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ARTICLE

Parental origin and mechanisms of formation of triploidy: a study of 25 cases

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Triploidy is one of the most frequently observed chromosome abnormalities in spontaneous abortions in humans. The parental origin of the additional chromosome set is known to have a major impact on the phenotype of the foetuses and to result in differences in size and structure of the placenta. Early studies based on cytogenetic polymorphisms indicated a preponderant diandric origin of the triploidies; such detection method, however, is known to be prone to error. Other studies revealed a predominant digynic origin in cases with longer intrauterine survival. It is now thought that, to some extent, a detection bias in favour of cases with associated partial hydatidiform moles may account for the high incidences of diandric cases reported in some studies. Furthermore, depending on the gestational age of the cases analysed there may indeed be differences in the proportion of diandric and digynic triploidies. We investigated the parental origin and mechanisms of formation of triploidy in a group of 25 probands with gestational ages ranging from 8 to 37 weeks. DNA samples were extracted from foetal material and from blood samples of the parents, and were analysed using microsatellite markers. The parental origin of the triploidies was found to be maternal in 20 cases and paternal in 5. Regarding the digynic cases, an error at meiosis I was inferred in 10 cases, whereas in the other half an error occurred at meiosis II. All five diandric cases included in this study were found to be due to dispermy. No significant differences in the average maternal ages were found amongst the different subgroups of patients. *European Journal of Human Genetics* (2000) **8**, 911–917.

Keywords: triploidy; parental origin; meiotic errors

Introduction

It is estimated that triploidy is one of the major causes of spontaneous abortion in humans.[1–3] Two distinct phenotypes are known to be associated with triploidy. A minority of foetuses presents with moderate growth retardation, proportionately sized body parts and particularly large placentas with partial hydatidiform mole (type I[4–6]). The second more common phenotype includes a more severe growth retardation. Typical in such cases is a relative macrocephaly resulting from the uneven development of body parts, with a particular growth retardation of the trunk and limbs (type II[4–6]). Features that are often observed in both groups include syndactylies, usually involving the third and fourth fingers and toes and heart defects.

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Mechanisms by which triploidies can occur are the fertilisation of a diploid gamete with a normal haploid gamete, the fertilisation of a normal ovum by two spermatozoa, or an initial mitotic error due to the duplication of one of the two pronuclei. Diploid gametes would result from a defective segregation at meiosis I or meiosis II or the incorporation of a polar body.

A number of studies are reported in the literature regarding the parental origin and mode of formation of triploidies. Whilst the reports are concordant regarding the association of a paternal origin of the additional haploid chromosome set with the type I phenotype and a maternal origin with the type II phenotype, they are discordant in regard to other issues. The proportion of diandric and digynic cases, for instance, is still unclear. Early studies, based on the analysis of cytogenetic polymorphisms, suggested a clear predominance of diandric cases.[7–9] More recent studies, based on the molecular analysis of microsatellite markers, clearly indicate that triploidies of maternal origin are far more frequent than

those of paternal origin in foetuses with gestational ages of 10 weeks or more.[5,10] Reasons for the discrepancies could be first of all related to the different methods used for ascertaining the parental origin of the triploidies; indeed, the use of molecular markers as opposed to cytogenetic polymorphisms allows a higher degree of accuracy. A further reason for the apparently contradictory results of different studies could be attributed to a detection bias in favour of cases associated with an abnormal placenta in early gestational ages. This aspect, together with a possible correlation between the parental origin of the triploidy and the gestational age at intrauterine death, could lead to marked variances in the observed ratio of digynic and diandric cases at different gestational ages.

The work presented here adds to the as yet limited number of reports addressing the origin and mode of formation of triploidies investigated using molecular markers.

Subjects and methods

The clinical features and gestational ages of the 22 foetuses and three live-born probands with triploidy are summarised in Table 1. When available, information regarding the placenta was also indicated. In our group of probands, abnormal sonographic findings were the most frequent instigation for further investigations and diagnosis of triploidy (cases 5–8, 11–14, 17–19, 21, 22 and 24). A second group (cases 1, 9, 10 and 16) were diagnosed by routine cytogenetic investigations carried out because of advanced maternal age; others were diagnosed at autopsy (cases 2, 3, 4 and 23). Case 25 was the product of an *in vitro* fertilisation; the abnormal phenotype was detected by chromosome analysis of a chorionic villus biopsy. The remaining three cases (15, 18, and 20) were referred to us without information as to when the diagnosis was made.

