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Parental Origin and Phenotype of Triploidy in Spontaneous Abortions: Predominance of Diandry and Association with the Partial Hydatidiform Mole

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The origin of human triploidy is controversial. Early cytogenetic studies found the majority of cases to be paternal in origin; however, recent molecular analyses have challenged these findings, suggesting that digynic triploidy is the most common source of triploidy. To resolve this dispute, we examined 91 cases of human triploid spontaneous abortions to (1) determine the mechanism of origin of the additional haploid set, and (2) assess the effect of origin on the phenotype of the conceptus. Our results indicate that the majority of cases were diandric in origin because of dispermy, whereas the maternally-derived cases mainly originated through errors in meiosis II. Furthermore, our results indicate a complex relationship between phenotype and parental origin: paternally-derived cases predominate among "typical" spontaneous abortions, whereas maternally-derived cases are associated with either early embryonic demise or with relatively late demise involving a well-formed fetus. As the cytogenetic studies relied on analyses of the former type of material and the molecular studies on the latter sources, the discrepancies between the data sets are explained by differences in ascertainment. In studies correlating the origin of the extra haploid set with histological phenotype, we observed an association between paternal—but not maternal—triploidy and the development of partial hydatidiform moles. However, only a proportion of paternally derived cases developed a partial molar phenotype, indicating that the mere presence of two paternal genomes is not sufficient for molar development.

Introduction

Triploidy is one of the most common chromosome abnormalities in humans, occurring in ~1% of all conceptuses. Most triploid conceptions die early in development, accounting for ~10% of all spontaneous abortions (Hassold et al. 1980). Rarely, triploid fetuses come to term, with the longest surviving nonmosaic cases dying at age ~11 mo (Sherald et al. 1986).

The high frequency of triploidy has led to many investigations of the parent and mechanism of origin of the additional haploid chromosome set and of the relationship between origin and phenotype. However, despite these efforts, the origin of triploidy remains controversial. Early cytogenetic studies of triploidy, based on analysis of pericentromeric chromosome heteromorphisms, concluded that over two-thirds of cases originated from the father (diandric triploidy), typically as a result of dispermy (Kajii and Ohama 1977; Jacobs et al. 1978, 1982; Uchida and Freeman 1985). Furthermore, when data on parental origin were compared to those on phenotype, the majority of paternally derived—but not of maternally derived—triploids were found to be partial hydatidiform moles, conceptuses with abnormal placentas characterized by trophoblastic proliferation and hydropic chorionic villi (Szulman and Surti 1978; Jacobs et al. 1982).

As these observations were based on studies of over 200 triploids, there seemed little reason to doubt their accuracy. Indeed, by the late 1980s it was generally assumed that (1) most triploids were paternal in origin, (2) there was a parent-of-origin effect on the phenotype of triploids, and (3) a large proportion of triploids were partial hydatidiform moles. Thus, it was somewhat surprising when, in 1993, a DNA polymorphism study of triploidy (McFadden et al. 1993) reported a preponderance of maternal cases (digynic triploidy), a conclusion later supported by two other molecular studies of triploidy (Dietzsch et al. 1995; Miny et al. 1995). Furthermore, McFadden and Pantzar (1996) subsequently reported that only 15% of triploids were partial hydatidiform moles, a level much lower than that estimated from the earlier cytogenetic data. Thus, the molecular data directly challenged two of the three major conclusions of earlier cytogenetic studies.

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Table 1

Microsatellite Markers Used to Determine Parent and Mechanism of Origin of Triploidy

Type and Locus	Chromosomal Location	Distance to Centromere (cM)
Pericentromeric set 1:		
D1S514	1p13.1	2
D1S442	1	0
D6S294	6p11-p12	3
D6S402	6q11	2
SPN	16q11.2	1
D16S285	16q12.1	1
D17S122	17p11.2	2
D17S798	17	1
Pericentromeric set 2:		
D2S388	2p11.2-p12	4
D2S135	2q11.2-q12	4
D3S1595	3p12-p11	2
D3S1603	3q12	2
D10S193	10p12-p14	5
D10S196	10q11.2	5
D18S453	18p11.1-11.2	5
D18S45	18q11.2-q11.2	5
D19S407	19p	3
D19S49	19q12-q13	3
D1S180	1q42	120
D1S1609	1q	110
D2S125	2q	170
D2S407	2q	150
D3S1297	3pter-p25	110
D3S2387	3p	110
D4S2417	4q	130
D4S1554	4q34-q35	140
D5S429	5q35	120
D5S1456	5q	120
Other loci:		
DXS991	Xp11.2	...
AR	Xq11.2-q12	...
DXS207	Xp22.2	...
D7S495	7q31-q35	...
D21S11	21q21	...

While the basis of these discrepancies is unclear, there are at least two possible explanations. First, the discrepancies might reflect methodological differences between cytogenetic and molecular approaches; that is, the cytogenetic data were based on analyses of cytologically detectable size and staining variants, an approach subject to considerable misinterpretation. Indeed, early cytogenetic studies of trisomy 21 indicated a much higher level of paternal nondisjunction than was found in subsequent molecular studies (Antonarakis et al. 1991; Lorber et al. 1992). Thus, as originally suggested by McFadden (1993), the cytogenetic studies of triploidy might have overestimated the frequency of diandric triploidy. Alternatively, the discrepancies might be attributable to differences in the study populations. The cytogenetic studies utilized tissue samples from surveys of spontaneous abortions, with most of the gestational ages being 8–20 wk. Material was collected irrespective of the phenotype of the conceptus, and, frequently, only extraembryonic material was evident in such cases. In contrast, the molecular studies were largely restricted to cases with a well-formed fetus (McFadden et al. 1993; Dietzsch et al. 1995; Miny et al. 1995), or to cases with embryos or cases ascertained during the embryonic period (<10 wk gestation) (McFadden et al. 1994; McFadden and Langlois 1997). Thus, if differences in origin exist between triploids with and without extensive fetal development or between triploids aborting extremely early and those aborting later, differences might be expected between the results of the cytogenetic and molecular studies.

Since triploidy is one of the most common human-chromosome abnormalities, and since there is continuing uncertainty regarding the frequency and natural history of partial hydatidiform moles (Redline et al. 1998), it is important to resolve these discrepancies. Therefore, we used DNA markers to reinvestigate the mechanism of origin of triploidy in a population of unselected spontaneous abortions of gestational ages <20 wk and have compared the information on origin with results of histological studies.

