Am J Hum Genet 33:44–54, 1981

Mutation Rates of Structural Chromosome Rearrangements in Man

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SUMMARY

The gametic mutation rates of human structural chromosome rearrangements have been estimated from rearrangements ascertained from systematic surveys of live births and spontaneous abortions. The mutation rates for rearrangements that survive long enough to give rise to clinically recognized pregnancies are 2.20×10^{-4} for balanced rearrangements, 3.54×10^{-4} for unbalanced Robertsonian translocations, and 3.42×10^{-4} for unbalanced non-Robertsonian rearrangements. These estimates give a mutation rate for all detectable structural chromosome rearrangements of approximately 1×10^{-3}. The most common single rearrangement, the Robertsonian translocation involving chromosomes 13 and 14, has a mutation rate of 1.5×10^{-4}.

INTRODUCTION

Most information on the frequency and mutation rates of structural chromosome rearrangements in man has come from studies of live-born children. Surprisingly little attention has been paid to structural chromosome abnormalities occurring among spontaneous abortions, although the frequency of structural abnormalities in spontaneous abortions is approximately 10 times greater than in the live born. Structural chromosome abnormalities are found in 1%–2% of all clinically recognized spontaneous abortions, and these represent over two-thirds of all human structural rearrangements. Failure to consider data from spontaneous abortions in the past has resulted in a loss of valuable information on both the frequency and mutation rates of chromosome rearrangements in our species.

Received March 27, 1980.

This work was supported by grant HD-07879 from the National Institutes of Health.

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In this paper, structural abnormalities of the chromosomes ascertained through systematic studies of spontaneous abortions are compared with those ascertained from surveys of the live born and the combined data used to estimate the significance, frequency, and mutation rate of various classes of rearrangement.

MATERIAL

The data on structural rearrangements in spontaneous abortions have been obtained from published surveys, augmented by information provided by the respective authors and recent data from our own laboratory. These data are summarized in table 1. The information on structural rearrangements in the live born was obtained from published surveys, and the pertinent data are summarized in table 2. We have considered only structural abnormalities involving one or more autosomes and only those that are present in all the cells examined. Thus, structural abnormalities of the X and Y chromosomes and mosaics having a normal cell line are not included in these analyses.

RESULTS

Balanced Structural Rearrangements

Balanced structural rearrangements have been divided into four classes: D/D Robertsonian translocations, D/G Robertsonian translocations, reciprocal translocations, and inversions. Data on the frequency of these four classes of balanced rearrangements both in spontaneous abortions and the live born are given in table 3. The overall frequency is very similar in spontaneous abortions and live births, the slight increase among the spontaneous abortions being due to an excess of reciprocal translocations and inversions. This nonsignificant excess is largely the result of an increased proportion of new mutants among the spontaneous abortions. It is possible, therefore, that a small proportion of apparently balanced de novo reciprocal translocations are incompatible with fetal life and result in abortion.

Gametic mutation rates for the four classes of balanced structural rearrangements among the live born are given in table 3, together with the rates for reciprocal

TABLE 1

STRUCTURAL CHROMOSOME ABNORMALITIES IN SURVEYS OF SPONTANEOUS ABORTIONS

SURVEY	TOTAL EXAMINED	BALANCED REARRANGEMENTS		UNBALANCED REARRANGEMENTS	
		No.	%	No.	%
Paris [1]*	1,500	2	0.13	34	2.27
Switzerland [2]	447	2	0.45	9	2.01
London [3]	941	1	0.11	9	0.96
Denmark [4]	255	2	0.78	4	1.57
Japan [5]†	583	1	0.17	3	0.51
New York‡	1,000	5	0.5	13	1.3
Hawaii [6]§	1,000	3	0.3	16	1.6
Total	5,726	16	0.28	88	1.54

*Also, personal communication from Boué et al., 1980.
†Also, personal communication from Dr. K. Ohama, 1980.
‡D. Warburton, personal communication, 1980.
§Also, personal communication from Hassold et al., 1980.