DNA was extracted by standard procedures from autopsy tissue samples of the probands 1–24, from chorionic villi of case 25, and blood samples of their parents. Determination of the parental origin and time of formation of the triploidies was carried out using microsatellite primers purchased from Research Genetics (Huntsville, AL, USA). The microsatellite markers were used in polymerase chain reactions (PCR) consisting of 35 cycles of a denaturing time of 30 s (3 min in the first cycle) at 94°C, an annealing temperature ranging from 52°C to 60°C, depending on the optimal temperature for each marker, for 45 s, and primer extension at 72°C for 1 min. The reactions were carried out using a Perkin Elmer PCR cycler. The PCR products were separated on 6% denaturing polyacrylamide gels and visualised by silver staining using standard procedures. The Généthon and GDB linkage maps were consulted for the localisation of the microsatellite markers.

The parental origin of the additional haploid chromosome set was determined based on a range of highly polymorphic microsatellite markers. The time and mode of formation was analysed using pericentromeric markers, whereby a number of chromosomes were investigated for each family. For digynic cases, informative markers that reveal two distinct maternal alleles at pericentromeric positions in the proband are suggestive of an error at the first meiotic division. The presence of only one of two distinct maternal pericentromeric alleles in the proband, on the other hand, is suggestive of an error at meiosis II. However, due to possible meiotic crossovers in proximity of centromeres, consistent results are not to be expected for all pericentromeric regions of a proband. Thus, for each digynic case, the mode of formation was defined based on the majority of different pericentromeric regions suggestive of either meiosis I or meiosis II. A mitotic duplication of the maternal pronucleus would result in the presence of only one of two distinct maternal alleles for all markers (pericentromeric as well as distal markers). Similarly, in cases of paternal origin, the vast majority of pericentromeric informative markers are expected to show two distinct paternal alleles in cases where an error occurred at meiosis I (this applies to probands with the karyotype 69,XXY) and only one of the paternal alleles in the cases where an error occurred at meiosis II (probands with the karyotypes 69,XXX and 69,XYY). A mitotic error would result in the presence of only one distinct paternal allele for all markers (probands with the karyotypes 69,XXX and 69,XYY). An additional mode of formation of diandric cases is dispermy, whereby the random segregation of chromosomes during spermiogenesis would lead to an approximately even distribution of two identical and two different paternal centromeres for all chromosomes in the zygote. The 69,XXY, 69,XYY and 69,XXX karyotypes can be expected in these cases. Three distinct alleles at pericentromeric regions, detected in a diandric 69,XXX case, are suggestive of dispermy. By the same token, two copies of the same paternal pericentromeric allele, in a 69,XXY proband, are also indicative of dispermy.

Results

Included in the study were all cases with triploidy referred to our Institute for which DNA samples from the probands and parents were available. The karyotypes of the probands, listed in Table 2, were previously determined using conventional cytogenetics, the majority of which were performed in our Institute. Fourteen cases had the karyotype 69,XXX and 11 had the karyotype 69,XXY.

The microsatellite analysis aimed at determining the parental origin of the triploidies revealed a maternal origin in 20 cases and a paternal origin in five cases. The markers informative as to the parental origin are underlined in Table 2; examples are given below. Of the digynic cases, 13 had the karyotype 69,XXX, and 7 had the karyotype 69,XXY; one diandric case had 69,XXX and four had 69,XXY. The assessment of the time and mode of formation of the triploidies was more arduous. For all probands at least one