Our results indicate a complex relationship between developmental age and parental origin of triploidy. Paternally-derived cases predominate among "typical" spontaneous abortions, whereas maternally derived cases are associated either with early embryonic demise or with relatively late demise involving a well-formed fetus. As the cytogenetic studies relied on analyses of the former type of material and the molecular studies on the latter, the discrepancies between the data sets are explained by differences in ascertainment.

Material and Methods

Study Population

The study population consisted of 91 nonmosaic, triploid conceptuses ascertained from two sources: University Hospitals of Cleveland ("Cleveland" cases) and Magee-Women's Hospital, Pittsburgh ("Pittsburgh" cases). In Cleveland, we collected material from 64 triploids, ascertained as part of a cytogenetic study of a consecutive series of spontaneous abortions with gestational ages ≤20 wk; thus, these cases were ascertained without regard to placental phenotype. In Pittsburgh, we obtained tissue from 27 triploid spontaneous abortions, ascertained for any of several reasons, including advanced maternal age and abnormal placental morphology. Thus, a proportion of these cases were ascertained because of molar changes on histological examination. Cases in which sufficient frozen tissue was available from chorionic villi and decidua were selected for the study.

Cytogenetic Studies

Culturing and cytogenetic analysis of tissue samples from triploids were performed using previously described procedures (Hassold et al. 1980). For each case, we attempted to score 10–15 cells.

Histological Studies

Hematoxylin-eosin stained tissue sections of chorionic villi for each case were examined microscopically by a single pathologist (R.R.), without knowledge of the results of the DNA analysis. Each case was evaluated to be a partial hydatidiform mole or nonmolar by scoring for the presence or absence of four features: circumferential trophoblastic hyperplasia, hydropic villi, irregular villous contour, and dimorphic villi. A case was scored as a partial mole when all four features were present (Szulman and Surti 1978). Each case was also evaluated for the presence or absence of fetal tissue, by gross examination for intact embryo/fetus proper or fragments of embryo/fetus and by histological analysis for fetal tissue. In addition, the age of the abortus was determined in two ways: by gestational age, defined as the time between the first day of the last menstrual period and the day of abortion; and by developmental age of the abortus (<6.0 wk, 6.0–8.5 wk, 8.5–11.5 wk, and >11.5 wk), using specific histologic criteria. Further details of the histological analysis are described elsewhere (Redline et al. 1998).

Molecular Analysis

Microsatellite polymorphisms were analyzed to determine the parent and mechanism of origin of the extra haploid set of chromosomes. For these studies, DNA was extracted from maternal decidua and fetal tissue dissected from paraffin blocks by the method of Lane et al. (1993) or by a commercially available DNA extraction kit (Qiagen). Alternatively, DNA was obtained from frozen tissues, chorionic villi, maternal decidua and parental blood samples, by standard methods. Subsequently, DNA was amplified in a total volume of 25 μl, by use of standard conditions and "low or high touchdown" protocols (Don et al. 1991) or by use of an annealing temperature of 55°C–65°C. PCR products were separated by polyacrylamide gel electrophoresis and were visualized by autoradiography.

DNA Markers

We utilized a total of 33 DNA markers, located on human chromosomes 1–7, 10, 16–19, 21, and X. Of these markers, 18 were designated as pericentromeric and 10 as distal (table 1); as described below, they were used to distinguish between meiosis I (MI), meiosis II (MII) and postmeiotic origins of triploidy. Mapping and PCR primer information for each locus was obtained from the Genome Database. Typically, 10–20 markers were analyzed per family.

There were two types of pericentromeric markers: *set 1* consisted of those in which the centromere (as defined by alphoid DNA)-to-marker genetic distances are available, with each marker <3 cM from the centromere, and *set 2* consisted of five pairs of markers bracketing the centromeric regions of chromosomes 2, 3, 10, 18, and 19, with each distance between markers estimated as $\leqslant$10 cM (Genome Database). The 10 distal markers consisted of two markers each for chromosomes 1–5, each estimated to be $\geqslant$100 cM from the centromere.

Analysis of Parental Origin

For each case, we first determined the parental origin of triploidy. A total of 91 cases were analyzed, including 3 (A115, A1015, and B96) involving "complete" families, in which DNA was available for the fetus and both parents, and 88 involving "incomplete" families, in which DNA was available only for the fetus and mother. For cases involving "complete families," parental origin determinations were straightforward, and, in each, the determination was based on at least three informative markers.

For cases involving "incomplete families," we were able to conclude a paternal origin if the fetus shared only a single allele with the mother at multiple loci. For most such cases, paternal determinations were based on at least three informative markers. However, assignments of maternal origin in "incomplete" families were not as straightforward, since information on the paternal genotype was not available. Thus, we concluded a maternal origin by one of two methods. First, in triploids with a 69,XXX chromosome constitution, the analysis of X-linked DNA markers DXS991, AR, and DXS207 frequently enabled us to specify a maternal origin. That is, if the fetus showed three different alleles, two must have come from the mother, since the father could only have contributed a single X-linked allele. Second, we used statistical methods to determine both the parental origin and mechanism of triploidy, given the results of the cytogenetic and DNA analysis. This method is briefly described in the following section and in detail in the Appendix.

Determination of Mechanism of Origin

We estimated the most likely mechanism of origin for each triploid. This analysis entailed assaying pericentromeric and distal genetic markers on multiple chromosomes and determining whether or not parental heterozygosity was maintained (nonreduction) or was reduced to homozygosity (reduction) in the triploid offspring. Expectations of nonreduction/reduction are

shown below for each of the possible mechanisms of origin of triploidy (table 2). On the basis of the pattern of nonreduction/reduction at pericentromeric markers, we could then exclude certain mechanisms. For example, if, at one pericentromeric marker, the mother was cd and the fetus abc (nonreduction), we could rule out all maternal errors and a paternal meiosis II error; this would leave dispermy or a paternal meiosis I error as the only possible sources of triploidy. If, at a second pericentromeric locus on a different chromosome, the mother was bc and the fetus aab (reduction), we could exclude a paternal meiosis I event; thus, dispermy would remain as the only possible mechanism of origin. Thus, no one pericentromeric marker could be conclusive, but, by combining results from several markers, specific mechanisms could be excluded. By use of this approach, we were able to specify a mechanism of origin in most cases.

However, to more formally distinguish between mechanisms by means of this approach, we developed a likelihood method to determine the most likely mechanism of origin. Our approach was similar to that of Jacobs and Morton (1977) for chromosome heteromorphism studies of polyploidy, but our approach was modified to take into account the effect of recombination, as detailed by Chakravarti and Slaugenhaupt (1987). Additionally, since the majority of our cases involved "incomplete" families, the method was modified accordingly (see Appendix). We applied this likelihood method to all cases; however, it was most useful in those cases in which straightforward analysis could not readily identify the most likely mechanism.

