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Inherited Structural Cytogenetic Abnormalities Detected Incidentally in Fetuses Diagnosed Prenatally: Frequency, Parental-Age Associations, Sex-Ratio Trends, and Comparisons with Rates of Mutants

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SUMMARY

Rates of structural chromosome abnormalities were analyzed in 24,951 fetuses studied prenatally in which there were no grounds to suspect an inherited abnormality. In about one in 200 prenatal cytogenetic diagnoses, an unexpected structural abnormality was found. The observed rate was 5.3 per 1,000, of which 1.7 per 1,000 were unbalanced and 3.6 per 1,000 balanced. The rate of inherited abnormalities was 3.1–3.7 per 1,000 (0.4–0.9 per 1,000 for unbalanced abnormalities and 2.6–2.8 per 1,000 for balanced abnormalities). The rate of mutants in this series was, by contrast, 1.6–2.2 per 1,000 (0.8–1.2 per 1,000 for unbalanced abnormalities and 0.8–1.0 per 1,000 for balanced abnormalities). The rate of balanced Robertsonian translocation carriers was 0.6 per 1,000 (about 0.25 per 1,000 for mutants and 0.35 per 1,000 for inherited abnormalities), and for other balanced abnormalities, 3.0 per 1,000 (about 0.6 per 1,000 for mutants and 2.4 per 1,000 for inherited abnormalities). The rates of unbalanced Robertsonian translocations was about 0.1 per 1,000, almost all of which were mutants. For supernumerary rearrangements, the rate was 0.9 per 1,000 (about 0.4 per 1,000 inherited and 0.5 per 1,000 mutant). The rates of all unbalanced (nonmosaic) inherited abnormalities (4.0–5.2 per 10,000) were intermediate between higher rates estimated in all conceptuses (9.1–15.8 per 10,000) and rates observed in newborns (1.5–2.5 per 10,000). This trend is probably attributable to fetal mortality associated with unbalanced rearrangements. The rates of balanced (nonmosaic) inherited abnormalities (26.0–28.0

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per 10,000), however, were considerably higher than the rates in all conceptuses (13–16.7 per 10,000) or in all live births (12.2–16.0 per 10,000). The major difference was in the rate of inversions. The use of "banding" methods in the studies of amniocentesis but not in most of the live births or abortus studies probably contributes to at least some of these differences. One trend in parental age among the inherited abnormalities was noteworthy. Paternal age was elevated for inherited balanced reciprocal structural abnormalities of paternal origin but not of maternal origin. With regard to sex ratio, there was a greater proportion of females than males among the unbalanced rearrangements both inherited and mutant. There was no obvious sex difference among the balanced rearrangements.

INTRODUCTION

Occasionally, prenatal cytogenetic study reveals an unsuspected structural chromosomal abnormality. These may be the result of a new mutation or a segregating familial abnormality of which there was no previous knowledge.

In an earlier paper, we reported on mutant structural abnormalities detected at prenatal cytogenetic diagnosis in about 27,000 fetuses [1]. In this paper, we report on inherited structural rearrangements detected in this series. We analyze specifically the rates detected in the subgroup of about 25,000 studied in whom there was no known or suspected risk of an inherited abnormality. These rates are compared with rates of mutants in the same subgroup. In addition, we examine trends in parental age and sex ratio of the inherited cases.

MATERIALS AND METHODS

The sources of data were 22,190 reports to the New York State Chromosome Registry [2] of prenatal cytogenetic diagnoses reported between January 1, 1977, and April 5, 1981, comprising essentially the experience of participating laboratories for 1977 to 1980, and 5,352 reports to the U.S. Interregional Chromosome Register System (I.C.R.S.) [3] received by August, 1980. There were a total of 27,542 prenatal studies reported from the centers included in this analysis. Extensive analyses of the mutant rearrangements detected in this group have been reported [1]. (See below for explanations of slight discrepancies between the totals used in the two analyses.)

To avoid possible ascertainment bias resulting from selective study of translocation carriers, we exclude results on 142 fetuses whose mothers were investigated because of a previously known parental translocation. We also exclude from this analysis results on 2,449 fetuses for which, although there was no known parental translocation, the history might suggest a greater likelihood of such a pattern. In this category are fetuses whose mothers were studied because they had a previous offspring or other relative with malformation (other than neural tube defect), usually multiple malformations. We also excluded fetuses whose parents had a history of offspring with previous chromosome abnormality, usually a trisomy. The latter were excluded because of the conjectured increase of trisomy births to balanced translocation carriers. (Our own data provide no evidence for such an association but are insufficient to exclude a modest effect.)

The primary analysis was done upon the remaining subgroup of 24,951 fetuses of which 20,305 were reported to the New York State Chromosome Registry, and 4,646 to the I.C.R.S. Studied because of advanced parental age were 21,672 (17,852 in the New York Registry and 3,820 in the I.C.R.S.), and 3,279 were studied following amniocentesis for other reasons such as diagnosis of inborn errors of metabolism (2,453 in the Registry and 826 in the I.C.R.S.). (A tabulation of specific reasons for study in this group appears below.)

In analysis of associations with maternal age, comparisons were made with the maternal age in the 24,143 of 24,951 fetuses with normal genotype diagnosed at amniocentesis in which maternal age was both known and under 50. Parental ages of fetuses with abnormalities were compared with those of normal genotype. In investigation of paternal-age effect, we did not have data readily available from the I.C.R.S., so analysis of this variable was restricted to cases reported to the New York State Registry. Those with chromosomal polymorphisms were classified as having normal chromosomal genotype in the analysis.

RESULTS

In table 1 is a list of reasons for study of the subgroup of 24,951 fetuses.

In table 2, we present a brief summary of the results on the 142 excluded because of a known parental translocation and on the 2,449 excluded because of putative high risk of an inherited translocation.

In table 3, the number of inherited abnormalities in each major cytogenetic category are noted, and these are compared with the results of de novo abnormalities and those of uncertain origin in the subgroup of 24,951 fetuses analyzed.

In table 4 appear the rates of inherited structural rearrangements detected in fetuses and the rate of structural abnormalities in parents ascertained through fetuses with abnormalities. The latter is a minimum estimate of parents with unsuspected structural abnormalities. Those with fetuses with normal chromosomes, of course, would not be detected in this survey.

