis	Mother, maternal uncle, half brother, half sister (4)
5	M	7(q21q32)	AD for maternal age	Mother (1)
6	M	7(q22q31)	Klinefelter's syndrome (XXY)	Father (1)
7	F	8(q21.2q22)	AD for previous child with NTD	Father (1)
8	F	8(q22q24)	Infertility, oligomenorrhoea, hirsutism	
9	M	9(q32q34)	AD for Down's syndrome in family of father	Mother (1)
10	M	11(q21q23)	Klinefelter's syndrome (XXY)	
11	F	11(q21q23)	Habitual abortion after AID	
12	M	11(q21q23)	Azoospermia	Mother (1)
13	M	12(q15q24)	Healthy volunteer for AID	
14	M	13(q14.1q22)	AD for previous child with NTD	De novo
15	M	14(q24.1q32)	AD for raised serum AFP in mother	Father (1)
16	M	15(q13q24)	AD for increased maternal age	Mother, sister, aunt (3)
17	M	16(q11q13)	Small for age	De novo
18	F	21(q21q22)	Down's syndrome (+21)	Mother, brother (2)

AD=antenatal diagnosis.
 NTD=neural tube defect.
 AID=artificial insemination by donor.

TABLE 2 Findings in 32 published cases of paracentric inversion.

Reference	Sex	Inversion	Reason for referral	Inversion carriers in family
8	F	1(p22p36)	MR	Father (1)
9	M	1(p31.2p36.22)	MR (product of brother-sister incest)	Mother +5 relatives (6)
10	F	1(p31.2p35.2)	Child with unbalanced karyotype	
11	M	3(p13p25)	MR	Mother, maternal uncle, grandmother (3)
12	M	3(p13p25)	MR	Mother (1)
12	M	3(p13p25)	AD for NTD in mother's family	Father (1)
13	F	3(p13p25)	Growth retardation	Mother (1)
14	M	3(p14p22)	Child with deletion 3p	
15		3(q13q26)	Trisomy 10q from mother	Father (1)
16	M	3(q21q28)	AD for maternal age	Mother (1)
17	F	4(p14p16.3)	AD for maternal age	Mother (1)
18	M	5(pter p13)	Child with unbalanced karyotype	
12	M	5(q13q34)	Father of trisomy 21	
19	M	5(q21q32)	Klinefelter's syndrome (XXY)	Mother (1)
20	F	7(p15p22)	Repeated abortions	Mother (1)
19	F	7(q11.3q22.3)	Turner's syndrome (XO)	Father, half brother (2)
21	F	7(q11q22)	Child with unbalanced karyotype	Mother (1)
22	F	7(q11q22)	AD for maternal age	Father (1)
23	F	7(q11q22)	Acute leukaemia	Father (1)
24	M	7(q22q31)	Survey bomb survivor	
25	M	7(q22q34)	Subfertility	Father (1)
26		11q	Repeated abortions	Familial
17	M	11(q11q23)	AD for maternal age	Mother (1)
27	M	11(q13q21)	AD for maternal age	Mother (1)
23	M	11(q13q23)	Hypoparathyroidism	Mother, brother (2)
28	M	12(p12.3p13.1)	AD	Para (4) and pericentric (8) of No 12
12	F	12(q12q24)	Repeated abortions	
29	M	12(q15q24)	Klinefelter's syndrome (XXY)	
30	M	13(q12q22)	MR	De novo
31	F	13(q14q22)	Child with unbalanced karyotype	
32	M	14(q13q24)	Microcephaly	De novo
33	M	16(q11q22)	Hypotonic newborn	Mother (1)

MR=mental retardation.
 AD=antenatal diagnosis.
 NTD=neural tube defect.

Pericentric inversions, that is, inversions in which the centromere is included in the inverted segment, have been widely reported and discussed in man.⁴⁻⁷ In contrast, paracentric inversions, that is, inversions involving only one arm of the chromosome,

were not reported in man before the advent of banding techniques. Since 1974 they have appeared with steadily increasing frequency in published reports. Details of 32 cases reported so far are presented in table 2.

TABLE 3 Chromosomes involved in 50 cases of paracentric inversions.