In brief, we first considered the most likely six mechanisms of origin of triploidy involving either a single diploid gamete (errors at maternal MI or MII; errors at paternal MI and MII) or two independent haploid gametes ("dieggy" and dispermy). The conditional likelihood for each of the six mechanisms was then determined for each of the three possible sex-chromosome constitutions of the fetus (Jacobs and Morton 1977) and for each of the 10 possible genotype results of the mother and fetus for each pericentromeric marker (see Appendix). The total likelihood for each mechanism was then calculated as the product of the likelihood of the results for the sex-chromosome constitution and the results for all pericentromeric markers. We considered an origin to be "known" if the most likely mechanism had a total likelihood at least five times greater than the next most likely mechanism. Cases in which the most likely mechanism did not meet these criteria were scored as "unknown."

We also considered triploidy originating from a postmeiotic "mitotic" error, a mechanism leading to homozygosity of all informative loci. To distinguish this type of error from a meiosis II error, we examined distal loci. If all loci were reduced, we scored the case as arising from a "mitotic" error, but if one or more loci were nonreduced, we scored the case as arising from a meiosis II error.

Finally, we used this approach to make determinations of maternal origin of triploidy. First, the posterior probability of each of the six mechanisms was calculated as the likelihood divided by the sum of the likelihood of all six mechanisms—that is, under the assumption that all six origins were equally likely a priori. The likelihood of maternal to paternal origin was calculated as the ratio of the sum of the probabilities of all maternal mechanisms to the sum of the probabilities of all paternal mechanisms. Maternal origin of triploidy was concluded when the likelihood of maternal origin was at least five times greater than that of paternal origin.

Results

In table 3, for all 91 cases, detailed information is provided on chromosome constitution, maternal age at delivery, developmental and gestational ages of the abortus, placental morphology, and parent and mechanism of origin. We were unable to make a parental-origin assignment in 4 of the 91 cases, in 2 cases (B134 and B136) because the amount of fetal or maternal DNA was insufficient for complete molecular analysis and in 2 cases (A403 and A638) because we were unable to dissect decidual tissue from the paraffin blocks. Thus, the final data set consisted of 87 cases.

Table 2

Predicted Outcomes of Tetratypes at Pericentromeric and Distal Markers under Different Assumed Mechanisms of Origin of Triploidy

Mechanism of Origin	Pericentromeric[a]	Distal[a]
Failure of meiosis I	N	N or R
Failure of meiosis II	R	N or R
Fertilization by or of two gametes (dispermy or "dieggy")	N or R	N or R
Fertilization involving tetraploid oogonium or spermatogonium	N or R	N or R
Premeiotic germ cell with meiotic failure	N	N
Postmeiotic "mitotic" error (e.g., endoreduplication)	R	R

[a] N = nonreduction; R = reduction to homozygosity.

Table 3

Results of Cytogenetic, Molecular and Histological Studies in 91 Cases of Triploidy

Series and ID	Chromosome Constitution	Maternal Age	Gestational Age (wk)	Developmental Stage[a] (wk)	Presence (+) or Absence (−) of[a]			Odds Maternal: Paternal Origin	Odds Mechanism 1: Odds Mechanism 2	Mechanism of Origin[b]
					Partial Mole	Trophoblastic Hyperplasia	Fetal Tissue			
Cleveland:										
A13	69,XXY	32	6	<6.0	−	−	−	10:1	5:1	MAT-"dieggy"
A16	69,XXY	33	14	>11.5	−	+	−	0:1	5:1	PAT- meiosis I
A41	69,XXX	34	7	<6.0	−	−	+	10:1	…	MAT
A80	68,XXY,-13	33	10	8.5–11.5	−	+	−	0:1	…	PAT
A108	69.XXY	21	6	8.5–11.5	−	−	−	0:1	5:1	PAT-meiosis I
A114	69,XXX	20	18	8.5–11.5	−	+	−	0:1	10^4:1	PAT-dispermy
A115	69,XXY	30	13	>11.5	+	+	+	0:1	5:1	PAT-meiosis I
A121	69,XYY	22	18	8.5–11.5	−	−	−	0:1	10^3:1	PAT-dispermy
A181	69,XXY	32	12	6.0–8.5	−	−	+	10^3:1	…	MAT
A183	69,XXY	26	18	>11.5	−	+	−	0:1	100:1	PAT-dispermy
A191	69,XXY	20	11	6.0–8.5	−	+	−	100:1	5:1	MAT-meiosis II
A214	69,XXY	27	10	6.0–8.5	−	−	−	10:1	…	MAT
A218	69,XXX	24	15	>11.5	−	−	+	10:1	…	MAT
A219	69,XXX	34	8	6.0–8.5	−	−	+	1:0	10^3:1	MAT-meiosis II
A222	69,XXX	38	5	6.0–8.5	−	+	−	0:1	…	PAT
A229	69,XYY	26	12	<6.0	−	−	−	0:1	1:0	PAT-dispermy
A308	69,XXY	38	13	>11.5	−	−	+[c]	100:1	10:1	MAT-meiosis II
A309	69,XXY	24	10	8.5–11.5	−	−	+	10^4:1	10:1	MAT-meiosis II
A319	69,XXY	28	10	6.0–8.5	−	−	+	10:1	…	MAT
A322	70,XXY,+2	22	8	6.0–8.5	+	+	−	0:1	5:1	PAT-meiosis I
A345	69,XXY	35	12	8.5–11.5	+	+	+	0:1	10:1	PAT-dispermy
A349	69,XXX	32	12	>11.5	−	−	−	0:1	…	PAT
A356	69,XXY	17	14	8.5–11.5	−	−	−	0:1	…	PAT
A358	69,XXY	42	13	>11.5	+	+	−	0:1	10:1	PAT-dispermy
A367	69,XXY	24	10	8.5–11.5	−	+	−	0:1	100:1	PAT-dispermy
A390	68,XX	26	13	>11.5	+	+	−	0:1	10:1	PAT-dispermy
A403	69,XXX	26	8	6.0–8.5	−	−	+[c]	2:1	…	Unknown
A443	69,XXX	18	6	6.0–8.5	+	+	−	0:1	10^3:1	PAT-dispermy
A452	69,XXY	30	13	8.5–11.5	+	+	−	0:1	100:1	PAT-dispermy