Table 1 Summary of the clinical data

Patient	*Gestational age*	*Clinical findings*
1	18 5/7	microcephaly, abn. ears, microgenia, nuchal bleb, h. kidn, slightly shorter right arm, spl. toes (left foot), abn. digits (bilat. 5th fingers and big toes), small placenta
2	27 6/7	live-birth, survived for 8 days, no clinical data available
3	29	hydrocephalus, hypertelorism, microgenia, brachydactyly, abn. digits (thumbs and big toes), synd. 2-3t (right foot), small placenta with abn. villi
4	34 1/7	live-birth, survived for 13 hours; polyhydramnios, microcephaly, microphthalmia right, microgenia, abn. ears, abn. digits, bilat. synd. 3–4f
5	17	oligohydramnios, macrocephaly, microgenia, bilat. synd. 3–4f, partial synd. 2–3t, small placenta with fibrous villi and calcifications
6	25	cleft palate, microgenia, synd. 3–4f (right hand) and 3–4t (both feet), abn. digits (5th finger, left hand), abn. ears, renal hypopl., small placenta with focal abn. development of the villi
7	20 4/7	oligohydramnios, relative macrocephaly, abn. ears, abn. structure of the gyri at the cerebral cortex, arthrogryposis of the upper extremities, less obvious in the lower limbs, synd. 3–4f (left hand), 2–3f (right hand), bilat. 2–3t and 4–5t, spl. toes, abn. pulmonary lobulation, agenesis of one umbilical artery, small placenta
8	17	oligohydramnios, hydrocephalus, no autopsy
9	17	incomplete cleft palate, bilat. synd. 3–4f, and 3–4t (left foot), 2–3–4t (right foot), abdominal wall defect with protrusion of the intestine, slight regressive abnormalities of the placenta
10	36 6/7	live-birth, survived for 15 h; microcephaly, narrow palpebral fissures, high palate, abn. digits, bilat. synd. 3–4f, and 3–4t (left foot), intersexual genitalia, hypospadias, short penis, 11 ribs, hypopl. renal glands, asymmetrical cerebral ventricles, MMC
11	17	oligohydramnios, relative macrocephaly with major deformations of the head, hypertelorism, abn. ears, microgenia, no signs of partial hydatidiform moles in the placenta, renal hypopl., no synd.
12	22	hypertelorism, high nasal septum, abn. ears, bilat. synd 3–4f and 3–4t, hypoplasia of the cerebellum, atrial septal defect, h. kidn, hypopl. renal glands, small placenta with defective focal development of the villi and fibrin deposits
13	24	oligohydramnios, macrocephaly, ectropy of the left lower eyelid, bilat. synd. 3–4f, h. kidn, heart defect
14	22 1/7	relative macrocephaly, aplasia of the corpus callosum, minor ventricular septal defect, MMC, bilat. synd. 2–3–4f, abn. digits
15	22 1/7	abn. ears, synd. 3–4f (right hand)
16	13 4/7	no autopsy
17	18 4/7	synd. 2–3–4t (left foot), renal hypopl. at the right, hypopl. adrenal glands, small placenta with abnormal villi
18	19	macrocephaly, microgenia, swollen abdomen, omphalocele, MMC, synd. 2–3f (left hand), 3–4f (right hand), abn. digits (3rd toe, left foot), increased AFP values, lung hypoplasia, splenomegaly
19	18 3/7	oligohydramnios, relative macrocephaly, hypertelorism, microgenia, no synd., omphalocele, bilat. synd. 2–3–4f, and 2–3–4t, no malformations of the inner organs, hypospadias, small placenta
20	17	no clinical data available
21	29 6/7	relative macrocephaly, hypertelorism, abn. ears, abn. digits, no synd., anal atresia, ventricular septum defect, hypopl. adrenal glands, small placenta with focal abnormal development of the villi
22	20 2/7	synd. 2–3f (right hand) and 2–3–4f (left hand), no apparent malformations of the inner organs, normal sized placenta
23	8	no clinical data due to the early gestational age
24	20	one twin affected, no clinical data available
25	8	product of in vitro fertilisation, no clinical data due to the early gestational age

Note: abn. digits: disproportionate length and/or position of fingers and/or toes; abn. ears: low-set and/or malformed ears; h. kidn.: horseshoe kidneys; hypopl. adrenal glands: hypoplastic adrenal glands; MMC: lumbo-sacral myelomeningocele; renal hypopl: renal hypoplasia; spl. toes: splayed toes: synd: syndactylies, bilat: bilateral, 2–3f: 2nd and 3rd fingers, 3–4f: 3rd and 4th fingers, 2–3t: 2nd and 3rd toes, 3–4t: 3rd and 4th toes, 4–5t: 4th and 5th toes.

