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ORIGINAL PAPER

Origin of nondisjunction in trisomy 8 and trisomy 8 mosaicism

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Causes of chromosomal nondisjunction is one of the remaining unanswered questions in human genetics. In order to increase our understanding of the mechanisms underlying nondisjunction we have performed a molecular study on trisomy 8 and trisomy 8 mosaicism. We report the results on analyses of 26 probands (and parents) using 19 microsatellite DNA markers mapping along the length of chromosome 8. The 26 cases represented 20 live births, four spontaneous abortions, and two prenatal diagnoses (CVS). The results of the nondisjunction studies show that 20 cases (13 maternal, 7 paternal) were probably due to mitotic (postzygotic) duplication as reduction to homozygosity of all informative markers was observed and as no third allele was ever detected. Only two cases from spontaneous abortions were due to maternal meiotic nondisjunction. In four cases we were not able to detect the extra chromosome due to a low level of mosaicism. These results are in contrast to the common autosomal trisomies (including mosaics), where the majority of cases are due to errors in maternal meiosis.

Keywords: trisomy 8; mosaicism; nondisjunction; Warkany syndrome; microsatellites; mitosis; meiosis

Introduction

Chromosomal aneuploidy is one of the major causes of pregnancy wastage,[1] and autosomal trisomies 21, 18, and 13, because of their high incidence in newborns, have substantial individual and socioeconomic consequences.[2] Our knowledge about the mechanisms underlying chromosomal nondisjunction in humans is, however, still poor. Advanced maternal age remains the only well documented risk factor in nondisjunction.[3] Our biggest knowledge about chromosomal nondisjunction in man comes from studies in trisomy 21 (Down syndrome). In free trisomy 21, almost 95% of cases are of maternal origin as determined by DNA polymorphism analysis,[4,5] and among the maternal errors approximately 3/4 are a result of nondisjunction in the first meiotic division and 1/4 of nondisjunction in the second meiotic division of oogenesis.[6] Both maternal meiosis I and II errors are associated with increased maternal age.[6] About 5% of cases are due to mitotic (postzygotic) nondisjunction of a chromosome 21 in the early embryo, with equal numbers of maternal and paternal chromosomes being duplicated and without association with advanced maternal age.[7] Nondisjunction in meiosis I is associated with reduced recombination,[5,8] whilst nondisjunction in meiosis II is associated with increased recombination occurring in meiosis I, suggesting that all errors originate in meiosis I.[9]

Nondisjunction studies by DNA polymorphism analysis in trisomies 18, 16, and 13 have likewise demonstrated that the vast majority of cases are due to errors in maternal meiosis, with only a small percentage of cases due to mitotic nondisjunction.[10–12] Two molecular studies of mosaic trisomies involving chromosomes 13 (n = 2), 18 (n = 1), and 21 (n = 21) in live births have shown that the majority of cases (15/24) result from a trisomic zygote with mitotic loss of one chromosome.[13,14]

Trisomy 8 is a rare condition in man, comprising 0.7% of spontaneous abortions,[1] and is estimated to occur in about 0.1% of recognised pregnancies.[15] In live births, trisomy 8 is almost always associated with mosaicism and more than 100 cases have been reported so far.[16,17] The exact incidence in live births is not known but is certainly low. One incidence study detected one case among 34 910 newborns.[18] Trisomy 8 mosaicism has a distinct clinical picture (Warkany syndrome) including moderate mental retardation, multiple skeletal and joint anomalies, urogenital malformations, congenital heart defects, deep palmar and plantar furrows, distinct facies (especially prominent lower lip, characteristic morphology of the ears and nose), and agenesis of the corpus callosum.[16,19,20] There is a great phenotypic variability, and the phenotypic severity does not seem to be related to the degree of mosaicism in blood and skin. There is a surplus of males, and mean parental ages are slightly increased.[16,20,21] The mental retardation is usually moderate compared with the other viable autosomal trisomies, and intelligence within normal range has been described in several cases with a high level of mosaicism in blood and skin.[22,23]

Trisomy 8 represents a common clonal chromosome aberration in myelodysplastic syndromes and acute myeloid leukemias, and individuals with constitutional trisomy 8 mosaicism have an apparent increased risk of myeloid malignancies,[24,25] which occasionally lead to diagnosis of congenital trisomy 8.[26,27]

In order to increase our understanding of the mechanisms underlying chromosomal nondisjunction we have performed a molecular study on 26 cases with trisomy 8 or trisomy 8 mosaicism, for which only a few cases have been studied so far.[14,25,28–30]

