Am J Hum Genet 35:301–308, 1983

The Frequency and Mutation Rate of Balanced Autosomal Rearrangements in Man Estimated from Prenatal Genetic Studies for Advanced Maternal Age

DANIEL L. VAN DYKE,[1] LESTER WEISS,
JACQUELYN R. ROBERSON, AND V. RAMESH BABU

SUMMARY

The frequencies of balanced chromosome rearrangements were estimated from three series of advanced maternal-age prenatal genetic studies, and were compared to the frequencies that had been estimated from consecutive newborn surveys. In the maternal-age prenatal studies, the frequencies were: Robertsonian translocations, 0.11%; reciprocal translocations, 0.17%; and inversions, 0.12%. The total frequency of balanced rearrangements in the prenatal genetic studies performed with banding (0.40%, or 1 in 250) was twice that in the consecutive newborn surveys performed without banding (0.19%, or 1 in 526). The difference was limited to inversions and reciprocal translocations; the frequency of Robertsonian translocations was similar in the prenatal series and the newborn surveys. Both familial and de novo rearrangements were more common than anticipated. The de novo cases provided a mutation rate estimate of 4.3 per 10,000 gametes per generation (compared with 1.78 to 2.2 per 10,000 gametes in other surveys). These higher estmates may more reliably approximate the true mutation rate and frequencies of balanced rearrangements in the newborn population than do the newborn surveys.

INTRODUCTION

Useful estimates of the frequency of chromosome abnormalities and variants were provided by several karyotype surveys of consecutive newborns that were conducted in the late 1960s to mid-1970s [1–9]. Because most of the surveys were carried out before or during the introduction of banding techniques, they did not detect all of the balanced chromosome rearrangements; those that did not change

Received February 9, 1982; revised June 14, 1982.

[1] All authors: The Medical Genetics and Birth Defects Center, Henry Ford Hospital, Detroit, MI 48202.

the chromosome number or alter the centromere positions could not be identified without banding. The newborn studies thus underestimated the frequencies of balanced chromosome rearrangements; the extent of the underestimates is uncertain, however.

As one approach to this question, we compared the frequencies of balanced chromosome rearrangements in prenatal genetic studies for advanced maternal age to those in surveys of consecutive newborns. For estimating the frequencies of trisomy or new dominant mutations, a maternal-age amniocentesis series would provide a biased population sample, but for reasons given below, it provides a reasonably unbiased population sample for estimating the frequencies of balanced chromosome rearrangements.

METHODS

The frequency of balanced rearrangements was estimated from a G-banded [10] advanced maternal-age amniocentesis series at Henry Ford Hospital combined with two other series for which appropriate data were available ([11, 12] and Loughman, personal communication, 1981, and Crandall, personal communication, 1982). Unfortunately, most of the published prenatal genetic series could not be included in the tabulation because studies were performed without banding or because the ascertainment of the balanced translocation cases was unclear. In our series, a patient was included in the advanced maternal-age group if the primary reason for the referral was maternal age over 35 at delivery. Known chromosome variants such as inv(9)(p11q12) were not counted. Case A1199 of Golbus et al. [11], in which there were two reciprocal translocations, was counted once only.

Since July 1978, all prenatal cytogenetic studies at Henry Ford Hospital have been GTG-banded. From that time until October 31, 1981, we performed 1,935 prenatal cytogenetic studies. Advanced maternal age was the primary indication in 1,549 studies, and 386 studies were performed for other reasons. To avoid the most obvious selection biases, we compared only the advanced maternal-age studies to the newborn studies. Reference below to prenatal genetic studies will specifically refer to those performed for advanced maternal age. The Henry Ford Hospital cases, the 2,404 cases from Golbus et al. ([11] and Loughman, personal communication, 1981), and the 4,205 cases from Crandall et al. ([12] and Crandall, personal communication, 1982) provided a total of 8,158 prenatal genetic studies.

We used the mostly unbanded karyotype studies of consecutive newborns or consecutive male newborns [1–7] summarized by Hook and Hamerton [13] as a basis for comparison with the maternal-age studies. Two surveys [8, 9] of consecutuve newborns that were performed with banding were compared separately. The frequencies were compared by *t*-tests for the equality of percentages [14].