Chromosome	No of cases
1	4
3	8
4	1
5	4
7	10
8	2
9	1
11	7
12	4
13	3
14	2
15	1
16	2
21	1

Fourteen different chromosomes are involved in the 50 different cases of paracentric inversions, with chromosomes 3, 7, and 11 being the most frequently represented (table 3). The most frequent breakpoints are in bands 3p13 (4), 3p25 (4), 7q11 (5), 7q22 (8), 11q21 (4), and 11q23 (5). Four cases of inv(3)(p13p25) in table 2 were found in Belgium and South Holland.¹¹⁻¹³ However, no relationship could be found between the Belgian families.^{11 12} Similarly no relationship was found between our three cases 10, 11, and 12 of inv(11)(q21q23) presented in table 1. It is possible that chromosomes 3, 7, and 11 are particularly prone to paracentric inversions. However, the bands in these chromosomes, particularly in 7 and 11, are very distinct. Any shift in the position of the bands, therefore, would be easily recognised and could lead to over-representation of these cases in published reports.

The mechanism by which chromosome imbalance is generated at meiosis in carriers of paracentric inversions has been well described both in plants and animals.^{3 34 35} The risk of chromosome imbalance, as in the case of pericentric inversions, depends on the chance of pairing and of cross over occurring within the inverted segment, which in turn is proportional to the length of the inverted segment.^{36 37} Unlike pericentric inversions, however, a cross over within the inverted loop of a paracentric inversion would lead to the formation of an acentric fragment and a dicentric bridge at anaphase I. An additional cross over in the interstitial segment (that is, the segment between the centromere and the inversion) does not affect the bridge if two different chromatids are involved in the interstitial and in the loop chiasma, or if the same two chromatids are involved. If, however, one of the two chromatids in the interstitial chiasma is also involved in the loop chiasma, there is a loop instead of a bridge at anaphase I and a bridge at

anaphase II. Depending on the number of cross overs and the chromatids involved there may be single or double bridges and fragments. This would lead to the formation of chromosomally unbalanced gametes because (a) the acentric fragments, which have no capacity for movement at anaphase, are excluded from the gamete, (b) the dicentric bridge may break, leading to varying degrees of deficiency or duplication, depending on where the dicentric breaks, and (c) occasionally the dicentric may be suspended between the two polar groups of chromosomes and be excluded from both telophase nuclei or be included in one of them. If the dicentric is included in one of the gametes it could begin a breakage-fusion-bridge cycle³⁸ after fertilisation. Alternatively, there is the theoretical possibility that, following inactivation or deletion of one of its centromeres, it could form a stable structure, a pseudodicentric.

The cases in tables 1 and 2 were referred for widely varying reasons. The four major groups of subjects with paracentric inversions are as follows.

NORMAL SUBJECTS

Out of the 50 cases, 34 were familial with one or more phenotypically normal carriers of the paracentric inversion in the family. Twenty of these came to light fortuitously during antenatal diagnosis for advanced maternal age or neural tube defects or during a survey or other investigation unrelated to the presence of the paracentric inversion. This is as expected. Most paracentric inversions, particularly those involving a relatively short chromosome segment, are likely to be harmless. The risk of production of unbalanced gametes by a carrier is expected to be small. Most of the zygotes resulting from the unbalanced gametes would be so grossly abnormal that they would be lost early, even before implantation.

PATIENTS WITH INFERTILITY

Six males and two females were referred because of infertility. Four of the males had Klinefelter's syndrome with a karyotype 47,XXY (cases 6 and 10 in table 1 and references 19 and 29) and one female had Turner's syndrome and a 45,X karyotype.¹⁹ The finding of a paracentric inversion in six patients with aneuploidy (five involving the X just mentioned and one trisomy 21, case 18 in table 1) raises the question of whether the presence of a paracentric inversion increases the risk of non-disjunction. However, the finding of six out of 50 cases of aneuploidy is not significantly different from the proportion of Klinefelter's, Turner's, or Down's syndrome patients referred to a cytogenetics laboratory.

The infertility in two males (case 12 in table 1 and reference 25) and one female (case 8 in table 1) may or may not be causally related to the presence of the paracentric inversion. It should be noted that the paracentric inversion in case 12 was inherited from the mother.