A456	69,XXY	21	9	8.5–11.5	−	−	+	0:1	…	PAT
A473	70,XXY,+7	24	7	6.0–8.5	−	+	−	0:1	10:1	PAT-dispermy
A487	69,XXY	23	…	<6.0	−	−	+[c]	100:1	…	MAT
A505	69,XYY	21	7	<6.0	−	−	−	0:1	1:0	PAT-dispermy
A507	69,XXY	39	…	>11.5	+	+	−	0:1	…	PAT
A528	69,XXX	23	12	8.5–11.5	+	+	−	0:1	10^4:1	PAT-dispermy
A539	69,XXY	33	12	6.0–8.5	−	+	−	0:1	100:1	PAT-dispermy
A557	69,XXX	26	8	8.5–11.5	−	−	−	10^3:1	10:1	MAT-meiosis I
A572	69,XXX	46	11	6.0–8.5	−	−	−	1:0	100:1	MAT-meiosis II
A574	69,XXY	19	11	<6.0	−	−	−	10^4:1	100:1	MAT-meiosis II
A576	69,XXX	29	12	8.5–11.5	−	+	+[c]	10^4:1	…	MAT
A592	69,XXX	26	11	6.0–8.5	+	+	−	0:1	10^6:1	PAT-dispermy
A638	69,XXY	21	14	6.0–8.5	+	+	+[c]	1:1	…	Unknown
A642	69,XXX	31	10	8.5–11.5	−	+	−	0:1	100:1	PAT-dispermy
A722	69,XXY	33	13	>11.5	−	+	−	0:1	5:1	PAT-dispermy
A753	69,XXX	17	12	8.5–11.5	−	−	+	1:0	10:1	MAT-meiosis II
A764	69,XXY	27	8	<6.0	−	−	−	10^4:1	100:1	MAT-meiosis I
A766	69,XXY	14	16	>11.5	+	+	−	0:1	10:1	PAT-dispermy
A770	69,XXY	33	14	8.5–11.5	−	+	−	0:1	…	PAT
A778	69,XXY	22	11	8.5–11.5	+	+	−	0:1	…	PAT
A790	69,XXY	19	16	>11.5	+	+	−	0:1	…	PAT
A805	69,XXY	24	13	>11.5	+	+	−	0:1	…	PAT
A830	69,XXY	30	16	8.5–11.5	+	+	+[c]	0:1	10:1	PAT-dispermy
A851	69,XXY	20	10	8.5–11.5	+	+	−	0:1	5:1	PAT-dispermy
A860	69,XXX	27	11	8.5–11.5	+	+	+	0:1	10^4:1	PAT-dispermy
A865	68,XX	26	10	6.0–8.5	−	−	+	10^5:1	100:1	MAT-meiosis II
A895	69,XXX	30	10	8.5–11.5	+	+	−	0:1	…	PAT
A949	69,XXY	26	9	8.5–11.5	−	−	+	100:1	10:1	MAT-meiosis II
A970	69,XXY	36	15	>11.5	+	+	+	0:1	…	PAT
A972	69,XXY	29	7	6.0–8.5	−	−	+	10^3:1	10:1	MAT-meiosis II
A985	69,XXY	32	9	8.5–11.5	−	−	−	10^5:1	100:1	MAT-meiosis II
A1002	69,XXY	49	…	<6.0	−	−	−	100:1	…	MAT
A1011	69,XXX	35	13	8.5–11.5	+	+	+	0:1	10^3:1	PAT-dispermy
A1015	69,XXY	32	…	6.0–8.5	−	−	−	10^5:1	100:1	MAT-meiosis I
A1036	69,XXY	…	…	<6.0	−	−	−	0:1	…	PAT
Pittsburgh:										
B65	69,XXY	30	14	6.0–8.5	−	−	−	0:1	100:1	PAT-dispermy
B66	69,XXX	36	15	>11.5	+	+	−	0:1	…	PAT
B67	69,XXY	30	14	>11.5	+	+	+[c]	0:1	100:1	PAT-dispermy

(*continued*)

Table 3 Continued

Series and ID	Chromosome Constitution	Maternal Age	Gestational Age (wk)	Developmental Stage[a] (wk)	Presence (+) or Absence (−) of[a]			Odds Maternal: Paternal Origin	Odds Mechanism 1: Odds Mechanism 2	Mechanism of Origin[b]
					Partial Mole	Trophoblastic Hyperplasia	Fetal Tissue			
B68	69,XXX	29	13	8.5–11.5	+	+	+[c]	0:1	100:1	PAT-dispermy
B87	69,XXY	36	15	8.5–11.5	+	+	−	0:1	5:1	PAT-dispermy
B88	68,XXY,-22	30	11	6.0–8.5	+	+	−	0:1	10:1	PAT-dispermy
B89	70,XXX,+11	27	13	6.0–8.5	−	+	−	100:1	…	MAT
B90	69,XXX	…	11	6.0–8.5	−	−	−	0:1	10:1	PAT-dispermy
B91	69,XXX	26	19	6.0–8.5	−	−	+[c]	1:0	100:1	MAT-meiosis I
B92	69,XXY	28	…	6.0–8.5	+	+	−	0:1	5:1	PAT-dispermy
B93	69,XXX	23	12	8.5–11.5	−	−	−	0:1	10^6:1	PAT-dispermy
B94	70,XXY,+2	32	13	8.5–11.5	+	+	−	0:1	…	PAT
B95	68,XXY,-3	27	10	>11.5	+	+	−	0:1	10:1	PAT-dispermy
B96	69,XXX	…	…	6.0–8.5	−	−	+[c]	10^4:1	10:1	MAT-meiosis II
B97	69,XXY	26	15	>11.5	+	+	+[c]	0:1	…	PAT
B98	69,XXX	…	12	>11.5	−	−	+[c]	10^4:1	40:1	MAT-"dieggy"
B99	69,XXX	…	13	6.0–8.5	−	−	−	0:1	200:1	PAT-meiosis II[d]
B100	69,XXX	30	19	8.5–11.5	+	+	−	0:1	10:1	PAT-dispermy
B104	69,XXX	27	11	6.0–8.5	−	+	−	0:1	25:1	PAT-meiosis II
B128	72,XXY,+2,+18,+20	23	…	8.5–11.5	−	+	−	0:1	…	PAT
B129	69,XXX	37	13	8.5–11.5	+	+	+[c]	0:1	10:1	PAT-dispermy
B130	69,XXY	26	13	NT	NT	NT	NT	0:1	10:1	PAT-dispermy
B132	69,XXY	26	…	>11.5	+	+	+[c]	0:1	5:1	PAT-dispermy
B133	69,XXY	31	13	>11.5	+	+	+[c]	0:1	100:1	PAT-dispermy
B134	69,XXX	32	11	8.5–11.5	+	+	−	4:1	…	Unknown
B135	69,XXX	…	9	NT	NT	NT	NT	0:1	100:1	PAT-dispermy
B136	69,XXX	21	…	NT	NT	NT	NT	2:1	…	Unknown

[a] NT = not tested.