In table 5 appear data on parental age and inherited abnormalities. There were no strong trends with regard to maternal age. Paternal-age analysis could be done only on data from the New York State Registry, and then, of course, only for cases in which paternal-age data had been reported. Reference data were available on 12,038 controls. Balanced reciprocal rearrangements of paternal origin were

TABLE 1

REASONS FOR AMNIOCENTESIS OF 24,951 FETUSES WITHOUT KNOWN RISK FACTOR FOR STRUCTURAL REARRANGEMENT

Reason	No.	Proportion of fetuses diagnosed with inherited structural rearrangements
Anxiety	783	0.3%
Previous child with neural tube defect	725	0.1%
α-Feto protein determination	614	0.2%
Diagnosis of inborn error of metabolism	250	0.0%
Radiation or chemical mutagen exposure	142	0.0%
Other or unstated	765	0.5%
Subtotal	3,279	0.2%
Advanced maternal age	21,672	0.3%
Total	24,951	0.3%

TABLE 2

OUTCOMES IN FETUSES OF PARENTS WHO WERE KNOWN TRANSLOCATION CARRIERS OR AT PUTATIVE HIGH RISK TO BE CARRIERS

Reason for study	No.	Proportion of fetuses diagnosed with inherited structural rearrangement
Parent is a known translocation carrier	142	51.4%
Previous offspring with Down syndrome	497	0.2%
Family history of Down syndrome	524	0.2%
Previous offspring with other or unspecified chromosome abnormality	771	0.4%
Previous spontaneous abortions	104	1.0%
Previous offspring with multiple malformation	113	1.8%
Family history of birth defects	162	0.6%
Other	278	0.4%
Total	2,591	3.2%
Total excluding translocation carriers	2,449	0.4%

associated with significantly greater paternal age than were controls ($P < .05$). There was no such association with maternal age nor was there any elevation in maternal age in balanced abnormalities of maternal origin. Data on parental-age associations with mutations appear in [1].

In table 6, we compare the rates (and their 95% confidence intervals) of mutants and inherited abnormalities in the subgroup of 24,951 fetuses. The ranges in rates reflect the uncertainties in assignment of cases of unknown origin.

TABLE 3

COMPARISON OF FAMILIAL AND MUTANT CASES DETECTED

	ORIGIN				PROPORTION INHERITED AMONG THOSE OF KNOWN ORIGIN
			INHERITED		
	De novo*	Not known*	Maternal	Paternal	
Unbalanced:					
Robertsonian	2(1)†	1	0	0	0
Rings	0	1	0	0	0
Supernumerary:					
Markers	9	4(2)	6	1	0.44
Fragments	2	1(1)	0	0	0
Deletions	5(2)	2	1(1)	0	0.17
Unbalanced:					
Derived aberration	. . .	. . .	1	1	. . .
Other	3(1)	1	1	1(1)	0.40
All	21(4)	10(3)	9(1)	3(1)	0.36
Balanced:					
Robertsonian	5(2)	2	5(2)	3	0.62
Reciprocal	12(1)	2(1)	13(3)	18(5)	0.72
Inversions	2	1	10(4)	16(7)	0.93
All	19(3)	5(1)	28(9)	37(12)	0.77

* De novo cases and those of unknown origin are as reported in [1] except for one case of unknown origin [46,XX,del(5)(pter→q31:), mat. age 37] that was found after a hand file review.

† Nos. in parentheses are of those reported to the ICRS. The others indicate the numbers reported to both data sources.

TABLE 4

RATES OF INHERITED STRUCTURAL ABNORMALITIES IN FETUSES AND ESTIMATED RATES IN PARENTS

Abnormality	Rates per 10,000 of structural abnormalities in parents ascertained through affected fetuses*	Rate per 10,000 of inherited abnormalities in fetuses†
Robertsonian (all are "balanced probands" born to a "balanced parent"):		
45,−13,−14,+t(13;14)	1.0	2.0
(45,−13,−22,+t(13;22))	(0.2)	(0.4)
(45,−13,−21,+t(13;21))	(0.2)	(0.4)
(45,−14,−22,+t(14;22))	(0.2)	(0.4)
All 45,−D,−G,+t(D;G)	0.6	1.2
All above	1.6	3.2
Reciprocal (all born to "balanced parents"):		
Balanced proband	6.2	12.4
Unbalanced probands	0.0	0.0
Both	6.2	12.4
Inversions	5.2	10.4
Supernumerary	1.4‡	2.8
Deletion	0.2	0.4
Total	16.8	33.6

* These rates are by definition half of the rates of affected fetuses.
† In parents with no reproductive history that might have been related to presence of familial translocation.
‡ 6/7 are of maternal origin.

In table 7, data are presented on the ratio of males to females among all structural abnormalities detected in the entire series. There was no evidence for any major difference in sex ratio among the inherited abnormalities according to the reason for study. Moreover, there appears no reason to expect any such variation. Therefore, data are presented on all inherited cases whether derived from a known translocation carrier or detected incidentally. Data are also presented on mutant cases and those of unknown origin. (The sex ratio of *all* fetuses studied prenatally including normals was 1.055 in the New York State Chromosome Registry data. We use this as a reference ratio. We do not have similar data on all fetuses in the I.C.R.S. data.)

In table 8, we compare the crude rates (and their standard errors) derived from data summarized by Jacobs on all (recognized) conceptuses and in live births [4]. Most of the live births and abortuses included in the series summarized were derived from unbanded studies. (See DISCUSSION.) We present results on those with inherited abnormalities and all those not known mutant. The latter include the known inherited rearrangements and instances in which both parents have not been studied, so that an inherited abnormality cannot be excluded. As Jacobs presented data only on *nonmosaics* and excluded sex-chromosome abnormalities, we do the same here. (A similar comparison of data on *mutations* detected at amniocentesis appears in table 3 of [1].)