In some species, such as *Drosophila*,³⁹ there is no serious reduction in fertility. This is because crossing over is absent in the male. In the female the dicentric bridge passes into the polar body and is excluded from the egg nucleus. A similar mechanism is known in *Zea mays*^{3 35} and *Sciara impatiens*,⁴⁰ in which the dicentric bridge is excluded from the megaspore and the egg nucleus respectively. However, fertility in certain male and female mouse inversion heterozygotes is significantly reduced.⁴¹ It is possible that fertility in human heterozygotes for certain paracentric inversions may be similarly affected. One possible mechanism may be that regular crossing over within the loop and the failure of the bridge to break leads to the formation of restitution nuclei and diploid spermatids. These spermatids may fail to differentiate further into functional sperm, as is the case in *Chironomus*.⁴²

COUPLES WITH RECURRENT ABORTIONS

Five cases were referred for repeated abortions. Of these, one had had artificial insemination by donor (case 11 in table 1). Although paracentric inversion in case 3 in table 1 had been initially identified in a female with repeated abortions, there was no history of abortions or abnormal children in eight other carriers in the family.

On rare occasions, chromosomally unbalanced gametes from certain paracentric inversion heterozygotes may result in zygotes which lead to a recognised pregnancy but which end in a spontaneous abortion or in the birth of an abnormal child. We can, therefore, expect to find paracentric inversion carriers among couples with repeated abortions or abnormal children.

PARENTS OF ABNORMAL CHILDREN

There are five reports of a child with an unbalanced karyotype resulting from a paracentric inversion in one of the parents.^{10 14 18 21 31} In one family,¹⁸ there are six normal carriers of the inversion in three generations. One female carrier has had three abortions, two children with a duplication, and one child with a deletion resulting from the breakage of the dicentric bridge in different places. The paracentric inversion, the chromosome with the duplication, and the chromosome with the deletion could be easily distinguished in this family.

Kelly *et al*¹⁴ presented a child with an interstitial deletion 3p14p22. The father had an inversion

inv(3)(p14p22). The deletion in the child could be caused by an excision of the inversion loop in the inverted chromosome followed by joining of the broken ends. A similar explanation offered for a deletion of 13q14q22 in the child of a mother with inv(13)(q12q22) by Sparkes *et al*³¹ is less convincing because the deleted segment is longer than the inverted segment. An alternative hypothesis for this case of an inverted insertion in the mother offered by Hoegerman⁴³ is more convincing.

Two cases^{10 21} required high resolution banding to demonstrate the difference between apparently similar inversions (using G banding) in the abnormal child and phenotypically normal parent. In both cases the child had an extra minute band (using a 850 band high resolution karyotype⁴⁴) which was attributed to an unequal crossing over at the base of the loop.

Six cases of apparently balanced paracentric inversions were found in children with mental retardation^{8 9 11 12 30} and microcephaly.³² Two of these^{30 32} had arisen de novo and it cannot be excluded that they may be chromosomally unbalanced. In one case⁹ the proband with mental retardation was a product of a brother-sister incestuous relationship and the inversion was found in six phenotypically normal relatives. In the other three cases of children with mental retardation and an inherited paracentric inversion, there may be minute karyotypic differences between the inversion in the parent and the child. Alternatively, the mental retardation may be coincidental to the inversion.

Conclusion

The vast majority of paracentric inversions are likely to be harmless. The risk of having an abnormal child for carriers of paracentric inversions is expected to be low. This risk would be increased with the finding of repeated abortions or abnormal children or both in carrier members of the family. Although patients with an increased risk should be offered antenatal diagnosis, the difficulty in interpreting the results should be recognised. This is because of the variety of unpredictable unbalanced chromosome products that can result from a paracentric inversion. Also, while deletions and duplications involving whole bands in a 400 band karyotype⁴⁴ can be easily recognised, it is very difficult, if not impossible, to detect with any confidence minute differences requiring a 850 band karyotype⁴⁴ between apparently similar parental and fetal inversions.