RESULTS

Thirty-three individuals with a balanced chromosome rearrangement were found among 8,158 consecutive prenatal genetic studies for advanced maternal age from three laboratories (table 1). These included nine individuals with Robertsonian translocations, 14 with reciprocal translocations (one of whom had two different reciprocal translocations), six with pericentric inversions, and four with paracentric inversions. Fifteen rearrangements were inherited from the mother and 11 from the father. In seven instances, the rearrangement was de novo, and in one, the origin was uncertain since the father declined to be karyotyped.

The pregnancy outcome was normal in 23 of 24 inherited cases where follow-up was available, but in one instance, mental delay was noted. One of the 23 cases was complicated by Klinefelter syndrome, but the infant was otherwise normal. Two

TABLE 1

BALANCED AUTOSOMAL REARRANGEMENTS FOUND IN PRENATAL GENETIC STUDIES FOR ADVANCED MATERNAL AGE

Case no.	Karyotype	Origin	Outcome	Reference
Robertsonian translocations:				
A79-616	45,XY,t(14;22)(p11;p11)	mat	Normal	Our case
327	45,XX,t(13q14q)	mat	Normal	[12]
564	45,XY,t(13q14q)	mat	Normal	[12]
2935	45,XY,t(13q14q)	de novo	Normal	[12]
3277	45,XX,t(13q14q)	pat	Normal	[12]
3623	45,XY,t(14q15q)	mat	Normal	[12]
4590	45,XY,t(13q14q)	pat	Normal	[12]
A949	45,XY,t(13q14q)	de novo	Normal	[11]
A981	45,XY,t(13q14q)	pat	Lost to followup	[11]
Reciprocal translocations:				
A80-125	47,XXY,t(15;17)(q22;q25)	mat	Klinefelter	Our case
A81-388	46,XX,t(11;22)(23;q11)	mat	Normal	Our case
731	46,XX,t(4;8)(q35;q12?)	de novo	Elective abortion	[12]
903	46,XY,t(2;4)(q37;q23)	pat	Normal	[12]
1095	46,XY,t(1;2)(p22;q21)	mat	Normal	[12]
1974	46,XY,t(2;9)(p11;q13)	pat	Normal	[12]
2723	46,XX,t(1;7)(q32;p22)	pat	Normal	[12]
2740	46,XX,t(1;11)(q11;p11)	pat	Normal	[12]
5355	46,XX,t(1;12)(p32;q12)	de novo	Normal	[12]
A1199	46,XX,t(1;6)(q23;p25),t(3;16)(q23;q24)	de novo, mat	Elective abortion	[11]
A4170	46,XX,t(14;15)(q32;q14)	pat	Mental delay	[11]
A1612-R	46,XX,t(2;8)(q11;q24)	de novo	Normal	[11]
A2073	46,XY,t(11;22)(q25;q12)	mat	Normal	[11]
A2400	46,XY,t(12;17)(q24;p13)	pat	Normal	[11]
Inversions:				
A80-96	46,XX,inv(2)(p11q13)	mat	Normal	Our case
A80-654	46,XX,inv(2)(p21q21)	*	Normal	Our case
A81-215	46,XY,inv(11)(q11q23)	mat	Normal	Our case
A81-287	46,XY,inv(11)(p13q21)	pat	Normal	Our case
A81-633	46,XX,inv(4)(p14p16.3)	mat	Normal	Our case
746	46,XX,inv(16)(p13q11)	de novo	Abnormal†	[12]
1447	46,XY,inv(3)(q21q28)	mat	Normal	[12]
3792	46,XY,inv(6)(p11p25)	mat	Normal	[12]
3927	46,XY,inv(18)(p11q21)	mat	Normal	[12]
5308	46,XX,inv(10)(p11q22)	pat	Normal	[12]

* Mother was 46,XX and father declined to be karyotyped.
† Mental retardation and multiple congenital anomalies.

de novo Robertsonian translocation carriers were normal. Two de novo reciprocal translocation carriers were normal, but the parents elected abortion in two other cases. The de novo pericentric inversion carrier had retardation and multiple congenital anomalies.

In the prenatal studies, the total frequency of chromosome rearrangements was 0.40%, whereas it was 0.23% in banded consecutive newborns and 0.19% in unbanded consecutive newborns (table 2). The frequency of rearrangements in the amniocentesis series was significantly greater than in the unbanded newborn surveys. The frequency of Robertsonian translocations was similar in all three groups, but about twice as many reciprocal translocations and nine times as many inversions were detected in the prenatal studies as in the unbanded consecutive newborn surveys. No significant differences were found between the maternal-age group and the banded newborn surveys, nor between the banded and unbanded newborn surveys.