marker each showed the presence of three distinct alleles (indicated in italics in Table 2, see below for detailed examples), excluding a mitotic error as the mode of formation. Pericentromeric microsatellite markers for a number of chromosomes were investigated for each family and are listed in Table 2 as either supportive of meiosis I (or dispermy) or meiosis II (or dispermy). Where more than one pericentromeric marker for a given chromosome was informative, only the most proximal marker per chromosome was considered when assessing the time and mode of formation. Of the 20 digynic triploidies, 10 cases were attributed to errors at meiosis I and at meiosis II. All five diandric cases were found to be due to dispermy, thus indicating that the error occurred at fertilisation.

Table 2 Summary of molecular results obtained for the 25 probands

Case	Karyotype	Parental origin and mode of formation	Parental ages mother/ father	Markers[a] at p12–q12 suggestive of MI or dispermy	Markers[a] at p12–q12 suggestive of MII or dispermy	Markers[a] at p12–q12 non-informative as to MI, MII or dispermy	Distal markers[a]
1	69,XXX	mat. MI	36/37	12, *26*, *33*	–	9, 18, 19	54
2	69,XXX	pat. dispermy	unknown	*4*, *6*, *11*	not informative[b]	7, 9, 12, 14, 18, 19, 26, 33–35	36, 39–41, 43, 45, 46, 50, 51, 54, 56, 59–61, 71
3	69, XXX	mat. MI	28/31	1, *16*, *19*, *26*, 33	–	4, 6, 9, 12, 18, 29	54
4	69,XXX	mat. MII	32/34	*4*, *5*, *12*	1, 15, 26, 29, 33	7, 9, 13, 14, 16, 19, 35	54
5	69,XXY	mat. MII	30/32	1, *26*	4, 5, 7, 12, 16, 18, 19, 29	9, 13, 18, 33	54
6	69,XXX	mat. MII	29/33	–	12, 26, 33	9, 19	54
7	69,XXX	mat. MII	32/32	*12*	18-21, 26, 29, 33	4, 9, 16, 23, 25	54
8	69,XXY	mat. MII	31/34	*1*, 18	4, *9*, 12, 13, 28	5, 16, 17, 19, 21, 26, 29, 33	54, *60*
9	69,XXY	mat. MI	36/39	*4*, 6, 9, 15, 19, *33*	1, 12	5, 13, 16, 26, 29	*37*, 38, 54, 57, *71*, 73, *75*, *77*, 80, 81
10	69,XXY	pat. dispermy	34/36	6, *7*, *9*, *11*, 18	4, 12, 31, 33	14, 19	*36*, 41, 43, *45*, 46, 50, 54, *56*, 59, *61*, 71, *73*
11	69,XXX	mat. MI	29/26	*12*, *13*, 18, 33	–	1, 5, 9, 19, 26	44, *54*, *56*, *71*
12	69,XXX	mat. MI	28/?	*18*, *19*, 33, *34*	–	9, 12, 26	54
13	69,XXX	mat. MII	31/31	*34*	7, 9, 12, 18, 19, 33	26, 35	39, 51, 54, 56, *60*, 71
14	69,XXX	mat. MI	25/24	*12*, *18*, *26*, *33*	–	9, 19, 34	40, *51*, *54*
15	69,XXY	pat. dispermy	29/30	*7*, 9, *26*	4, 6, 11, 12	10, 14, 18, 19, 30, 31, 33, 34	36, 41, 43, 45, 46, 49, 50, 53, 59, 61, 68, *76*
16	69,XXX	mat. MII	39/44	–	1, 5, 7, 12, 13, 19, 33	9, 12, 15, 26	*64*, *65*
17	69,XXX	mat. MI	35/35	*2*, *8*, *9*, *12*, *26*	3	10, 19, 33	42, 43, 52, 53, 55, 77
18	69,XXY	pat. dispermy	30/30	*1*, *4*, 7, *9*, *12*, *19*, 24	13, 15, 28, 33, 35	5, 6, 11, 16, 27, 29, 32	36, 41, 43, 45, 54, 58, 59, 62, 69, 70, 72, 78, 79, 82–84
19	69,XXY	mat. MII	31/31	*7*	9, 12, 18, 19, 33–35	–	39, 40, 51, 54, 56, *60*, 71
20	69,XXX	mat. MII	30/30	*1*	4, 9, 19, 29, 33	5, 11, 12, 13, 16, 20	*54*
21	69, XXY	mat. MI	35/36	6, *12*, *13*, *15*, *28*	1, 8, 23	4, 5, 16, 29, 30	40, 67, *77*
22	69,XXX	mat. MII	30/30	*1*, *5*, 13, *28*	4, 8, 12, 16, 23, 29	35	40, 67, 74
23	69,XXY	pat. dispermy	29/29	–	4, 6, 7, 11	14	*36*, 41, *45*, 46, 50, *59*, 61, 63, *66*
24	69,XXY	mat. MI	31/34	*1*, *7*, *12*, 13, *28*, 30, 35	5, 15, 23	4, 11, 16, 29	47, *48*
25	69,XXY	mat. MI	35/34	*1*, *4*, 6, 7, 18	–	11, 13, 16, 23, 29	76, *79*