Subjects and Methods

Ascertainment of Cases

The material consisted of 26 probands with trisomy 8 or trisomy 8 mosaicism and their parents. The 26 cases represented 20 live births, 4 spontaneous abortions, and 2 prenatal diagnoses (Table 1). The karyotypes were 13 of 46,XY/47,XY, + 8, six of 46,XX/47,XX, + 8, six of 47,XY, + 8, and one of 47,XX, + 8. The karyotype of one patient in addition showed an extra band distal on chromosome 1p, which by chromosome painting with a chromosome 1- specific library was shown to be of chromosome 1 origin (Table 1, case 12). Another liveborn child in addition to the trisomy 8 mosaicism (Table 1, case 21) had a fragile site on the long arm of a chromosome 16 (16q22) in 6% of the metaphases analysed.[31] The mean maternal age of all cases was 29.4 years (range 22–41), and mean paternal age was 31.5 years (range 23–45). The sex ratio was 19M:7F.

The liveborn cases were diagnosed with characteristic features of Warkany syndrome. The age at cytogenetic diagnosis ranged from 3 days to 12 years. One child with normal phenotype (Table 1, case 7) was diagnosed at the age of 11 years as having constitutional trisomy 8 mosaicism due to development of myelodysplastic syndrome with trisomy 8 in all analysed bone marrow cells.[27] One patient with apparent non-mosaic trisomy 8 in both blood and skin

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(Table 1, case 4) showed a clinical picture similar to mosaics.[32] The symptoms of the patient with the extra band on 1p were all attributable to the trisomy 8 syndrome. The level of mosaicism in the liveborn cases varied from 0% to 100% (mean 45%) in blood and from 0% to 100% (mean 64%) in skin.

The spontaneous abortions occurred in the first trimester and were non-mosaic. In three cases the karyotype was performed with the direct method (Table 1, cases 13–15) and in one case on cultured villus tissue (Table 1, case 2). Two of the mothers were primogravidae, whilst two had had one or more previous spontaneous abortions (Table 1, cases 2 and 13). Preliminary results of nondisjunction analysis for the spontaneous abortions have been reported elsewhere.[33]

The prenatal diagnoses were chorionic villus samplings (CVS). One was due to advanced maternal age (Table 1, case 16), with 67% trisomic cells in CVS culture and with a subsequent amniocentesis showing one trisomic cell out of 200 analysed metaphases. A normal child was born, and 100 mitoses from the umbilical cord showed normal karyotype, whereas 240 cells investigated from 8 placental biopsies showed 6 cells with trisomy 8. The other case was due to intrauterine growth retardation and demise in week 27 of gestation (Table 1, case 3). The karyotype was done on CVS culture; the foetal cells failed to grow. The foetus was growth-retarded with oligohydramnios. Autopsy showed no malformations.

DNA Analysis

DNA analysis for scientific purposes was done after informed consent was obtained from the parents. Genomic DNA was extracted from white blood cells and/or skin fibroblasts of the liveborn cases, from chorionic villi of the spontaneous abortions and of the CVS for prenatal diagnosis, and from white blood cells of the parents. For the DNA polymorphism analysis a total of 19 short sequence repeat (microsatellite) polymorphisms was analysed. The markers studied were the microsatellites at loci D8S264, D8S277, D8S265, D8S261, LPL, D8S133, D8S136, D8S137, D8S87, ANK1, D8S285, D8S279, D8S257, D8S85, D8S198, D8S266, D8S263, D8S256, and D8S272. Characteristics of the polymorphisms have been described elsewhere.[34,35] The markers were distributed along the length of chromosome 8 and the order of markers was known from linkage analysis.[36] The average interval size between adjacent markers was 9 cM.[36] The polymorphisms were detected after PCR amplification of genomic DNA, with end-labelling of the one primer with ^{32}P, PAGE of the amplification products, and autoradiography of the dried gels as described in detail elsewhere.[37]

Origin of Nondisjunction

The parental origin of the additional chromosome was determined by scoring three different alleles in the proband or by dosage comparison of two different alleles in the proband.[38] The visual scoring was done by two independent

Table 1 Origin of nondisjunction in 26 cases of trisomy 8 and trisomy 8 mosaicism