DISCUSSION

The difference between the prenatal studies and the newborn surveys have a number of possible explanations. Briefly, either the true frequency of subjects with reciprocal translocations and inversions could differ or their rate of detection could differ, or both could apply.

First, all of the rearrangement carriers identified prenatally lived to term, except for two elective abortions, so differential in utero survival is not a consideration.

Second, if the mutation rate for balanced chromosome rearrangements increases with advancing maternal or paternal age, then de novo rearrangements would be more frequent in the maternal-age amniocenteses than in the newborns. However, the available evidence suggests that there is no correlation between the genesis of de novo rearrangements and parental age [15, 16]. In any event, the de novo cases could not by themselves account for the higher observed frequency of reciprocal translocations in the prenatal studies, and, in particular, could not account for the higher frequency of inversions (nine of the 10 inversions identified prenatally were familial).

A third confounding factor would exist if couples with inherited chromosome rearrangements were overrepresented in the advanced maternal-age amniocentesis group. For example, the prenatal studies might be biased with respect to reproductive outcome in the following way: since couples who carry chromosome rearrangements may have reduced fertility or multiple miscarriages [17, 18], they might extend their childbearing years beyond age 35 to complete their idealized families. They might then be preferentially referred for prenatal diagnosis because of heightened anxieties about the outcome of a much wanted pregnancy, and because they might be more closely followed by their obstetricians due to their poorer reproductive histories. Prenatal studies are biased with respect to geographic, socioeconomic, and ethnic factors [19–22], but to our knowledge, bias with respect to reproductive risk (other than parental age) has not been investigated, so the impact of this factor is difficult to evaluate. Whereas there is a priori reason to expect overrepresentation of couples with familial chromosome rearrangements in the prenatal studies, we believe this source of bias was not serious for several reasons: (1) A

TABLE 2

FREQUENCY OF BALANCED AUTOSOMAL REARRANGEMENTS IN MATERNAL-AGE AMNIOCENTESES COMPARED TO THE FREQUENCIES IN CONSECUTIVE NEWBORN SURVEYS

	No.	rob	%	rcp	%	inv	%	rea	%
Maternal-age amniocenteses	8,158	9	0.11	14	0.17	10	0.12	33	0.40
Newborns, banded	4,765	3	0.06	5	0.10	3	0.06	11	0.23
Newborns, unbanded	56,930	52	0.09	50	0.09*	8	0.01†	110	0.19†

	95% confidence limits for the frequencies of balanced rearrangements			
	rob	rcp	inv	rea
Maternal-age amniocentesis	0.04–0.18	0.08–0.26	0.05–0.20	0.27–0.54
Newborns, banded	0.00–0.13	0.01–0.19	0.00–0.13	0.09–0.37
Newborns, unbanded	0.07–0.12	0.06–0.11	0.004–0.02	0.16–0.23

NOTE: Frequencies and 95% confidence intervals are provided for Robertsonian (rob) and reciprocal (rcp) translocations, inversions (inv), and total rearrangements (rea).

* Significantly different from the amniocenteses with $P < .05$.

† Significantly different from the amniocenteses with $P < .001$.

large bias in the maternal-age group might have increased the proportion of balanced rearrangements that were inherited, but this proportion was similar in the maternal-age amniocenteses, consecutive newborns, and spontaneous abortions; about 75% were inherited and 25% de novo in all three groups. (2) The differences between the prenatal genetic studies and the newborn surveys were limited to the reciprocal translocations and inversions. Although the sample size permits little confidence, one might expect to find a difference for Robertsonian translocations as well if a serious bias existed, because Robertsonian translocation carriers are known to be overrepresented in multiple miscarriage surveys [18] and in male infertility [23, 24]. (3) Data from one large study of consecutive newborns [25] suggests that carriers of balanced rearrangements have their children at the usual age: the mean maternal and paternal ages for children with normal karyotypes was 26.2 and 29.5, respectively, and for children with balanced rearrangements, 27.3 and 28.9, respectively.