[b] Parent and mechanism of origin were assigned whenever odds were ⩾5:1—that is, when the likelihood of maternal origin was at least five times greater than that of paternal origin, maternal origin was concluded. Mechanism of origin was assigned when the likelihood of the most likely mechanism (mechanism 1) was at least fives times greater than that of the next most likely mechanism (mechanism 2).

[c] Gross examination revealed the presence of intact or fragments of an embryo or fetus.

[d] Results of distal markers consistent with postmeiotic "mitotic" origin.

A proportion of maternal assignments were based on likelihood ratios, with maternal:paternal odds of 5:1 or higher arbitrarily taken as evidence of maternal origin (see Material and Methods); if we had used a 10:1 cutoff value, no parental-origin assignments would have changed, but if we had required odds of 100:1, we would have made five fewer parental-origin assignments. Similarly, determinations of the exact mechanism of origin were based on likelihood ratios, with a specific mechanism being assigned only if its likelihood was at least five times greater than the next most likely origin. Using this cutoff value, we were able to specify a mechanism of origin in 61/87 cases (table 3); had we chosen a 10:1 value, 50/87 would have been informative. The likelihood ratios for both parent and mechanism of origin are provided in table 3 (conditional likelihoods and probabilities for each case are available upon request to the corresponding author).

DNA Studies of the Origin of Triploidy

The results of the DNA studies for parent and mechanism of origin of triploidy are provided in detail in table 3 and are summarized in table 4. Of the 87 cases, 60 (69%) were diandric and 27 (31%) were digynic in origin. The results were also considered separately for the Cleveland and Pittsburgh study populations, since ascertainment varied between the two series (table 4). In the Cleveland series, 63% of cases were diandric, whereas in the Pittsburgh series there was a higher—although not significantly different—proportion of paternal cases, since 84% were diandric in origin (table 4).

We were able to specify a mechanism of origin of triploidy for 61 of the 87 cases, including 43 of the cases of paternal origin and 18 of the cases of maternal origin (table 4). Among the diandric triploids, the most common mechanism of origin was dispermy, which accounted for 37 (86%) of the 43 cases. Of the remaining six cases, four (A16, A108, A115, and A322) were scored as arising at meiosis I and one (B104) at meiosis II. The final case (B99) was scored as resulting from a postmeiotic "mitotic" error.

In contrast, most digyny originated from a diploid egg, in 12 (67%) of 18 cases from failure of meiosis II and in 4 cases (22%) from failure of meiosis I. Surprisingly, two cases (A13 and B98) were scored as arising from the fusion of two ova (i.e., "dieggy,") with likelihoods >5 times and >40 times, respectively, that of an origin from failure of maternal meiosis II.

Histological Studies of Placental Morphology

Histological preparations were available on 88 of the 91 cases of triploidy (table 3). Of these, 51 cases (58%) were scored as having trophoblastic hyperplasia, and 35 (40%) were diagnosed as partial hydatidiform moles. The incidence of partial moles was slightly higher among the Pittsburgh cases, but the difference between the series was not significant.

Table 4

Parent and Mechanism of Origin of Triploidy

Population and Parental Origin	Total No. of Cases	Mechanism of Origin			
		Meiosis I	Meiosis II	"Dieggy" or Dispermy	Unknown
Cleveland:					
Maternal	23	3	11	1	8
Paternal	39	4	0	22	13
Unknown	2	0	0	0	2
Pittsburgh:					
Maternal	4	1	1	1	1
Paternal	21	0	2[a]	15	4
Unknown	2	0	0	0	2

[a] One case consistent with postmeiotic "mitotic" error.

Association of Placental Morphology with the Origin of Triploidy

Subsequently, we correlated the results of the histological and DNA studies, to determine if the parental origin of the additional set of chromosomes influenced the phenotype. First, we compared the frequency of each of three "phenotypic" features—diagnosis as a partial mole, presence or absence of trophoblastic hyperplasia, and presence or absence of fetal tissue—between diandric and digynic triploids (table 5). Significant differences were observed for each of the three variables. Diandric triploids were more commonly diagnosed as partial moles ($\chi^2 = 25.1$; df 1; $P < .001$), were more likely to have trophoblastic hyperplasia ($\chi^2 = 35.1$; df 1; $P < .001$) and were less likely to contain fetal tissue ($\chi^2 = 11.1$; df 1; $P < .001$) than were maternal triploids.

Second, we compared the results on parental origin with the developmental ages of the abortuses (table 5). The majority of diandric triploids had developmental ages in excess of 8.5 wk, whereas most of the digynic triploids aborted earlier, before developmental age 8.5 wk; this difference in distribution was highly significant ($\chi^2 = 12.7$; df 1; $P < .001$).

Third, we asked whether the developmental age of the abortus influenced the likelihood of diagnosis of partial mole. Since none of the maternally derived triploids were molar, this analysis was restricted to paternal triploids (table 6). We observed a significant increase in the proportion of moles among the "older" (>8.5 wk) than younger (<8.5 wk) paternal triploids ($\chi^2 = 4.6$; df 1; $P < .05$), but, notably, some 33% of paternal triploids of developmental age <8.5 wk were diagnosed as moles.

Table 5

Parental Origin and Phenotype of Triploidy

Origin	Total No. of Cases	Gross Phenotypic Features			Developmental Stage (wk)			
		Partial Mole	Trophoblastic Hyperplasia	Fetal Tissue	<6.0	6.0–8.5	8.5–11.5	>11.5
Maternal	27	0 (0%)	3 (11%)	16 (59%)	6	12	6	3
Paternal	58	33 (57%)	46 (79%)	13 (22%)	3	12	25	18

Note.—Includes cases in which results from both the DNA analysis and histological study were available.

Discussion

Most Triploid Abortions Are Androgenetic in Origin

Over the past 25 years, considerable attention has been given to determining the parent and mechanism of origin of numerical chromosome abnormalities (for review, see Jacobs and Hassold [1995]). For most such conditions, the results are unambiguous—for example, most trisomies involve maternal nondisjunction, most sex-chromosome monosomy results from loss of a paternal sex chromosome, and most tetraploids derive from early cleavage division errors. Thus, it is somewhat surprising that the origin of one of the most common numerical abnormalities, triploidy, remains controversial. Early cytogenetic studies of triploid spontaneous abortions reported an excess of paternally derived cases (Jacobs et al. 1982; Uchida and Freeman 1985), leading Jacobs et al. (1982) to conclude that the data sets were in agreement "in finding the additional haploid set in the majority of triploids to be paternal." However, recent molecular studies of triploid fetuses (McFadden et al. 1993; Dietzsch et al. 1995; Miny et al. 1995) and of early triploid gestations (McFadden et al. 1994; McFadden and Langlois 1997) have reported a predominance of digyny, leading McFadden and Langlois (1997) to conclude that "digyny is the most common origin of triploidy."