		Trisomy 8			
Case	*Ascertainment*[a]	*Blood (%)*	*Skin etc (%)*[b]	*Parental origin*	*Division of error*
1	LB	10	99	Maternal	Mitotic
2	SAB	–	100	Maternal	Mitotic
3	CVS	–	100	Maternal	Mitotic
4	LB	100	100	Maternal	Mitotic
5	LB	95	–	Maternal	Mitotic
6	LB	35	–	Maternal	Mitotic
7	LB	19	20[c]	Paternal	Mitotic
8	LB	45	–	Paternal	Mitotic
9	LB	6	0	–	–
10	LB	50	–	Paternal	Mitotic
11	LB	0	80	Paternal	Mitotic
12	LB	65	100	Maternal	Mitotic
13	SAB	–	100	Paternal	Mitotic
14	SAB	–	100	Maternal	Meiotic
15	SAB	–	100	Maternal	Meiotic
16	CVS	–	67	Maternal	Mitotic
17	LB	95	–	Maternal	Mitotic
18	LB	28	–	Paternal	Mitotic
19	LB	1	–	–	–
20	LB	24	–	Maternal	Mitotic
21	LB	8	–	–	–
22	LB	100	50	Paternal	Mitotic
23	LB	100	–	Maternal	Mitotic
24	LB	26	–	Maternal	Mitotic
25	LB	10	–	–	–
26	LB	80	–	Maternal	Mitotic

[a]LB = liveborn, SAB = spontaneous abortion, CVS = chorionic villus sampling; [b]Skin fibroblasts of liveborns, chorionic villi of spontaneous abortions and chorionic villus samplings; [c]Trisomy 8 in 100% of bone marrow cells.

observers. We were able to detect the extra chromosome by dosage analysis, when the trisomic cell line was present in at least 20% of the cells of the tissue from which DNA was extracted. The parental origin in such cases was confirmed by multiple markers. Unfortunately, no centromeric markers were available for this study, and no attempt was made to determine the meiotic division error. Loci heterozygous in the parent contributing the extra chromosome were identified and scored in the proband as reduced to homozygosity or non-reduced.[39] A crossover was inferred when switching from a non-reduced marker to a reduced one.[39] Mitotic non-disjunction was defined as reduction to homozygosity at all informative loci and assuming that recombination is negligible in mitosis.[7]

Results

The results of the molecular analysis are summarised in Table 1. The extra chromosome could be detected in 22 cases either by dosage analysis or by the presence of three alleles (two cases). In four cases we were not able to detect the extra chromosome due to the low level of mosaicism (1–10%, Table 1, cases 9, 19, 21, and 25). In one case where the father was not available for DNA analysis (Table 1, case 7), his genotype was deduced at most loci from analysis of a sister of the proband. In two further cases where one of the parents was not available (Table 1, cases 1 and 8), the proband shared two identical alleles at all informative loci with one of the alleles of the parent available for analysis, and therefore the most likely cause was mitotic non-disjunction of the chromosome of that parent. In total, 15 cases showed maternal origin of the extra chromosome and 7 cases paternal origin.

In two non-mosaic spontaneous abortions showing maternal origin of the extra chromosome, three different alleles were detected at more than one locus, indicating the meiotic origin of the extra chromosome. In both cases some loci showed non-reduction and other loci reduction to homozygosity, demonstrating that recombination had taken place between the nondisjoined chromosomes in meiosis I. In the other 20 cases (13 maternal, 7 paternal origin), no third allele was detected at any locus and all informative loci showed reduction to homozygosity consistent with a mitotic (postzygotic) duplication of a chromosome 8 in the early embryo. The possibility of nullichiasmatic meiosis I followed by nondisjunction in meiosis II cannot be excluded in those cases. As the linkage map of chromosome 8 suggests at least three recombination events in a normal meiosis I,[36] and as there was no obvious indication that the extra chromosome was maternally derived in our sample, this possibility is less likely. The mitotic cases included two non-mosaic spontaneous abortions, one non-mosaic CVS, one seemingly non-mosaic live birth, and one non-mosaic live birth examined only in blood.

In one of the CVS cases (Table 1, case 16), the DNA from a subsequent amniocentesis showed biparental inheritance of chromosome 8 markers.