[a]Microsatellite markers: Markers mapping at positions between p12 and q12 of the respective chromosomes: 1: D2S2271; 2: D2S283; 3: D2S282; 4: D4S1627; 5:D6S455; 6: D6S430; 7: D7S672; 8: D7S663; 9: EGFR; 10: D7S699; 11: D8S532; 12: D8S166; 13: D10S1732; 14: D10S197; 15: D13S221; 16: D13S115; 17: TCRD; 18: D15S543; 19: D15S541; 20: D15S11; 21: GABRB3; 22: D15S165; 23: D15S122; 24: D15S128; 25: ACTC; 26: D15S217; 27: D15S97; 28: MYH6; 29: D18S452; 30: D18S62; 31: D18S57; 32: D21S258; 33: D21S215; 34: D22S283; 35: D22S448. Markers mapping at more distal positions: 36: APOA2; 37: D1S1656; 38: D1S216; 39: D1S242; 40: D1S180; 41: D1S236; 42: D2S367; 43: D2S121; 44: D3S1578; 45: D3S1278; 46: D3S659; 47: D4S2367; 48: D5S1470; 49: D5S2006; 50: D5S2027; 51: FTHP1; 52: D7S507; 53: D7S636; 54: D7S482; 55: D7S640; 56: D8S272; 57: D9S286; 58: D9S304; 59: D9S175; 60: D11S922; 61: D11S527; 62: D13S173; 63: D13S118; 64: D13S170; 65: D13S122; 66: D13S263; 67: D14S77; 68: D15S807; 69: D18S70; 70: D18S61; 71: D18S554; 72: D18S461; 73: D18S170; 74: D18S63; 75: D21S267; 76: D21S1437; 77: D21S11; 78: D21S1253; 79: D21S1255; 80: DXS441; 81: DXS984; 82: DXS996; 83: DXS1237; 84: KAL. [b]Only the maternal DNA sample was available. Underlined markers are those that were informative as to the parental origin of the additional haploid set of chromosomes. Markers indicated in italics indicate those markers that showed three distinct allele sizes in the proband.

Information regarding the interpretation of the results is also provided in the Methods section and a detailed description of the results obtained for a couple of probands should now clarify the different information gained from various markers. For instance, a total number of seven markers for proband 4 showed a maternal origin of the additional haploid set (underlined markers); three markers showed the presence of three distinct alleles which exclude a mitotic error (italics); and an error during meiosis II was inferred in this case because a larger number of markers at different pericentromeric regions was suggestive of MII (five markers) compared with those suggestive of MI (three markers). A second example is proband 10: a total of eight markers demonstrated the paternal origin of the additional haploid