To resolve this discrepancy, we used DNA markers to reexamine the parental origin of triploid spontaneous abortions. In our series of unselected spontaneous abortions (i.e., the Cleveland cases) with gestational ages of 5–18 wk, diandry was the typical source of triploidy, accounting for nearly two-thirds of the cases (39 of 62). These results are in good agreement with previous estimates of diandry of 73% (Jacobs et al. 1982) and 62% (Uchida and Freeman 1985) in cytogenetic studies of triploid abortuses, indicating that the chromosome-heteromorphism approach was reliable. Further, taken together with the earlier cytogenetic data, our results provide compelling evidence that most triploid abortuses are paternal in origin.

Complex Relationship between Gestational Age and the Parental Origin of Triploidy

If our interpretation is accurate, what is the basis for the discrepancy between our results and other molecular studies of triploidy? We can think of at least two possible explanations: first, there may be biological differences between the study populations, so that diandry is more common in some (e.g., the present study population and the Hawaii-based population of Jacobs et al. 1982) and digyny in others (e.g., the British Columbia–based population of McFadden and Langlois [1997] and the German-based population of Miny et al. [1995]). However, there is little precedent for geographic variation in the incidence or causes of human chromosome abnormalities, and thus we think this explanation is implausible. Second, and more likely, there may be among-study differences in ascertainment schemes, with some enriching for diandry and others for digyny. At first glance, this may seem implausible; however, as suggested by our data, there is a complex relationship between gestational age and the parental origin of triploidy, thus providing a basis for such selection. For example, in agreement with the earlier reports of Jacobs et al. (1982), we observed an association between the parental origin of triploidy and the gestational age of the abortus. Digynic triploids aborted relatively early compared to diandric triploids, with mean gestational ages of 9.9 ± 2.3 wk and 11.9 ± 3.3 wk, respectively. This association is

Table 6

Proportion of Partial Hydatidform Moles by Developmental Age among Triploids of Paternal Origin

Origin	Developmental Age (wk)			
	<6.0	6.0–8.5	8.5–11.5	>11.5
Dispermy	0/2	4/8	11/16	7/9
Meiosis I	0/0	1/1	0/1	1/2
Meiosis II	0/0	0/1	0/0	0/0
Mitotic	0/0	0/1	0/0	0/0
Unknown	0/1	0/1	3/8	6/7

illustrated in figure 1 for 57 abortuses ascertained in Cleveland, as well as for 111 cases reported in the Hawaii study of triploidy (Jacobs et al. 1982; P. A. Jacobs and T. J. Hassold, unpublished data). For both studies, the proportion of digynic triploidy was greatest early in gestation, comprising ~45%–65% of cases. However, this proportion decreased markedly with gestational age, with digyny accounting for <10% of abortuses of 12–20 wk gestation. Later in gestation, this relationship appears to change yet again, as molecular studies of mid- and third-trimester triploid fetuses have reported a predominance of digyny (McFadden et al. 1993; Dietzsch et al. 1995; Miny et al. 1995).

Taken together, these results indicate that most diandric triploids abort at 10–20 wk gestation, whereas digynic triploids either are lost early in development or survive later into gestation and form well-developed fetuses. This indicates that the discrepancy between the cytogenetic and molecular studies is, indeed, due to the analysis of different populations of triploidy—that is, spontaneous abortions in the former studies and early embryonic losses and/or fetal triploidy in the latter.

Further, these results imply that the molecular studies may have overestimated the importance of digyny by studying cases that represent a relatively small proportion of all triploid conceptuses. That is, in the Cleveland series, only 39% of triploids were "early abortions" (<8.5 wk), consistent with a previous study of >100 triploid abortuses in which only one-third were <10 wk in gestation (Warburton et al. 1991). Similarly, "older" triploids are uncommon; that is, assuming (1) that 15% of all clinically recognized pregnancies spontaneously abort and 2% are stillborn (French et al. 1962) and (2) that 6% of spontaneous abortions, 0.6% of stillborns, and 0.002% of live borns are triploid (Hook and Hamerton 1977; Hassold et al. 1980; Angell et al. 1984), we estimate that only 1%–2% of all triploids are stillborn or live born. Thus, we conclude that the vast majority of triploid conceptions spontaneously abort at 10–20 wk, with most of these being androgenetic in origin.

Errors in the Block to Polyspermy or in Maternal Meiosis II Account for Most Cases of Triploidy

Previous cytogenetic studies lacked the ability to determine precisely the mechanism of origin of triploidy (Jacobs et al. 1982; Uchida and Freeman 1985). Furthermore, since these analyses included only pericentromeric markers, triploidy caused by meiosis II errors could not be distinguished from those arising from "mitotic" errors.

Using information from DNA markers located near the centromere and distally on the chromosome arms, we calculated the most likely mechanism of origin for each case. Our results indicate that there are two common mechanisms of origin, each presumably attributable to maternal factors. The single most common mechanism, dispermy, likely involves failure of the zona reaction, which acts normally to prevent polyspermy. The second major contributor is digyny of meiosis II origin. This could involve any of several abnormal meiotic processes, including failure of sister chromatid separation in meiosis II or suppression of polar body formation. Alternatively, it could be that triploids scored as arising at maternal meiosis II actually involve errors at meiosis I. For example, in the Lt/Sv mouse, oocytes frequently undergo an anomalous MI arrest; upon fertilization, the arrested oocytes complete separation of homologous chromosomes, produce a first polar body, and develop as triploid zygotes. Thus, the triploid embryos genetically resemble those arising from meiosis II errors, even though the precipitating event was an aberrant meiosis I arrest (Eppig et al. 1994).