Appendix table 1 presents data on each fetus with an inherited abnormality in the main group of 24,951 analyzed concerning the reason for study, maternal age, paternal age, parental origin of the inherited abnormality, and cytogenetic

TABLE 5

PARENTAL AGE AND INHERITED REARRANGEMENTS IN FETUSES

	DATA FROM BOTH SOURCES, MATERNAL AGE ONLY						DATA FROM N.Y. REGISTRY, MATERNAL AND PATERNAL AGE AVAILABLE									
	MATERNAL ORIGIN			PATERNAL ORIGIN			MATERNAL ORIGIN					PATERNAL ORIGIN				
	No.	MA	(SD)	No.	MA	(SD)	No.	MA	(SD)	PA	(SD)	No.	MA	(SD)	PA	(SD)
Balanced rearrangements:																
Inversions	10	36.3	(1.5)	14	35.9	(3.5)	5	35.8	(1.9)	36.8	(6.5)	7	36.1	(3.4)	38.6	(4.4)
Reciprocal	13	35.8	(2.7)	18	36.6	(4.7)	8	35.4	(3.2)	37.4	(5.7)	11	37.2	(2.7)	44.5*	(8.0)
Robertsonian	5	37.6	(3.3)	3	36.3	(1.2)	2	37.5	(4.9)	42.0	(8.5)	3	35.7	(1.2)	33.3	(7.8)
All balanced	28	36.3	(2.4)	35	36.2	(4.0)	15	35.8	(2.9)	37.8	(6.1)	21	36.6	(2.8)	41.0	(7.9)
Unbalanced rearrangements	9	36.8	(2.4)	3	36.3	(2.5)	6	36.5	(2.9)	35.2	(4.0)	2	37.5	(2.1)	32.0	(5.7)
Balanced and unbalanced rearrangements	37	36.4	(2.4)	38	36.2	(3.9)	21	36.0	(2.8)	37.0	(5.6)	23	36.7	(2.7)	40.2	(8.0)
Control group	24,143	36.2	(3.7)	24,143	36.2	(3.7)	12,038	36.3	(3.5)	38.0	(6.4)	12,038	36.3	(3.5)	38.0	(6.4)

NOTE: No. = no. cases, MA = mean maternal age, PA = mean paternal age, (SD) = standard deviation.
* $P < .05$ in comparison with control.

TABLE 6

ESTIMATED RATES PER 10,000 OF MUTANT STRUCTURAL REARRANGEMENTS AND (UNANTICIPATED) INHERITED STRUCTURAL REARRANGEMENTS IN FETUSES OF WOMEN UNDERGOING AMNIOCENTESIS

	MUTANTS		KNOWN INHERITED ABNORMALITIES		BOTH	
	Rate	95% confidence interval*	Rate	95% confidence interval	Rate	95% confidence interval†
Unbalanced:						
Robertsonian	0.8–1.2	(0.1–3.5)	0–0.4	(0–2.2)	1.2	(0.2–3.5)
Rings	0–0.4	(0–2.2)	0–0.4	(0–2.2)	0.4	(0–2.2)
Supernumerary	4.4–6.4	(2.2–10.4)	2.8–4.8	(1.1–8.4)	9.2	(5.8–13.8)
Deletions	2.0–2.8	(0.7–5.8)	0.4–1.2	(0–3.5)	3.2	(1.4–6.3)
Derived segregating	...	...	0.8	(0.1–2.9)	0.8	(0.1–2.9)
Other	1.2–1.6	(0.2–4.1)	0.8–1.2	(0.1–3.5)	2.4	(0.9–5.2)
All	8.4–12.4	(5.2–17.6)	4.8–8.8	(2.5–13.3)	17.2	(12.5–23.2)
Balanced:						
Robertsonian	2.0–2.8	(0.7–5.8)	3.2–4.0	(1.4–7.4)	6.0	(3.4–9.9)
Reciprocal	4.8–5.6	(2.5–9.4)	12.4–13.2	(8.4–18.6)	18.0	(13.2–24.1)
Inversion	0.8–1.2	(0.1–3.5)	10.4–10.8	(6.8–15.7)	11.6	(7.8–16.7)
All	7.6–9.6	(4.6–14.3)	26.0–28.0	(20.1–35.4)	35.6	(28.6–43.9)
All balanced and unbalanced	16.0–22.0	(11.5–28.7)	30.9–36.9	(24.4–45.2)	52.9	(43.5–61.9)

* Including mosaics. Note the rates of mutants in the series of 24,951 fetuses are slightly different from the rates observed in the entire group of about 27,500 fetuses studied at amniocentesis (Hook et al. [1]). (See text also.)

† The lower 95% limit is for the rate at the lower end of the range; the upper 95% limit is for the rate at the upper end of the range.

TABLE 7

RATIO OF MALES TO FEMALES AMONG STRUCTURAL ABNORMALITIES DIAGNOSED PRENATALLY

	UNBALANCED ABNORMALITY							BALANCED ABNORMALITY				
	Robert-sonian	Super-numerary	Deletion	Derived abnormality	Rings	Other	All	Robert-sonian	Inversion	Reciprocal	All	TOTAL
Inherited*	1/2	2/5	0/1	3/6	0/0	1/5	7/19	19/25	11/16	37/26	67/67	74/86
Unknown status ..	0/1	2/3	0/2	0/0	0/1	1/0	3/7	2/0	2/0	1/1	5/1	8/8
Mutant	1/1	4/10	4/3	0/0	0/0	1/2	10/16	3/3	0/2	4/8	7/13	17/29
Total	2/4	8/18	4/6	3/6	0/1	3/7	20/42†	24/28	13/18	42/35	79/81	99/123

NOTE: Male sex is inferred from presence of a Y chromosome, female sex from apparent absence of a Y chromosome.

* Includes data on all inherited anomalies, independent of reason for study.

† $P < .005$ in comparison with expectation of 1.055 ratio in all fetuses in New York State Registry.