set; eight markers showed the presence of three distinct alleles which exclude a mitotic error; an error during meiosis II could be excluded based on the karyotype 69,XXY and dispermy was inferred because an even number of informative markers was detected at different pericentromeric regions which were suggestive of either 'MI or dispermy' (five markers, four different chromosomes) or 'MII or dispermy' (four markers). For proband 10, marker 9 resulted in the following alleles: proband 'abd', mother 'bc', father 'ad'. Thus, in Table 2 this pericentromeric marker is underlined because two of the proband's alleles are clearly derived from the father. It is shown in italics because three distinct alleles are present and because both of the paternal alleles are present it is listed under the column 'markers at p12–q12 suggestive of MI or dispermy'. Further markers for this proband listed in the same column are, for example, marker 7 (proband 'abc', mother 'ac', father 'bc'), which is shown in italics but is not informative as to the parental origin of the triploidy; and marker 6 (proband 'aab', mother 'aa', father 'ab') which is not informative as to the parental origin nor are there three distinct alleles. However, given that the triploidy is of paternal origin the proband must have inherited alleles 'ab' from the father (thus the two different paternal alleles) and 'a' from the mother. Whilst in some cases clear intensity differences can be seen between the probands' alleles (eg marker 33: proband 10 'bbc', mother 'ac', father 'ab', whereby the proband inherited two copies of the same paternal allele), in other cases determination of parental origin based on intensity differences can be difficult (eg marker 12: proband 10 'bc', mother 'cc', father 'ab'). Again, given that the triploidy is of paternal origin, the proband must have inherited two copies of the allele 'b' from the father (thus only one of the two distinct paternal alleles) and 'c' from the mother. Markers which are not informative as to MI, MII or dispermy are, for instance, marker 14 for proband 10 (only the allele 'a' is present in the family) and marker 19 (proband 10 and both parents have the alleles 'ab'). Marker 19 in proband 6 (proband 'acc', mother 'cc', father 'ab') is informative as to the maternal origin of the triploidy but is not informative as to MI or MII because it is not possible to distinguish the two maternal alleles.

Listed in Table 3 are the numbers of cases in each category, ie MI, MII or dispermy, subdivided according to the parental ages. An overview of the gestational ages of the probands, their sex, parental origin, mode of formation and maternal age are schematically illustrated in Figure 1.

Table 3 Distribution of the triploidy cases according to parental ages

	Dygnic cases		*Diandric cases*	
Maternal age	*Meiosis I*	*Meiosis II*	*Paternal age*	*Dispermy*
20–25	1	–	–	–
26–30	3	4	26–30	3
31–35	4	5	36	1
Above 35	2	1	–	–
Maternal age unknown	–	–	Paternal age unknown	1

Discussion

Parental origin

The results we obtained by investigating a group of 25 cases for parental origin of triploidies corroborate previous molecular studies which reported a preponderant maternal origin of triploidies in foetuses with gestational ages of 10 weeks or more. Of the 23 cases above the 10th week of gestation we detected a maternal origin in 19 (82.6%). This value is slightly higher than that reported in other studies based on molecular analysis. In a group of eight foetal triploidies, McFadden and colleagues[5] determined a digynic origin in 75% of cases; and 78.5% of digynic cases was reported by Miny et al[10] in a study of 14 foetal triploidies. The foetal phenotypes detected in our group of patients are in agreement with those typically detected according to the parental origin of the additional haploid chromosome set.

Mode and time of formation

We assigned half of the digynic cases described in this study to errors at meiosis I and the other half to errors at meiosis II. However, it must be said that the high rate of meiotic crossovers at pericentromeric positions during oogenesis made the distinction between errors at meiosis I or II rather difficult in some digynic cases (eg cases 4, 21 and 22). Our

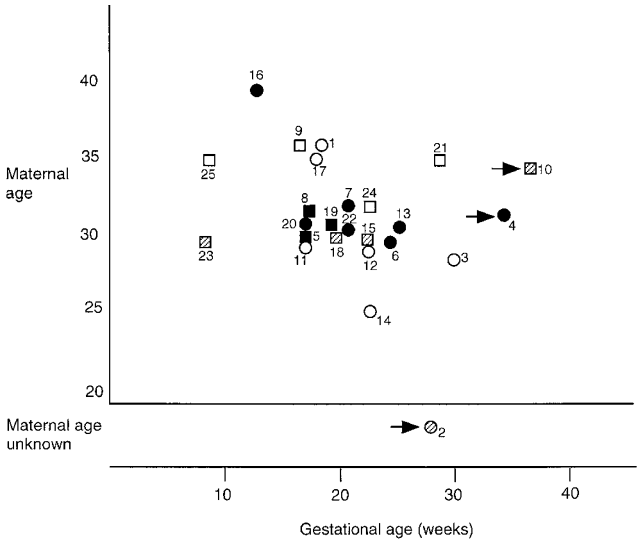

Figure 1 Gestational ages of the probands, the parental origin of the additional haploid chromosome set and the mode of formation in relation to maternal ages. Circles and squares indicate females and males, respectively; the numbers beside each symbol indicate the cases reported in Tables 1 and 2. Open and filled symbols indicate cases due to errors at meiosis I and meiosis II, respectively; hatched symbols indicate cases due to dispermy; arrows indicate live births.