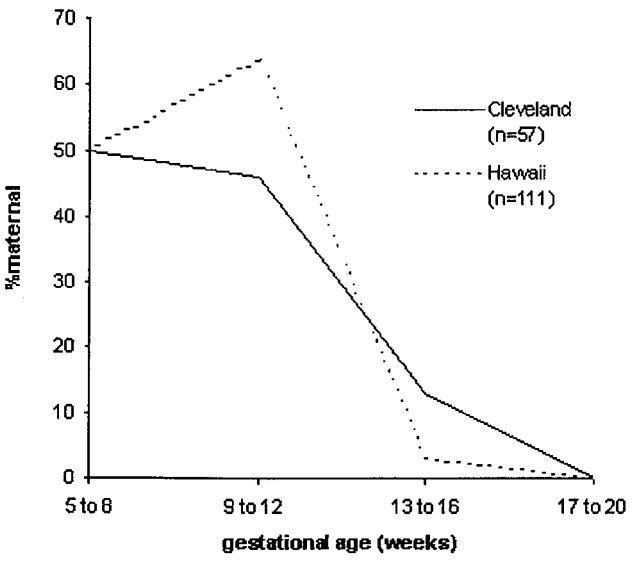

Figure 1 Correlation between gestational age and proportion of cases of maternal origin in two studies of spontaneously aborted triploids, one based in Hawaii (Jacobs et al. 1978; T. J. Hassold and P. A. Jacobs, unpublished data) and the second in Cleveland (present study).

Unlike digynic triploidy, our results indicate that few diandric triploids are due to meiotic abnormalities; indeed, in the entire series, only five cases could have arisen from paternal meiotic errors. Nevertheless, these results indicate that a large proportion, if not a majority, of diploid human sperm are capable of fertilization and production of a triploid conceptus. That is, recent FISH sperm studies indicate that ~0.1%–0.2% of human sperm are diploid (e.g., see Martin et al. 1995), while an estimated 0.06% of clinically recognized pregnancies are triploids involving a paternal meiotic error (i.e., ~1% of all clinically recognizable pregnancies are triploid [Ja-

cobs et al. 1982], with ~6% of these resulting from a paternal meiotic error [table 4]). Thus, it seems likely that ⩾30%–60% of diploid sperm are capable of contributing to human pregnancies.

Our results also indicate unusual origins for at least three of the triploid cases. In one instance (B99), results at distal markers of six different chromosomes were consistent with an origin from a "mitotic" error, a mechanism previously proposed, but never proven, in humans (Beatty 1957; Niebuhr 1974). This could result from an error at the pronuclear stage; for example, following fertilization and prior to the first mitotic cleavage division, one pronucleus might divide abnormally, resulting in complete homozygosity of one chromosome set. Alternatively, it might be that postmeiotic endoreduplication occurred in the sperm or ova, resulting in a diploid—but completely homozygous—gamete.

In two other cases (A13 and B98) our results were consistent with "dieggy," the fertilization of two ova by a single haploid sperm. Similar results have been reported for at least one case of human triploidy (Jacobs et al. 1978) and for one ovarian teratoma (Hoffner et al. 1992), suggesting that, rarely, two independent maternal genomes may contribute to the same conceptus. Alternatively—and possibly more likely—the genetic expectations for "dieggy"-derived triploidy are the same as those for triploidy arising from a tetraploid oogonium (table 2). Studies of the Chinese hamster (Funaki and Mikmo 1980) suggest that, at least in this species, digynic triploidy occasionally arises from giant diploid oocytes derived from tetraploid oogonia; possibly, a similar origin is the explanation for the extra maternal sets in our two cases.

Many, but Not All, Androgenetic Triploids Develop into Partial Moles

The most common feature associated with triploidy is the partial hydatidiform mole (Szulman and Surti 1978). An association with diandric triploidy was originally suggested by cytogenetic studies of triploidy (e.g., Jacobs et al. 1982) and more recently confirmed by molecular analyses of partial moles (e.g., Lawler et al. 1991). On the basis of these and other previous studies and the results of the present report, it seems clear that the partial molar phenotype is a correlate of androgenetic, but not of gynogenetic, triploidy. However, what is less clear is whether all androgenetic triploids are destined to develop into partial moles. Several cases of nonmolar diandric triploidy have been reported previously (e.g., see Jacobs et al. 1982; Procter et al. 1984) and in the present study, only one-half of all androgenetic triploids were diagnosed as partial moles. However, as originally suggested by Jacobs et al. (1982), this could be an "artifact" of gestational age; that is, the characteristic features of partial moles might not be evident until relatively late in gestation, leading to misdiagnosis of early aborting triploids as nonmolar.

To assess this possibility, we examined the relationship between histological phenotype and gestational age in paternal triploids (table 6). Our results indicate a strong relationship between age and partial moles, with molar diagnoses being assigned to 0%, 42%, 56%, and 78% of paternal triploids of developmental ages <6 wk, 6–8.5 wk, 8.5–11.5 wk, and >11.5 wk, respectively. However, the mole/age correlation was not absolute, since a number of "young" triploids were diagnosed as molar and nearly 25% of the oldest ones were nonmolar. Thus, age of the abortus is important in the development of partial mole but is not the sole determinant.

Other factors that might play a role in the development of the molar phenotype are unclear. One obvious candidate, the specific mechanism of origin leading to diandric triploidy, does not seem to be involved. That is, we found no obvious difference in phenotype between triploids originating from dispermy or paternal meiotic errors (table 6). Further, the phenotype was not significantly worse for the mitotically derived case. Although homozygous for the paternal genome—similar to the situation for most complete hydatidiform moles (Kajii and Ohama 1977)—the case was diagnosed as nonmolar. Thus, it seems unlikely that the timing of the paternal error affects the phenotype, nor is paternal homozygosity sufficient for the partial molar phenotype.

The sources of the phenotypic variability among diandric triploids are unclear, and the phenotypes of maternal triploids are also puzzling. Though most digynic triploids fail early in gestation, several survive well into the fetal period and some come to term. Thus, another question regarding the relationship of parental origin and phenotype in triploidy asks why some maternal triploids have "exceptional" phenotypes—that is, why a small proportion form well-developed fetuses. One possibility is abnormal imprinting. Recently, abnormalities in imprinting have been observed in parthenogenetic mouse embryos derived from immature oocytes (Kono et al. 1996; Obata et al. 1998), with these embryos having more advanced placental development than parthenogenetic embryos derived from mature oocytes (Obata et al. 1998). Since the imprinting mechanisms that modify parental alleles occur during oocyte growth and maturation, it has been suggested that the advanced placental development might reflect abnormal expression of imprinting genes, resulting from the failure to complete the imprinting process (Kono et al. 1996). Possibly a proportion of human digynic triploidy arises from fertilization of immature oocytes, gametes that are not competent to complete meiosis and that have failed to complete imprinting. If so, the abnormal expression of imprinted loci might result in more advanced develop-

ment of the triploid conceptus, a possibility that could be tested by comparing allele-specific expression of imprinted loci in typical digynic triploids with that observed in "exceptional" digynic triploids.