TABLE 2

STRUCTURAL CHROMOSOME ABNORMALITIES IN SURVEYS OF THE NEWBORN

SURVEY	TOTAL EXAMINED	BALANCED REARRANGEMENTS		UNBALANCED REARRANGEMENTS	
		No.	%	No.	%
Edinburgh [7]	11,680	22	0.19	5	0.04
Denmark [8]	11,148	32	0.29	8	0.07
Ontario [9]	2,081	1	0.05	2	0.10
Winnipeg [10]	13,939	25	0.18	4	0.03
Boston [11]	13,751	23	0.17	9	0.07
New Haven [12]	4,353	6	0.14	0	0
Moscow [13]	2,500	4	0.16	3	0.12
Total	59,452	113	0.19	31	0.05

translocations among spontaneous abortions—the only class in which there are sufficient data to permit the calculation of such an estimate. The mutation rate among all conceptions that survive long enough to give rise to a clinically recognizable pregnancy has been estimated by assuming that 15% of all such conceptions abort while 85% are live born [15]. The estimate of mutation rate at conception for all balanced structural rearrangements is 2.20×10^{-4} per gamete per generation, the majority (1.63×10^{-4}) resulting in reciprocal translocations.

It is generally agreed that approximately 50% of all spontaneous abortions for which medical attention is sought are associated with an abnormal chromosome constitution [1, 6, 15]. Furthermore, it has been suggested that one structural chromosome rearrangement may predispose to further abnormalities involving quite different chromosomes [16]. If such a nonspecific effect were a widespread phenomenon, we might expect an unusual proportion of balanced structural rearrangements to be associated with additional chromosome abnormalities among spontaneous abortuses. Inspection of the 16 balanced structural rearrangements ascertained in spontaneous abortions showed seven to be associated with an additional abnormality while nine were not. The additional abnormalities included three trisomies: one triploid, one 45,X, one unbalanced structural rearrangement, and one triploid with three additional chromosomes. Thus, the frequency and distribution of abnormalities associated with balanced structural rearrangements is no different from that found among spontaneous abortions generally and provides no evidence for a nonspecific effect of balanced chromosome abnormalities in our species.

Unbalanced Robertsonian Translocations

The three classes of unbalanced Robertsonian translocations, D/D, D/G, and G/G, have been considered separately. Data on frequency and mutation rates for both spontaneous abortions and live births are given in table 4, which shows that the frequency of all such translocations is approximately 100 times higher in the spontaneous abortions than in the live born. Thus, the estimates of mutation rates in the live born are based on extremely small numbers. The mutation rate at

TABLE 3

BALANCED STRUCTURAL REARRANGEMENTS

POPULATION	NO. EXAMINED	NO. ABNORMAL	ROBERTSONIAN TRANSLOCATIONS D/D				ROBERTSONIAN TRANSLOCATIONS D/G				RECIPROCAL TRANSLOCATIONS				INVERSIONS				TOTAL			
			DE NOVO	FAMILIAL Pat	FAMILIAL Mat	?	DE NOVO	FAMILIAL Pat	FAMILIAL Mat	?	DE NOVO	FAMILIAL Pat	FAMILIAL Mat	?	DE NOVO	FAMILIAL Pat	FAMILIAL Mat	?	DE NOVO	FAMILIAL Pat	FAMILIAL Mat	?
Spontaneous abortions	5,726	16	0	1	3	0	0	0	0	1	4	1	4	0	0	1	0	1	4	3	7	2
Live births	59,452	113	2	12	15	12	2	6	3	0	13	16	14	9	1	3	4	1	18	37	36	22
%:																						
Spontaneous abortions			0.070				0.017				0.157				0.035				0.279			
Live births			0.069				0.018				0.087				0.015				0.190			
Gametic mutation rate:																						
Spontaneous abortions			0				?				3.49×10^{-4}				?				3.99×10^{-4}			
Live births			0.24×10^{-4}				0.16×10^{-4}				1.31×10^{-4}				0.09×10^{-4}				1.88×10^{-4}			
All recognized conceptions			0.20×10^{-4}				0.16×10^{-4}				1.63×10^{-4}				0.09×10^{-4}				2.20×10^{-4}			

TABLE 4

UNBALANCED ROBERTSONIAN TRANSLOCATIONS

POPULATION	NO. EXAMINED	NO. ABNORMAL	D/D				D/G				G/G				TOTAL			
			DE NOVO	FAMILIAL			DE NOVO	FAMILIAL			DE NOVO	FAMILIAL			DE NOVO	FAMILIAL		
				Pat	Mat	?		Pat	Mat	?		Pat	Mat	?		Pat	Mat	?
Spontaneous abortions	5,726	46	15	1	11*	6	4	0	4*	2	1	0	0	2	20	1	15	10
Live births	59,452	4	1	0	1	1	0	0	0	0	1	0	0	0	2	0	0	1
%:																		
Spontaneous abortions			0.576				0.175				0.052				0.803			
Live births			0.005				0				0.002				0.007			
Gametic mutation rate:																		
Spontaneous abortions			16.00×10^{-4}				4.37×10^{-4}				2.60×10^{-4}				22.32×10^{-4}			
Live births			0.13×10^{-4}				0				0.10×10^{-4}				0.23×10^{-4}			
All recognized conceptions			2.51×10^{-4}				0.66×10^{-4}				0.48×10^{-4}				3.54×10^{-4}			

*Includes two sibs.

conception is 3.54×10^{-4} per gamete per generation with the majority (2.51×10^{-4}) accounted for by the D/D class.