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References

- 1 Sturtevant AH. Genetic studies on *Drosophila simulans*. I. Introduction: hybrid with *Drosophila melanogaster*. *Genetics* 1921;5:488-500.
- 2 Dobzhansky T. *Genetics and the origin of species*. 2nd ed. New York: Columbia University Press, 1941.
- 3 Swanson CP, Merz T, Young WJ. *Cytogenetics: the chromosome in division, inheritance and evolution*. 2nd ed. Englewood Cliffs, NJ: Prentice-Hall, 1981.
- 4 Ferguson-Smith M. Clinical cytogenetics. In: Crow JF, Neel JV, eds. *Proceedings of the third international congress of human genetics*. Baltimore: Johns Hopkins University Press, 1966.
- 5 Madan K, Bobrow M. Structural variation in chromosome No 9. *Ann Genet (Paris)* 1974;17:81-6.
- 6 de la Chapelle A, Schröder J, Stenstrand K, et al. Pericentric inversions of human chromosomes 9 and 10. *Am J Hum Genet* 1974;26:746-66.
- 7 Vine DT, Yarkoni S, Cohen MM. Inversion homozygosity of chromosome No 9 in a highly inbred kindred. *Am J Hum Genet* 1976;28:203-7.
- 8 Deroover J, Fryns JP, Haegeman J, Van Den Berghe H. Paracentric inversion in the short arm of chromosome 1. *Hum Genet* 1979;49:117-21.
- 9 Romain DR, Columbano-Green LM, Whyte S, et al. Familial paracentric inversion of 1p. *Am J Med Genet* 1983;14:629-34.
- 10 Haapala K, Herva R, Leisti J. Paracentric inversion of chromosome 1 in a mother with unbalanced progeny. *Abstracts of the 8th International Chromosome Conference, Lübeck*, 1983.
- 11 Fryns JP, Van Den Berghe H. Familial paracentric inversion of the short arm of chromosome 3. *Ann Genet (Paris)* 1979;22:163-4.
- 12 Fryns JP, Van Den Berghe H. Paracentric inversion in man: personal experience and review of the literature. *Hum Genet* 1980;54:413-6.
- 13 Peters-Slough MF, Planteydt HT, Timmerman MJ, vd Vooren MJ. A familial paracentric inversion in the short arm of chromosome 3: a case report. *Clin Genet* 1982;22:102-4.
- 14 Kelly TE, Wyandt H, Kasprzak R, et al. Paracentric inversion: probable mechanism for an interstitial 3p deletion in a patient with multiple anomalies. *Am J Hum Genet* 1979;31:100A.
- 15 Bass HN, Sparkes RS, Crandall BF, Tannebaum SM. Familial partial trisomy 10q(q23→qter) syndrome and paracentric inversion 3(q13q26) in the same patient. *Ann Genet (Paris)* 1978;21:74-7.
- 16 Crandall BF, Lebherz TB, Rubinstein L, et al. Chromosome findings in 2500 second trimester amniocenteses. *Am J Med Genet* 1980;5:345-56.
- 17 Van Dyke DL, Weiss L, Roberson JR, Babu VR. The frequency and mutation rate of balanced autosomal rearrangements in man estimated from prenatal genetic studies for advanced maternal age. *Am J Hum Genet* 1983;35:301-8.
- 18 Valcárcel E, Benítez J, Martínez P, Rey JA, Sánchez Cascos A. Cytogenetic recombinants from a female carrying a paracentric inversion of the short arm of chromosome number 5. *Hum Genet* 1983;63:78-81.
- 19 Canki N, Dutrillaux B. Two cases of familial paracentric inversion in man associated with sex chromosome anomaly. *Hum Genet* 1979;47:261-8.
- 20 Stetten G, Rock JA. A paracentric chromosomal inversion associated with repeated early pregnancy wastage. *Fertil Steril* 1983;40:124-6.
- 21 Hoo JJ, Lorenz R, Fischer A, Fuhrmann W. Tiny interstitial duplication of proximal 7q in association with a maternal paracentric inversion. *Hum Genet* 1982;62:113-6.
- 22 Ridler MAC, Sutton SD. A case of a paracentric inversion inv(7)(q11q22). Prenatal detection and counselling. *Prenatal Diagnosis* 1981;1:81-4.