TABLE 8

RATES (AND STANDARD DEVIATIONS) OF NONMOSAIC STRUCTURAL REARRANGEMENTS THAT ARE INHERITED OR NOT KNOWN MUTANT PER 10,000 FETUSES IN WOMEN WITH NO KNOWN RISK OF CYTOGENETIC DISORDER: COMPARISON WITH ESTIMATED RATES IN CONCEPTUSES AND IN LIVE BIRTHS

	Recognized conceptuses				Fetuses at amniocentesis				Live births			
	Inherited			Not known mutant	Inherited			Not known mutant	Inherited			Not known mutant
	Mat	Pat	All		Mat	Pat	All		Mat	Pat	All	
Unbalanced:												
Robertsonian	4.1*	0.3	4.3	7.1*	0	0	0	0.4	0.2	0	0.2	0.3
	(1.0)	(0.3)	(1.1)	(1.4)	...	...	...	(0.4)	(0.2)	...	(0.2)	(0.2)
Rings	0	0	0	0.5	0	0	0	0	0	0	0	0
	...	...	...	(0.4)	...	...	...	...	...	...	...	...
Supernumerary	0.7	0.1	0.9	1.3	1.6	0.4	2.0	2.0	0.8	0.2	1.0	1.5
	(0.3)	(0.1)	(0.4)	(0.4)	(0.8)	(0.4)	(0.9)	(0.9)	(0.4)	(0.2)	(0.4)	(0.5)
Deletions and other unbalanced	1.7	2.2†	4.0	6.9†	1.2	0.8	2.0	2.8	0.2	0.2	0.3	0.7
	(0.7)	(0.8)	(1.0)	(1.3)	(0.7)	(0.6)	(0.9)	(1.1)	(0.2)	(0.2)	(0.2)	(0.3)
Deletions	...	...	...	...	0‡	0	0	0.4	...	...	...	...
	...	...	...	...	...	...	...	(0.4)	...	...	...	...
Derived segregating	...	...	...	...	0.4	0‡	0.4	0.4	...	...	...	...
	...	...	...	...	(0.4)	...	(0.4)	(0.4)	...	...	...	...
Other	...	...	...	...	0.4	0.4	0.8	1.20	...	...	...	...
	...	...	...	...	(0.4)	(0.4)	(0.6)	(0.7)	...	...	...	...

Balanced:												
Robertsonian	3.4 (0.8)	2.8 (0.7)	6.2 (1.0)	8.2 (1.2)	2.0 (0.9)	1.2 (0.7)	3.2 (1.1)	4.0 (1.3)	3.0 (0.7)	3.0 (0.7)	6.1 (1.0)	8.1 (1.2)
Inversions	0.6 (0.3)	0.7 (0.4)	1.3 (0.5)	1.7 (0.6)	4.0 (1.3)	6.4 (1.6)	10.4 (2.0)	10.8 (2.1)	0.7 (0.3)	0.5 (0.3)	1.2 (0.4)	1.4 (0.5)
Other reciprocals	3.1 (0.8)	2.6 (0.6)	5.6 (1.0)	6.9 (1.1)	5.2 (1.5)	7.2 (1.7)	12.4 (2.2)	13.2 (2.3)	2.4 (0.6)	2.7 (0.7)	5.0 (0.9)	6.6 (1.1)
All unbalanced	6.5 (1.3)	2.6 (0.8)	9.1 (1.5)	15.8 (2.0)	2.8 (1.1)	1.2 (0.7)	4.0 (1.3)	5.2 (1.5)	1.2 (0.5)	0.3 (0.2)	1.5 (0.5)	2.5 (0.7)
All balanced	7.0 (1.1)	6.1 (1.0)	13.1 (1.5)	16.7 (1.7)	11.2 (2.1)	14.8 (2.4)	26.1 (3.2)	28.1 (3.4)	6.1 (1.0)	6.2 (1.0)	12.3 (1.4)	16.0 (1.6)
All Robertsonian	7.4 (1.3)	3.1 (0.7)	10.5 (1.5)	15.3 (1.8)	2.0 (0.9)	1.2 (0.7)	3.2 (1.1)	4.4 (1.3)	3.2 (0.7)	3.0 (0.7)	6.2 (1.0)	8.4 (1.2)
All balanced and all unbalanced	13.5 (1.7)	8.7 (1.3)	22.2 (2.1)	32.5 (2.6)	14.0 (2.4)	16.0 (2.5)	30.1 (3.5)	33.3 (3.7)	7.2 (1.1)	6.6 (1.1)	13.8 (1.5)	18.5 (1.8)

* Includes two sets of siblings.
† Includes three siblings.
‡ Two cases involving sex chromosomes were deleted.

diagnosis. (A similar list has been published of the mutant abnormalities and of those of uncertain origin detected in the entire series of fetuses diagnosed prenatally [1].) Since that publication, further editing and data review have revealed a total of 27,231 cases of known maternal age (and under 50 years), six more than stated in the paper and 311 of unknown maternal age (or stated age 50 years or greater), three less than stated in the paper. In addition, after a review by hand of all entries, one additional case of unknown origin was detected, the details of which are noted in the footnote * to table 3.

Appendix tables 2 and 3 present data on fetuses with an inherited rearrangement in those studied because a parent was a known translocation carrier or at presumptive high risk of being a carrier.

DISCUSSION

In every 10,000 fetuses there were about 53 structural abnormalities detected that were not previously suspected. Of these, about 31–37 were inherited from previously unknown carriers and about 16–22 were the result of a recent mutation. (Most of the latter category, at least 75%, appear to have resulted from a germinal event [1].)

The rates of mutants observed may be a slight overestimate of the rates in all fetuses because of the apparent association of maternal age with some types of mutations [1] and the elevated maternal age of the population studied. The rates of inherited abnormalities are probably not overestimated for this reason, however, at least not by as much, because of lesser evidence for parental-age effects.

As data on fetuses of parents known to be translocation carriers or of parents with a history that might suggest a translocation were excluded, the proportions of those affected by inherited rearrangements are probably slight underestimates of the proportion of all affected fetuses. The underestimate is not likely to be large, however, because the number of individuals with structural cytogenetic abnormalities in the general population is known to be quite small, less than 1%.

The data on balanced rearrangements may be compared with the results of Van Dyke et al. [5], who reported on a series of about 8,200 fetuses detected prenatally in women studied for advanced maternal age. Their rate of 40 per 10,000 is quite close to the rate of 35.6 per 10,000 in this study. The rates of specific abnormalities in their series were 11 per 10,000 for balanced Robertsonian rearrangements, 17 per 10,000 for balanced reciprocal rearrangements, and 12 per 10,000 for inversions. By contrast, the results in this series were, respectively, six per 10,000, 18 per 10,000, and 12 per 10,000, almost identical except for Robertsonian translocations. The difference with regard to this category may well be attributable to sampling fluctuation. The proportions of balanced mutant rearrangements in the series of Van Dyke et al. may be estimated from their table 1 as between 8.6 per 10,000 and 9.8 per 10,000 in contrast to the very similar range of 7.6 per 10,000 to 9.6 per 10,000 in this series. Similarly, we estimate the range of balanced inherited abnormalities in their series as 30.6–31.9 per 10,000, close to the range of 26.0–28.0 per 10,000 in our data. The confidence intervals about the observed rates are considerably narrower in our series because of the larger numbers studied.