results are in contrast to those of McFadden and Langlois (McFadden DE and Langlois S, 2000, personal communication), where the majority of digynic cases (in a group of 11 foetal cases) were reported to be due to errors at meiosis II. An unusually high level of pericentromeric crossovers, and thus an incorrect assignment to meiosis I or II, could be a possible reason for this discrepancy. Our results emphasise the importance of analysing the pericentromeric regions of a large number of chromosomes in order to determine the time of formation of digynic triploidies.

The mode of formation of diandric cases, on the other hand, was easier to ascertain because of the valuable indication provided by the karyotypes with respect to the sex chromosomes. All five diandric cases in this study were due to dispermy. Such a high level of dispermy is in agreement with previous studies based on cytogenetic polymorphisms.[2,11] To the best of our knowledge this is the first report addressing the mode of formation of diandric cases using molecular analysis. No significant differences in the average maternal ages were detected in our series (cases due to digynic meiosis I errors: 31.8 years; digynic meiosis II errors: 31.5 years; and diandric: 30.5 years). The average maternal age for live births in Switzerland was 30.2 years in 1998 (data from the Swiss National Office of Statistics).

Intrauterine and postnatal survival

In the vast majority of cases triploidy leads to embryonic or foetal loss. Only a small number of pregnancies result in a live birth, and the newborns usually survive for only a couple of days. Rare cases have been reported where infants with triploidy survive beyond the neonatal stage,[12–17] the longest survival reported as yet in an infant with non-mosaic triploidy was $10\frac{1}{2}$ months.[16] The lack of detection of triploid foetuses with the karyotype 69,XYY in this and other studies appears to reflect a very early loss of the conceptus[2,5,10,11] An explanation for this phenomenon could be an insufficient ratio of X chromosomes per haploid set. It is generally thought that triploidies of maternal origin have a longer intrauterine survival compared with those of paternal origin. A larger number of cases will be needed in order to confirm this hypothesis. The difficulties in assessing the intrauterine survival in relation to the parental origin of triploidy are manifold. In the early gestational weeks a detection bias is to be expected in favour of cases with placental abnormalities, and many spontaneous abortions without placental abnormalities will not be detected.[8,18,19] Furthermore, an induced abortion, following prenatal detection of triploidy, is highly recommended due to the inevitably bad prognosis for the foetus and the risks for the mothers especially with respect to severe midtrimester gestosis/pre-eclampsia in diandric triploids with hydatidiform placental changes. As far as live-born neonates are concerned the available intensive care and ethical aspects may have an influence on the survival time. In our group of probands the high number of cases with gestational ages of about 18 to 22 weeks reflect the frequent induced abortions following prenatal diagnosis, such that comparisons of intrauterine survival are not meaningful. Interestingly, however, the triploidies in two of the three live-born infants are of paternal origin and the overall survival of the triploidies of paternal origin in our group of patients is comparable with that of digynic cases.

In practice, the most important conclusion of this and similar studies is that, unlike other numerical chromosome aberrations (eg trisomies), the incidence of triploidies does not increase in women of advanced childbearing age. Thus, the early detection of affected foetuses relies primarily on prenatal screenings routinely performed for the majority of pregnancies such as ultrasonography[20,21] (which allows the detection of growth retardation, disproportionately large head, hydatidiform placental changes, myelomenigocele, and syndactylies), the AFP test,[22] low maternal estriol excretion and, in a proportion of diandric triploidies, excessive maternal serum-gonadotropin levels. On the basis of the results presented in this report, it would seem that the determination of paternal versus maternal origin of the triploidy does not allow any conclusion as to the survival of the foetuses and prognosis.