- 23 Orye E, Van Bever H. Paracentric inversions: two new familial cases, inv(7)(q22q11) and inv(11)(q23q13). *J Med Genet* 1983;20:231.
- 24 Shimba H, Ohtaki K, Tanabe K, Sofuni T. Paracentric inversion of a human chromosome 7. *Hum Genet* 1976;31:1-7.
- 25 Faed MJM, Robertson J, Lamont MA, et al. A cytogenetic survey of men being investigated for subfertility. *J Reprod Fertil* 1979;56:209-16.
- 26 Trunca C. Paracentric inversions: a probable cause of fetal wastage. *Am J Hum Genet* 1978;30:96A.
- 27 Verjaal M, Leschot NJ, Treffers PE, der Weduwen JJ. Unexpected chromosomal aberrations in prenatal diagnosis in older women. In: Murken JD, Stengel-Rutkowski S, Schwinger E, eds. *Prenatal diagnosis*. Stuttgart: Ferdinand Enke, 1979.
- 28 Poulsen H, Mikkelsen M, Holmgren G. Peri- and paracentric inversions in chromosome 12: prenatal diagnosis and family study. *Prenatal Diagnosis* 1981;1:35-42.
- 29 Singh RP. Klinefelter's syndrome with a 47.XXY,inv(12)(q15q24) karyotype. *Clin Genet* 1981;19:188-90.
- 30 Riccardi VM, Holmquist GP. De novo 13q paracentric inversion in a boy with cleft palate and mental retardation. *Hum Genet* 1979;52:211-5.
- 31 Sparkes RS, Muller H, Klisak I. Retinoblastoma with 13q-chromosomal deletion associated with maternal paracentric inversion of 13q. *Science* 1979;203:1027-9.
- 32 Jaeken J, Fryns JP, Standaert L, de Cock P, Van den Berghe H. De novo paracentric inversion in a microcephalic boy: 46,XY,inv(14)(q13q24). *Ann Genet (Paris)* 1980;23:105-7.
- 33 Del Solar C, Uchida IA. Identification of chromosomal abnormalities by quinacrine-staining technique in patients with normal karyotypes by conventional analysis. *J Pediatr* 1974;84:534-8.
- 34 Sybenga J. *Meiotic configurations, a source of information for estimating genetic parameters*. Berlin, Heidelberg, New York: Springer Verlag, 1975.
- 35 Schulz-Shaefcr J. *Cytogenetics, plants, animals, humans*. New York, Heidelberg, Berlin: Springer Verlag, 1980.
- 36 Winsor EJT, Palmer CG, Ellis PM, Hunter JLP, Ferguson-Smith M. Meiotic analysis of a pericentric inversion, inv(7)(p22q32), in the father of a child with a duplication-deletion of chromosome 7. *Cytogenetic Cell Genet* 1978;20:169-84.
- 37 Trunca C, Opitz JM. Pericentric inversion of chromosome 14 and the risk of partial duplication 14q(14q31→14qter). *Am J Med Genet* 1977;1:217-28.
- 38 McClintock B. The stability of broken ends of chromosomes in *Zea Mays*. *Genetics* 1941;26:234-82.
- 39 Sturtevant AH, Beadle GW. The relation of inversions in the X chromosome of *Drosophila melanogaster* to crossing over and disjunction. *Genetics* 1936;21:554-604.
- 40 Carson HL. The selective elimination of inversion dicentric chromatids during meiosis in the eggs of *Sciara impatiens*. *Genetics* 1946;31:95-113.
- 41 Ford CE, Evans EP, Burtenshaw MD. Meiosis and fertility in mice heterozygous for paracentric inversions. In: Jones K, Brandham PE, eds. *Current chromosome research*. Amsterdam: Elsevier/North-Holland, Biomedical Press, 1978.
- 42 Beerman W. Inversions heterozygotie und Fertilität der *Mannchen von Chironomus*. *Chromosoma* 1956;8:1-11.
- 43 Hoegerman SF. Chromosome 13 long arm interstitial deletion may result from maternal inverted insertion. *Science* 1979;205:1035-6.
- 44 ISCN (1981). An international system for human cytogenetic nomenclature: high-resolution banding. *Cytogenet Cell Genet* 1981;31:1-32.

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