There are, to our knowledge, no other data sets on *unbalanced* rearrangements detected at amniocentesis (in which results are distinguished by inherited or mutant status) which may be compared with our data.

The data comparing rates of (nonmosaic) inherited structural abnormalities in recognized conceptuses, at amniocentesis, and in live births must be interpreted cautiously. As suggested by Van Dyke et al., there may be greater effort to detect subtle abnormalities at amniocentesis because of the prognostic implications. Moreover, unlike the data from amniocentesis reports, many of the studies of live births and abortuses did not use banding methods. Thus, the latter studies may have missed inversions and reciprocal abnormalities in particular.

Some data summarized by Van Dyke et al. are pertinent to the possible difference made by banding. The rate of *balanced* structural abnormalities was about 50% higher in the relatively small numbers of newborns studied with banding methods than in the much larger number of newborns studied with conventional staining [5]. Inversions, in particular, were significantly more frequent in the "banded" than "unbanded" studies of live births, six per 10,000 vs. one per 10,000. (Both mutant and inherited abnormalities were pooled in this comparison.) Thus, differential use of banding may well account for at least some of the differences in balanced rearrangements in many conceptuses, amniocentesis results, and live births (table 8).

With regard to comparisons among the inherited *unbalanced* rearrangements, it is more difficult to determine the extent to which the factors cited above have introduced distortions. The observed rates were 9.1–15.8 per 10,000 in all conceptuses, 4.0–5.2 per 10,000 at amniocentesis, and 1.5–2.5 per 10,000 in live births. The trend in rates is in the direction predicted if, as expected, there was fetal loss of (inherited) unbalanced rearrangements from the time of recognition of conception to the time of amniocentesis, and from the time of amniocentesis to live birth [6]. (Parental age does not appear to be associated with unbalanced inherited abnormalities. Therefore, higher mean ages of the inherited cases studied at amniocentesis should not affect comparisons with live births and all recognized conceptuses.)

With regard to supernumerary markers (or fragments), a previous analysis of (nonmosaic) *mutants* found a much higher rate at amniocentesis (2.6 per 10,000) than in live births (0.3–0.8 per 10,000) or in all conceptuses (0.3–0.7 per 10,000). It was conjectured that such aberrations may be less likely to survive in tissues from aborted embryos and fetuses studied cytogenetically or in blood of newborns than in tissues that shed cells into amniotic fluid. In the nonmosaic *inherited* abnormalities analyzed here, there is the same trend but it is much weaker and not significant. The rates were 0.9–1.3 per 10,000 in all conceptuses, 2.0 per 10,000 at amniocentesis, and 1.0–1.5 per 10,000 in live births. Further data are needed to determine if this reflects a true difference.

The trend to increased paternal age (about +6 years) of inherited reciprocal balanced translocations of paternal origin is significant although the numbers are quite small. It is of interest that there was evidence also for a similar trend in fetuses studied because of the presence of a *known* parental translocation. Data were available on maternal and paternal age of 22 balanced translocations of

maternal origin (plus four unbalanced rearrangements) and eight balanced translocations of paternal origin (plus two unbalanced rearrangements). The maternal ages for these cases were: balanced-maternal origin, 27.7 ± 4.6; balanced-paternal origin, 27.6 ± 5.7. The mean paternal-age–maternal-age differences for these two groups were, respectively, +0.4 (±3.6) and +3.1 (±2.9). (The results are essentially the same if the few unbalanced rearrangements are pooled with the balanced abnormalities.) Because of selection biases, there is no obvious comparison group in the general population with regard to the absolute value of maternal age or paternal age. While maternal ages are about the same for each origin, paternal age is almost 3 years greater for cases of paternal origin than of maternal origin. This is the same trend seen in table 5, at least for balanced reciprocal translocations. Thus, the evidence on this point is consistent within these data. It will be of interest to determine if the trend is confirmed in other data sources.

The data on those born to translocation carriers or those at putative high risk of being carriers are of interest. Among the fetuses born to 142 translocation carriers, about 50% had an abnormality, either balanced or unbalanced. Among the 2,449 fetuses born to parents at ostensible high risk of being carriers, the rate of abnormality was four per 1,000. This is actually lower than the rate of 5.2 per 1,000 in the main subgroup of 24,951 studied. Yet, in some specific subcategories, the rates were considerably higher than this (see table 2). But in view of the small numbers, this variation may well be attributable to sampling fluctuation. Appendix table 2 indicates the specific abnormalities detected in this group of individuals. Unfortunately, data are not available on karyotypes of those chromosome abnormalities which may have led to the original study. These may have been numerical abnormalities. Detection of an inherited structural abnormality may thus have been only coincidental.

With regard to sex ratio, in analysis of results in *live births*, the rate of all structural rearrangements, both balanced and unbalanced, was increased in females although none of the trends was significant [7]. In the data on fetuses reported here, the male-female ratio is decreased. The difference in comparison with the reference ratio of 1.055 is statistically significant only for unbalanced rearrangements. (The trend is present for both inherited and mutant unbalanced abnormalities, although not significant at the .05 level for either subcategory.) There is also a suggestive but not significant female preponderance for mutant balanced rearrangements but no such trend for inherited balanced rearrangements. The differences in sex may be attributable to statistical fluctuation and must still be confirmed in future series. If not due to chance, then either sex differentials in fetal mortality or some aspects of meiotic segregation may contribute to the difference.

One noteworthy observation is the 46,X del(X)(q25) genotype inherited by one individual. The affected mother had no obviously abnormal phenotype. She did have menstrual irregularities that might have been attributable to the genotype or else to anorexia (P. Martens and R. L. Summitt, personal communication, 1983). We are not aware of previous reports of inherited X deletions.