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Appendix

Statistical Methods for Determining the Probabilities of Different Types of Origin of Triploidy

The lack of parental tissue/blood samples is a common problem that hinders studies of the origin of constitutional chromosome abnormalities. However, in instances where placental material is recovered (e.g., spontaneous abortions) both maternal and fetal tissue can be identified and genotyped and used to assess mechanism of origin. We have developed statistical methods to estimate the most likely parent and stage of origin of each abnormality. Here we describe our approach for triploidy, which is based on similar methods for the analysis of human polyploidy and trisomies in "complete" families (Jacobs and Morton 1977; Chakravarti and Slaugenhaupt 1987).

We considered six possible mechanisms of origin of triploidy: failure of maternal meiosis I, failure of maternal meiosis II, failure of paternal meiosis I, failure of paternal meiosis II, "dieggy" and dispermy. Conditional likelihoods for each of these six, and additional, mechanisms were previously provided by Jacobs and Morton (1977) for a marker locus located at the centromere. We extended these results to a genetic marker arbitrarily located on the chromosome by considering the effect of recombination between the marker locus and the centromere (Chakravarti and Slaugenhaupt 1987). We considered two parameters, ϕ and χ, which are the probabilities of heterozygosity at a marker in a diploid gamete arising from errors in meiosis I and meiosis II, respectively. When there is no chiasma interference, the probabilities, ϕ and χ, are related to the map distance (in cM) between the marker and the centromere (w), through the tetratype frequency y: $\phi = 1 - y/2$, $\chi = y$, $y = 2/3(1 - e^{-3w/100})$.

The likelihoods of observations are direct functions of these parameters. In many analyses, such as ours, paternal genotype data are not available. Consequently, the log-likelihoods were summed over all possible paternal genotypes for each mother-fetus pair. In addition, in this study, we did not assign specific alleles across families but only the patterns of allele sharing within a family (table A1). We combined all possible mating types and progeny types considering both parents into 10 possible revised classes (table A1). Each class is defined by homozygosity (type 1–4) or heterozygosity (type 5–10) of the mother and by the number of alleles shared with the fetus. For each of the 10 classes, the conditional likelihood for each mechanism was determined by the sum of the products of the likelihood and the population frequency for each mating type. The mating type frequencies were calculated in terms of the parameters f_1–f_7 which are defined by the gene frequency moments, a_1, a_2, a_3, and a_4 (table A2) of the particular marker (Chakravarti 1989). For a marker with n distinct alleles, the gene frequency moments a_1, a_2, a_3, and a_4 are related to the allele frequencies x_1, x_2,..., x_n, as $a_r = \sum x_i^r$ (r = 1,2,3,4). The total conditional likelihood of each mechanism for each of the 10 classes for a single, noncentromeric, autosomal marker locus are provided in table A1. For each pericentromeric marker used in the study, the conditional likelihood of each mechanism was calculated as in table A1 by use of the genetic distance between the marker and centromere (w), the allele frequencies of the marker and the above equations. Allele

Table A1

Conditional Likelihoods of Marker Genotypes of Mother and Triploid Fetus under Six Possible Mechanisms of Origin

	Genotype							
Type	Fetus	Mother	Maternal Meiosis I	Maternal Meiosis II	Paternal Meiosis I	Paternal Meiosis II	Maternal "Dieggy"	Paternal Dispermy
1	aaa	aa	a_3	a_3	$a_4 + (1-\phi)(a_3-a_4)$	$a_4 + (1-\chi)(a_3-a_4)$	a_3	(a_3+a_4)
2	aab	aa	a_2-a_3	a_2-a_3	$2\phi(a_3-a_4)$	$2\chi(a_3-a_4)$	$a_2 - a_3$	a_3-a_4
3	abb	aa	0	0	$f_2 + (1-\phi)(a_2-a_2^2 -a_3+a_4)$	$f_2 + (1-\chi)(a_2-a_2^2 -a_3+a_4)$	0	$(a_2+a_2^2-a_4-a_3)$
4	abc	aa	0	0	$f_4\phi$	$\chi(a_2-a_2^2-2a_3+2a_4)$	0	f_4
5	aaa	ab	$(1-\phi)(a_2-a_3)$	$(1-\chi)(a_2-a_3)$	$(a_3-a_4) + (1-\phi)(a_2 -2a_3+a_4)$	$(a_3-a_4) + (1-\chi)(a_2 -2a_3+a_4)$	(a_2-a_3)	(a_2-a_4)
6	aab	ab	$(1+\phi)(a_2-a_3)$	$(1+\chi)(a_2-a_3)$	$(1+\phi)(a_2^2-a_4) + (1-\phi)(a_2 -a_2^2) + (2\phi-1)(a_3-a_4)$	$(1+\chi)(a_2^2-a_4) + (1-\chi)(a_2 -a_2^2) + (2\chi-1)(a_3-a_4)$	3/2 (a_2-a_3)	$(a_2+2a_2^2-3a_4)$
7	aac	ab	$(1-\phi)(3/2\ f_4+f_7)$	$(1-\chi)(3/2\ f_4+f_7)$	ϕf_4	χf_4	$(1-a_2+2a_3)$	f_4
8	abc	ab	$\phi(3/2\ f_4+f_7)$	$\chi\ (3/2\ f_4+f_7)$	ϕf_4	χf_4	$(1-3a_2+2a_3)$	f_4
9	acc	ab	0	0	$(1-\phi)(3/2\ f_4+f_7)$	$(1-\chi)(3/2\ f_4+f_7)$	0	$(1-2a_2-a_2^2+2a_4)$
10	acd	ab	0	0	ϕf_7	χf_7	0	$(1-3/2\ a_2+3a_2^2+8a_3-6a_4)$

Table A2

General Mating Types and Frequencies for an Autosomal Marker Locus (Chakravarti 1989)

Mating Type	Frequency
aa × aa	$f_1 = a_4$
aa × bb	$f_2 = a_2^2 - a_4$
aa × ab	$f_3 = 4(a_3 - a_4)$
aa × bc	$f_4 = 2[a_2(1 - a_2) - 2(a_3 - a_4)]$
ab × ab	$f_5 = 2f_2$
ab × ac	$f_6 = 2f_4$
ab × cd	$f_7 = 1 - 6a_2 + 8a_3 - 6a_4 + 3a_2^2$

frequencies and mapping information for each marker were obtained from the Genome Database. Allele frequencies of D17S122 were unavailable; therefore, these values were calculated by use of genotype information of unrelated individuals in our study population.

Electronic-Database Information

The URL for data in this article is as follows:

Genome Database, http://www.gdb.org (for mapping and PCR primer information)

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