Discussion

In trisomy 8 very little is known about the origin of the additional chromosome, as very few cases have been studied so far (Table 2). In one molecular study, four spontaneous abortions showing 100% trisomic cells were all of maternal meiotic origin, whilst one live birth with apparent non-mosaic trisomy 8 was consistent with a mitotic gain of the extra chromosome.[29] Studies of trisomy 8 mosaicism in live births have demonstrated 12 cases of mitotic duplication and only one case of probable meiotic origin.[14,25,28,29] Three cases of confined placental mosaicism involving trisomy 8 ascertained through mothers undergoing CVS for advanced maternal age also showed somatic (postmeiotic) origin of the trisomic cell line,[30] as expected in theory.[15] Our results add 20 mitotic cases (including five seemingly non-mosaic cases: two live births, two spontaneous abortions, one CVS) and two maternal meiotic cases (two non-mosaic spontaneous abortions) (Table 2). The etiology of trisomy 8 therefore seems to differ from that of common autosomal trisomies, even when considering only liveborn mosaic cases,[13,14] and represents a new addition to the expanding category of mitotically derived chromosome abnormalities, as previously described in some cases of homologous Robertsonian translocations and isochromosomes[40,41] and unbalanced *de novo* translocations.[42,43]

An excess of males was observed in the present study (19M:7F) as previously reported from clinical series.[16,20] Looking only at the mitotic cases in our study, the skewed sex ratio persists (15M:5F). A postzygotic (mitotic) duplication of a chromosome 8 in the early embryo would be expected to occur equally frequently

Table 2 Origin of the extra chromosomes in trisomy 8 and trisomy 8 mosaicism, all studies compiled

Ascertainment	*Mitotic*	*Meiotic*
Live births	29	1
Spontaneous abortion	2	6
CVS	5	0

Data from the literature[14, 25, 28–30] and present study.

in male and female embryos, and therefore the findings suggest a selection mechanism against female conceptuses with trisomy 8.

The mean maternal age at birth of the proband was reported to be slightly higher in live birth series, ranging from 28.1 years (n = 47),[16] 29 years[21] to 29.8 years (n = 44).[20] For six spontaneous abortions of maternal meiotic origin the mean maternal age was 36.7 years (Ref. 29 and present study) compared with 30.3 years for 21 live births of mitotic of the liveborn cases of mitotic origin is not known, but the sample size is small (possible ascertainment bias).

About 1–2% of prenatal CVS show chromosomal mosaicism, most often between a numerical aberration and a normal diploid cell line.[44] In most cases the mosaicism is confined to the placenta (CPM) and does not involve the foetus proper.[45] Theoretical considerations and direct observations of the distribution of abnormal cells between the cytotrophoblast (direct preparations) and extra-embryonic mesoderm (long-term culture) in cases of CPM for trisomy 8 estimated a $<5\%$ contribution of meiotic nondisjunction to the observed overall incidence of 50:100 000 samples.[15] The few cases studied so far by molecular analysis are in agreement with this estimate (Table 2). CPM for trisomy 8 in most reported cases (16/19) occurred in CVS culture, whilst the direct method showed normal karyotype.[15] One case with 100% trisomic cells by the direct method and normal karyotype in culture had adverse pregnancy outcome (intrauterine growth retardation.[30] Proposed explanations for the non-random distribution of trisomic cells in CPM include lethality of trisomy 8 in cytotrophoblast, cell-lineage specific mitotic nondisjunction, and presence of genes on chromosome 8 controlling early blastocyst development to influence the migration of cells at the morula stage.[15,30] It is interesting that trisomy 8 in CVS for prenatal diagnosis is of mitotic origin, while trisomy 8 in spontaneous abortions is of meiotic origin in the majority of cases (Table 2). Trisomy 8 of meiotic origin does not seem compatible with a continuing pregnancy.

A mosaic autosomal trisomy in CVS is usually followed by amniocentesis for trisomies likely to be found in liveborn infants. Because the cytogenetic analysis is done primarily on cells of foetal origin, a normal karyotype after amniocentesis usually reassures that the abnormality is not likely to involve the foetus. For trisomy 8 mosaicism, however, several cases of normal cytogenetic results after amniocentesis followed by mosaic trisomy 8 in the live birth have been reported.[46–48] It seems that amniotic fluid is not the best sample to reveal trisomy 8 mosaicism,[49] which represents a diagnostic and counselling problem. Trisomy 8 seems to have a very low rate of foetal uniparental disomy due to trisomic zygote rescue.[15,30]

In conclusion, the findings for trisomy 8 contrast with the common autosomal trisomies (including mosaics), where the majority of cases are due to errors in maternal meiosis. Survival of trisomy 8 seems to depend on mitotic origin of the trisomy. Maternal meiotic nondisjunction of chromosome 8 is associated with increased maternal age. Further studies are needed to determine the meiotic division error in the rare meiotic cases and to elucidate whether aberrant recombination plays a role in meiotic nondisjunction of chromosome 8.

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