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ADDENDUM

Since this manuscript was accepted for publication, we became aware of another paper providing comparable data on the same topic [8]. A total of 29 "unexpected" structural rearrangements were reported. This series, however, included "pathologic pregnancies." Fetuses of such pregnancies are likely to have a significantly higher risk of structural chromosomal abnormality than those studied for such reasons as maternal age or sexing of the fetus. Excluding the abnormalities in such fetuses (one mutant deletion and one mutant ring), there were 12 reported mutants (six balanced and one unbalanced Robertsonian rearrangements, two balanced reciprocals, one deletion, one mosaic deletion and isochromosome, and one other unbalanced) and 15 inherited rearrangements (four balanced Robertsonian translocations, seven inversions, and four other balanced rearrangements). Supernumerary markers were, however, excluded from this report, but there were two detected in the same series, one in a male, the other in a female fetus (A. Boué, personal communication). Thus, there were 29 abnormalities comparable with those summarized in our report. These were found in a total of 5,315 fetuses, including 3%–4% studied because of pathologic pregnancies (A. Boué, personal communication). Excluding these,

the overall rate of abnormality is about 29/5130 = 5.7 per 1,000. The rate of unbalanced abnormalities is 1.2 per 1,000; of balanced abnormalities, 4.5 per 1,000. The rate of mutants is 2.7 per 1,000; of inherited arrangements, 2.9 per 1,000. Considering the smaller number of cases studied, the rates are quite close to those in our larger series.

Boué et al. cite suggestive evidence in their population that the women seeking amniocentesis ostensibly only because of advanced maternal age include, selectively, many with reproductive problems. Such problems could result, of course, from inherited translocations. This would raise spuriously—probably only slightly—the rate of observed inherited rearrangements over that in the entire population of fetuses (with the same maternal- and gestational-age distribution as those studied at amniocentesis). Such an artifactual increase could also be present in our results on inherited rearrangements. This would occur if in our study, as in that of Boué et al., the women on whom ostensibly unbiased rates are presented selectively include those with cryptic reproductive difficulties. We cannot exclude such a possibility in our data.

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APPENDIX TABLE 1

INHERITED STRUCTURAL CHROMOSOMAL REARRANGEMENTS DETECTED IN FETUSES WITH NO PREVIOUSLY KNOWN CYTOGENETIC RISK

Classification	Registry no.	R.F.S.*	Maternal age	Paternal age	Origin	Diagnosis
Unbalanced:						
Marker	BDI 40498	a	39	29	mat	48,XX,+21,+mar
	BDI 40386	j	32	33	mat	47,XX,+mar
	BDI 40169	f	39	· · ·	mat	47,XX,+mar
	BDI 40396	a	36	28	pat	47,XY,+mar(+s)
	BDI 40677	a	35	36	mat	47,XX,+mar
	BDI 40385	a	36	35	mat	mos 46,XX/47,XX,+mar
	BDI 40184	a	37	41	mat	mos 46,XY/47,XY,+mar
Derivative of parental translocation	BDI 40382	a	39	36	pat	46,X,−Y,+der(Y)rcpt(Y;DorG)(q12;p11)
	BDI 40240	a	40	37	mat	46,XX,−13,+der(13),t(13p;4q)
Deletion	ICRS 4126	a	37	40	mat	46,X,del(X)(q25)
Other	BDI 40685	a	36	· · ·	mat	47,XX,+dict(D?;G?)
	ICRS 1590	l	34	38	pat	92,XXXX,2t(6;8)(q21;q22.3)
Balanced:						
Robertsonian	BDI 40269	a	35	42	pat	45,XX,−13,−14,+t(13;14)
	BDI 40605	a	35	31	pat	45,XY,−13,−14,+t(13;14)
	BDI 40175	a	41	48	mat	45,XX,−13,−14,+t(13;14)
	BDI 40558	a	37	27	pat	45,XX,−13,−14,+t(13;14)
	BDI 40675	a	34	36	mat	45,XX,−13,−22,+t(13;22)
	BDI 40503	a	35	· · ·	mat	45,XX,−13,−21,+t(13;21)
	ICRS 12183	a	37	· · ·	mat	45,XX,−14,−22,+t(14;22)
	ICRS 5360	a	41	39	mat	45,XY,−13,−14,+t(13;14)

(*Table continued on p. 438.*)

APPENDIX TABLE 1 (*continued*)

Classification	Registry no.	R.F.S.*	Maternal age	Paternal age	Origin	Diagnosis
Inversion	BDI 40587	a	39	48	mat	46,XX,inv(6)(p21q21)
	BDI 40542	a	34	39	pat	46,XY,inv(2)(p11q13)
	BDI 40459	a	35	36	mat	46,XX,inv(10)(p12q21)
	BDI 40456	a	34	34	mat	46,XX,inv(12)(p12q14)
	BDI 40334	k	32	40	pat	46,XX,inv(18)(p11q21)
	BDI 40192	a	36	. . .	mat	46,XX,inv(1)(p13q21)
	BDI 40479	a	36	32	pat	46,XX,inv(4)(p14q21)
	BDI 40399	a	35	31	mat	46,XY,inv(12)(p13q11)
	BDI 40672	a	36	35	mat	46,XX,inv(12)(pq)
	BDI 40257	a	. . .	. . .	pat	46,XY,inv(10)(p11q11)
	BDI 40539	a	37	40	pat	46,XX,inv(8)(qq)
	BDI 40612	a	43	46	pat	46,XX,inv(7)(q11q36)
	BDI 40582	e	27	. . .	pat	46,XX,inv(5)(q13q34)
	ICRS 3818	a	36	38	pat	46,XY,inv(2)(p12q14)
	ICRS 24463	a	37	36	pat	46,XY,inv(5)(p11or12q22)
	ICRS 24476	a	37	40	pat	46,XX,inv(13)(q22q34)
	ICRS 24776	a	37	40	mat	46,XX,inv(1)(p36q42)
	ICRS 4288	a	38	33	mat	46,XX,inv(20)(p12q11)
	ICRS 4599	a	. . .	33	pat	46,XY,inv(2)(p11.2q13)
	ICRS 6635	a	36	36	pat	46,XY,inv(10)(p12q21)
	ICRS 47157	a	36	36	mat	46,XY,inv(2)(p11.6q13)
	ICRS 4921	a	37	37	mat	46,XY,inv(10)(p11.2q21.2)
	ICRS 47012	a	37	38	pat	46,XX,inv(2)(p11.6q13)
	ICRS 47567	a	39	30	pat	46,XY,inv(11)(q21q23.9)
	BDI 41259	a	35	35	pat	46,XX,inv(8)(q22q24)
	BDI 41268	a	36	38	pat	46,XY,inv(12)(pq)