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References

1 Creasy MR, Crolla JA, Alberman ED: A cytogenetic study of human spontaneous abortions using banding techniques. *Hum Genet* 1976; **31**: 177–196.
2 Kajii T, Niikawa N: Origin of triploidy and tetraploidy in man: 11 cases with chromosome markers. *Cytogenet Cell Genet* 1977; **18**: 109–125.
3 Brajenovic-Milic B, Petrovic O, Krasevic M, Ristic S, Kapovic M: Chromosomal anomalies in abnormal human pregnancies. *Fetal Diagn Ther* 1998; **13**: 187–191.
4 McFadden DE, Kalousek DK: Two different phenotypes of fetuses with chromosomal triploidy: correlation with parental origin of the extra haploid set. *Am J Med Genet* 1991; **38**: 535–538.
5 McFadden DE, Kwong LC, Yam IYL, Langlois S: Parental origin of triploidy in human fetuses: evidence for genomic imprinting. *Hum Genet* 1993; **92**: 465–469.
6 McFadden DE, Pantzar JT: Placental pathology of triploidy. *Hum Pathol* 1996; **27**: 1018–1020.
7 Jacobs PA, Angell RR, Buchanan IM, Hassold TJ, Matsuyama AM, Manuel B: The origin of human triploids. *Ann Hum Genet* 1987; **42**: 49–57.
8 Procter SE, Gray ES, Watt JL: Triploidy, partial mole and dispermy. An investigation of 12 cases. *Clin Genet* 1984; **26**: 46–51.
9 Uchida IA, Freeman VC: Triploidy and chromosomes. *Am J Obstet Gynecol* 1985; **151**: 65–69.
10 Miny P, Koppers B, Dworniczak B *et al*: Parental origin of the extra haploid chromosome set in triploidies diagnosed prenatally. *Am J Med Genet* 1995; **57**: 102–106.

11 Couillin P, Hors J, Boué J, Boué A: Identification of the origin of triploidy by HLA markers. *Hum Genet* 1978; **41**: 35–44.
12 Cassidy AB, Whitworth T, Sanders D, Larber CA, Engel E: Five month extrauterine survival in a female triploid (69,XXX) child. *Ann Genet* 1977; **20**: 277–279.
13 Fryns JP, Van de Kerckhove A, Goddeeris P, Van den Berghe H: Survival in a case of full triploidy of maternal origin. *Hum Genet* 1982; **38**: 147–155.
14 Faix RG, Barr J, Waterson JR: Triploidy: case report of a live-born male and an ethical dilemma. *Pediatrics* 1984; **74**: 296–299.
15 Arvidsson CG, Hamberg H, Johnsson H, Myrdal U, Anneren G, Brun A: A boy with complete triploidy and unusually long survival. *Acta Paediactr Scand* 1986; **75**: 507–510.
16 Sherard J, Bean C, Bove B *et al*: Long survival in a 69,XXY triploid male. *Am J Med Genet* 1986; **25**: 307–312.
17 Niemann-Seyde SC, Rehder H, Zoll B: A case of full triploidy (69,XXX) of paternal origin with unusually long survival time. *Clin Genet* 1993; **43**: 79–82.
18 Jauniaux E, Kadri R, Hustin J: Partial mole and triploidy: screening patients with first-trimester spontaneous abortion. *Obstet Gynecol* 1996; **88**: 616–619.
19 Redline RW, Hassold T, Zaragoza MV: Prevalence of the partial molar phenotype in triploidy of maternal and paternal origin. *Hum Pathol* 1998; **29**: 505–511.
20 Gonen R, Dar H, Degani S: The karyotype of fetuses with anomalies detected by second trimester ultrasonography. *Eur J Obstet, Gynecol, Reprod Biol* 1995; **58**: 153–155.
21 Wladimiroff JW, Bhaggoe WR, Kristelijn M *et al*: Sonographically determined anomalies and outcome in 170 chromosomally abnormal fetuses. *Prenat Diagn* 1995; **15**: 431–438.
22 Feuchtbaum LB, Cunningham G, Waller DK, Lustig LS, Tompkinson DG, Hook EB: Fetal karyotyping for chromosome abnormalities after an unexplained elevated maternal serum alpha-fetoprotein screening. *Obstet Gynecol* 1995; **86**: 248–254.