The differences between the amniocentesis studies and the unbanded newborn surveys may alternatively be influenced by the ability to detect reciprocal translocations and inversions. First, fewer cells were examined per subject in most of the newborn surveys than in the three prenatal genetic studies. A rearrangement is occasionally not detected until several cells have been analyzed. Second, the perceived consequences of technical error in a consecutive newborn survey almost certainly differ from that in a prenatal genetic study, serving to further improve the identification of rearrangements in the latter. Third, and most important, some chromosome rearrangements were missed in the unbanded newborn surveys because paracentric inversions are undetectable in mitotic cells without banding, as are many reciprocal translocations and pericentric inversions. Among the 34 banded rearrangements detected in the present series, we surmise that only 20 (59%) could have been detected without banding. These 20 would have been comprised of all nine Robertsonian translocations, eight of the 15 reciprocal translocations, and three of the 10 inversions. Since the prenatal genetic studies were undertaken more recently than the banded newborn surveys, qualitative differences in the banding were also likely; this may be evidenced by the intermediate frequencies of rearrangements in the banded newborn studies. Unlike the inversions and reciprocal translocations, the Robertsonian translocations were probably completely ascertained in the newborn surveys and amniocentesis studies alike, and their true frequency is approximately 0.10%. Robertsonian translocations are detectable with or without banding, because the carrier has 45 chromosomes, including a bisatellited reciprocal translocation product (e.g., [26]), are also detectable without banding.

Thus, the differences among the studies are mostly attributable to technical factors: there is substantial evidence that the ascertainment of balanced chromosome rearrangements was more complete in the prenatal series, and there is little to suggest that selection biases seriously impaired the population sample. The frequency of chromosome rearrangements in the prenatal studies for advanced maternal age therefore provides a reasonable estimate of the true frequency of chromosome rearrangements in humans. In a series of 2,330 G-banded prenatal genetic studies performed for indications other than structural rearrangement,

Boue and Boue [18] found a similar frequency to that observed in the present series (0.38% had a balanced rearrangement). The estimates provided here relate to G-banded midmetaphase preparations of amniotic fluid cell karyotypes. Detection of more subtle rearrangements is likely to improve as cytogenetic technology continues to improve (cf., [27]).

Jacobs et al. [15, 16] used data from newborn and spontaneous abortion surveys to estimate a mutation rate of 1.78 to 1.88 per 10,000 gametes per generation for balanced chromosome rearrangements that result in a live-born individual (2.20 per 10,000 when all recognized conceptions are considered). However, they have long maintained that these are underestimates [15, 16]. In the prenatal series, seven de novo balanced rearrangements detected among 8,158 cases provide a mutation rate estimate of 4.3 per 10,000 gametes per generation. This estimate ignores bias of nonpaternity, possible parental-age effects, and assumes that the two electively aborted fetuses would have survived to term. If the higher estimate is reliable, it almost certainly reflects and underscores the importance of improved ascertainment of balanced chromosome rearrangements.

NOTE ADDED IN PROOF: A newly published survey of 1,830 consecutive newborns with banded chromosomes (I.-L. Hansteen et al., *Clin Genet* 21:309–314, 1982) adds substantially to the sample size of this category. This survey, pooled with the other banded newborn surveys, provides a total sample size of 6,595 consecutive newborns, with frequencies of rob 0.11%, rcp 0.15%, inv 0.06%, and total rea 0.32%. There are no significant differences between the two series that employed banding (amniocenteses vs. newborns), but inversions are significantly more frequent in the banded newborn surveys compared with the unbanded surveys ($P < .05$). This adds credence to the notion that the real frequencies (and mutation rates) of reciprocal translocations and inversions are greater than were estimated by the unbanded studies of consecutive newborns. Pooling the banded newborn and the amniocentesis series, the frequency estimates (and 95% confidence intervals) are rob 0.11% (0.06–0.16), rcp 0.16% (0.10–0.23), inv 0.10% (0.05–0.15), and total rea 0.37% (0.27–0.47).

ACKNOWLEDGMENTS

We appreciate the generosity of Drs. Barbara F. Crandall and William D. Loughman in sharing their unpublished data. We also wish to express our gratitude to Dr. Wayne Stanley for his comments on the manuscript, to Dr. Patricia L. Cornett for editoral assistance, and to Juanita Clark, Debbie Anderson, Joanne H. Beisel, Timothy Drumheller, Lucie Gemus, Maria Worsham, and Tonia Moore for expert technical support.

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