Other reciprocals	BDI 40308	a	35	33	pat	46,XY,t(9;11)(q31;q25)
	BDI 40618	a	37	38	mat	46,XY,t(1;8)(q11;q24)
	BDI 40608	a	41	56	pat	46,XX,t(3;17)(q25;q25)
	BDI 40690	a	36	51	pat	46,XY,t(12;18)(q13;q11)
	BDI 40324	a	41	42	pat	46,XY,t(18;21)
	BDI 40211	a	41	58	pat	46,XY,t(9q;16q)
	BDI 40215	a	38	37	mat	46,XY,t(12q;22q)
	BDI 40458	a	35	38	pat	46,XY,t(3;20)(q24;p13)
	BDI 40624	a	36	39	mat	46,XY,t(3;19)
	BDI 40499	a	35	40	pat	46,XX,t(2;3)
	BDI 40225	j	33	. . .	pat	46,XY,t(12;21)
	BDI 40437	a	40	47	mat	46,XY,t(6;18)(p12;p11)
	BDI 40678	a	35	36	mat	46,XY,t(4;10)
	BDI 40683	a	38	42	pat	46,XY,t(3;9)
	BDI 40599	a	35	34	mat	46,XX,t(5;19)(p11;p12)
	BDI 40353	a	39	. . .	mat	46,XX,t(13;18)(q22;q23)
	BDI 40534	a	36	37	pat	46,XY,t(5;11)(q31;p15)
	BDI 40488	a	36	. . .	mat	46,XX,t(11;22)(q23.9;q11.1)
	BDI 40617	a	34	49	pat	46,XY,t(7;8)
	BDI 40265	a	40	. . .	pat	46,XX,t(1;11)(q21;q13)
	BDI 40493	l	30	27	mat	46,XY,t(7;17)(q31;p13)
	ICRS 24237	a	35	39	mat	46,XY,t(1;2)(p13;p12)
	ICRS 4424	a	36	34	pat	46,XY,t(10;17)(q24;q21)
	ICRS 23512	a	36	41	mat	46,XX,t(3;8)(q11;q24)
	ICRS 4450	a	38	41	pat	46,XY,t(2;12)(q21;q21.2)
	ICRS 24958	a	40	48	pat	46,XY.t(4;11)(q35;q21)
	ICRS 23983	a	41	44	pat	46,XY,t(9;17)(9p17p;9q17q)
	ICRS 25334	l	21	27	pat	46,XY,t(2;8)(p21;p21)
	ICRS 5578	a	37	. . .	mat	46,XX,t(1;7)(p32.1;q11)
	BDI 41248	a	32	41	mat	46,XX,t(1p−,12p+)(1pter→p32:)
	BDI 41267	a	37	44	pat	46,XY,t(21p;yq)

NOTE: Mutant rearrangements or those of unknown origin are listed in [1]. One additional case is mentioned in footnote * to table 3.

* R.F.S. = reason for study, coded as follows: a = advanced maternal age, e = alpha-fetoprotein determination, f = previous child with neural tube defect, j = anxiety, k = advanced paternal age, l = other, unspecified.

APPENDIX TABLE 2

INHERITED ABNORMALITIES IN FETUSES OF PARENTS AT PUTATIVE HIGH RISK OF BEING TRANSLOCATION CARRIERS

Classification	Registry no.	R.F.S.*	Maternal age	Paternal age	Origin	Diagnosis
Unbalanced:						
Derivative of a parental translocation	BDI 40400	m	31	...	pat	46,XX, −18, +der(18),t(3;18)(q21;q21)
	ICRS 11794	q	30	...	mat	46,XX, −18, +der(18),t(7;18)(q31.2;q22.2)
Robertsonian	ICRS 4912	q	23	27	mat	46,XY, −22, +t(21;22)
Other	BDI 40676	c	15	16	pat	46,XX,4p+ (? extra material on 4; fluorescent part of y.)
Balanced:						
Robertsonian	BDI 40261	m	24	...	mat	45,XX, −13, −14, +t(13;14)
	BDI 40536	b	38	...	mat	45,XY, −14, −21, +t(14;21)
Reciprocal	BDI 40237	p	31	33	mat	46,XX,t(7;13)(q34;q22)
	BDI 40501	q	...	...	mat	46,XY,t(4;22)
	ICRS 21922	n	23	26	mat	46,XY,t(3;11;20)(p13;p11;q13)
	ICRS 27349	r	30	32	pat	46,XX,t(2;10)(q33;p13)

* R.F.S. = reason for study, coded as follows: b = previous offspring with DS, c = family history of DS, m = previous offspring with multiple malformation, n = family history of unspecified chromosome abnormality, p = previous spontaneous abortion(s), q = previous offspring with unspecified chromosome abnormality, r = family history of birth defects.

APPENDIX TABLE 3

INHERITED ABNORMALITIES IN FETUSES OF KNOWN TRANSLOCATION CARRIERS

Classification	Registry no.	R.F.S.*	Maternal age	Paternal age	Origin	Diagnosis
Unbalanced:						
Derivative of a parental translocation	BDI 40380	s	25	29	pat	46,XY, −13, +t(y;13)(q12;p12)
	BDI 40220	s	25	28	pat	46,XY, −17, +der(17),t(1;17)(q41;p13)
	BDI 40668	s	...	...	mat	46,XX, −5, +der(5),t(5;8)(p15;p11)
	BDI 40707	s	32	39	mat	46,XX, −5, +der(5),t(5;11)(p15;q25)
	ICRS 1412	s	25	...	mat	47,XX, +der(15),t(1;15)(p36;q13)
Robertsonian	BDI 40315	s	30	31	mat	46,XX, −14, +t(14;21)
	ICRS 23641	s	31	37	mat	46,XX, −14, +t(14;21)
Other	BDI 40603	s	28	30	mat	46,XX, −1, −5, +der(1), +der(5), t(1;5;18)(1pter→1q42:: 5q15→5qter;5pter→5q15:: 18q11→18qter)
	BDI 40318	s	21	21	mat	46,XX, −18, +rec(18q−)
	BDI 40166	s	20	...	mat	mos 46,XY/47,XY, +22q−

(*Table continued on p. 441.*)

APPENDIX TABLE 3 (*continued*)

Classification	Registry no.	R.F.S.*	Maternal age	Paternal age	Origin	Diagnosis
Balanced:						
Robertsonian	BDI 40615	s	35	43	pat	45,XX,−13,−14,+t(13;14)
	BDI 40273	s	30	35	mat	45,XY,−13,−14,+t(13;14)
	BDI 40179	s	25	· · ·	mat	45,XY,−13,−14,+t(13;14)
	BDI 40425	s	21	21	mat	45,XY,−13,−14,+t(13;14)
	BDI 40199	s	26	27	mat	45,XY,−13,−14,+t(13;14)
	BDI 40100	s	30	· · ·	mat	45,XY,−13,−14,+t(13;14)
	BDI 40356	s	34	· · ·	mat	45,XY,−14,−15,+t(14;15)
	BDI 40208	s	17	· · ·	mat	45,XX,−13,−14,+t(13;14)
	BDI 40760	s	27	· · ·	mat	45,XX,−13,−14,+t(13;14)
	BDI 40056	s	23	· · ·	mat	45,XY,−14,−21,+t(14;21)
	BDI 40195	s	24	24	mat	45,XX,−14,−21,+t(14;21)
	BDI 40601	s	22	· · ·	pat	45,XY,−14,−21,+t(14;21)
	BDI 40735	s	34	31	mat	45,XY,−14,−21,+t(14;21)
	BDI 40693	s	28	31	pat	45,XY,−14,−21,+t(14;21)
	BDI 40691	s	29	· · ·	pat	45,XX,−14,−21,+t(14;21)
	BDI 40055	s	32	34	mat	45,XX,−D,−G,+t(D;G)
	BDI 40216	s	22	26	pat	45,XX,−14,−21,+t(14;21)
	BDI 40183	s	30	30	mat	45,XX,−14,−21,+t(14;21)
	BDI 40706	s	21	21	pat	45,XX,−14,−21,+t(14;21)
	BDI 40506	s	21	· · ·	mat	45,XX,−13,−21,+t(13;21)
	BDI 41249	s	31	· · ·	mat	45,XX,−14,−21,+t(14;21)
	BDI 41250	s	21	24	pat	45,XY,−14,−22,+t(14;22)
	BDI 41251	s	30	31	mat	45,XX,−13,−22,+t(13;22)
	BDI 41261	s	29	29	pat	45,XX,−15,−21,+t(15;21)
	BDI 41262	s	30	36	mat	45,XX,−14,−21,+t(14;21)
	ICRS 2259	s	22	23	mat	45,XY,−14,−21,+t(14;21)
	ICRS 2993	s	24	27	mat	45,XY,−13,−14,+t(13;14)
	ICRS 332	s	31	31	mat	45,XY,−14,−21,+t(14;21)
	ICRS 9350	s	21	22	mat	45,XY,−13,−14,+t(13;14)
	ICRS 23507	s	24	28	mat	45,XX,−14,−21,+t(14;21)
	ICRS 12253	s	27	· · ·	mat	45,XX,−14,−21,+t(14;21)
	ICRS 26539	s	29	31	pat	45,XX,−13,−14,+t(13;14)
	ICRS 4506	s	31	35	mat	45,XX,−13,−14,+t(13;14)
	ICRS 7394	s	35	28	mat	45,XY,−14,−21,+t(14;21)

Inversion	ICRS 21652	s	29	· · ·	mat	46,XX,inv(8)(p23 or 24 q13)
Reciprocal	BDI 40531	s	26	· · ·	mat	46,XX,t(13;15)(q14;q26)
	BDI 40217	s	32	33	pat	46,XX,t(6;18)(p11;p11)
	BDI 40586	s	25	26	mat	46,XX,t(4;11)(q23?;q13?)
	BDI 40444	s	29	· · ·	mat	46,XY,t(4p;13p)
	BDI 40412	s	28	29	mat	46,XX,t(12;15)(q24;q23)
	BDI 40611	s	29	30	mat	46,XY,t(12;15)(q24;q23)
	BDI 40719	s	27	28	mat	46,XY,t(4;11)(q22;q11)
	BDI 40727	s	35	23	mat	46,XX,t(1;6)(p36;p21)
	BDI 40729	s	22	· · ·	mat	46,XX,t(6;10)(q21;q26)
	BDI 40316	s	33	· · ·	pat	46,XY,t(1;17)
	BDI 40181	s	32	31	mat	46,XY,t(1;15)(p36;q24)
	BDI 40182	s	33	39	pat	46,XX,t(15;20)(q;p)
	BDI 40279	s	27	27	mat	46,XX,t(9;17)(p22;p11)
	BDI 40435	s	26	· · ·	mat	46,XX,t(11;22)(q23;q11)
	BDI 40102	s	32	· · ·	mat	46,XY,t(19;21)(p or q13;q22)
	BDI 40595	s	19	17	mat	46,XY,t(10;12)(q26;p11)
	BDI 40745	s	· · ·	· · ·	pat	46,XY,t(3;12)(p21;p13)
	BDI 40679	s	29	29	mat	46,XY,t(3;11)
	BDI 40167	s	29	· · ·	mat	46,XX,t(6;21)
	BDI 40689	s	22	· · ·	mat	46,XX,t(7;10)(q36;q24)
	ICRS 21281	s	22	24	mat	46,XX,t(3;15)(q27;q22)
	ICRS 4450	s	16	20	pat	46,XX,t(2;12)(q21;q21.2)
	ICRS 1412	s	26	· · ·	mat	46,XY,t(1;15)(p36;q13)
	ICRS 12221	s	26	· · ·	mat	46,XX,t(14;18)(q11;p11)
	ICRS 20969	s	30	36	mat	46,XY,t(3;9)(q21;p22)
	BDI 41256	s	18	17	mat	46,XY,t(10q;12p)
	BDI 41254	s	25	· · ·	mat	46,XY,t(11;22)(q25;q13)
	BDI 41260	s	32	33	mat	46,XX,t(4;7)(q35;q11)

* R.F.S. = reason for study; s = parent known to be a translocation carrier.