Unbalanced Non-Robertsonian Rearrangements

The data on unbalanced rearrangements, other than Robertsonian translocations, are given in table 5. They are classified into stable, structurally abnormal chromosomes (monocentric chromosomes that have missing and/or additional material), ring chromosomes, and supernumerary chromosomes (heterochromatic chromosomes as small or smaller than the G-group chromosomes, present in addition to an apparently normal chromosome complement). The frequency of non-Robertsonian unbalanced rearrangements is approximately 25 times higher among the spontaneous abortions than in the live born. The mutation rate at conception for all unbalanced non-Robertsonian rearrangements is 3.42×10^{-4}, almost identical with that for unbalanced Robertsonian translocations.

Total Mutation Rate

An estimate of the total gametic mutation rate at conception based on all pregnancies that survive long enough to be clinically recognizable can be obtained by adding together the total for balanced, unbalanced Robertsonian, and unbalanced non-Robertsonian rearrangements. Table 6 shows such rates under the conservative assumption that only 15% of all clinically recognizable pregnancies terminate as spontaneous abortions. The total gametic mutation rate is 9.03×10^{-4}, with Robertsonian translocations accounting for approximately 43% of all mutants.

Robertsonian translocations constitute the single most frequent class of structural rearrangement in our species. Among all possible types of Robertsonian translocations, the D/D class is the most frequent, and among the D/D class, the 13/14 is by far the most common. The mutation rate for the Robertsonian translocation involving a chromosome 13 and a chromosome 14 has been estimated using data from a subset of 3,030 spontaneous abortuses in which banding studies were used to identify the abnormalities. In the great majority of newborn surveys banding was used to identify the abnormal karyotypes. However, this was often done retrospectively and was not possible for every case. Therefore, two data sets have been used for the newborn; the first assumes that all the unbanded D/D translocations were of the 13/14 type (maximum estimate), and the second assumes that none of the unbanded D/D translocations were of the 13/14 type (minimum estimate). The great majority of D/D translocations are between a chromosome 13 and a chromosome 14, and, therefore, the maximum estimate is likely to be more realistic than the minimum. Table 7 shows that the total gametic mutation rate for 13/14 translocations, irrespective of whether they result in a chromosomally balanced or unbalanced fetus or in a live birth, is between 1.37 and 1.6×10^{-4}.

Parental Origin

Where a structural rearrangement involves one or more chromosomes with a pronounced heteromorphic band, it is often possible to determine the parent in

TABLE 5

UNBALANCED STRUCTURAL REARRANGEMENTS (NON-ROBERTSONIAN)

POPULATION	NO. EXAMINED	NO. ABNORMAL	STABLE STRUCTURALLY ABNORMAL CHROMOSOMES				RINGS				SUPERNUMERARY				TOTAL			
			DE NOVO	FAMILIAL			DE NOVO	FAMILIAL			DE NOVO	FAMILIAL			DE NOVO	FAMILIAL		
				Pat	Mat	?		Pat	Mat	?		Pat	Mat	?		Pat	Mat	?
Spontaneous abortions	5,726	42	15	8*	6	10	1	0	0	2	0	0	0	0	16	8	6	12
Live births	59,452	18	3	1	1	2	0	0	0	0	2	1	5	3	5	2	6	5
%:																		
Spontaneous abortions			0.681				0.052				0				0.733			
Live births			0.012				0				0.018				0.030			
Gametic mutation rate:																		
Spontaneous abortions			17.60×10^{-4}				2.6×10^{-4}				0				19.53×10^{-4}			
Live births			0.36×10^{-4}				0				0.23×10^{-4}				0.58×10^{-4}			
All recognized conceptions			2.95×10^{-4}				0.39×10^{-4}				0.20×10^{-4}				3.42×10^{-4}			

*Includes three sibs.

TABLE 6

MUTATION RATES FOR ALL STRUCTURAL REARRANGEMENTS

Population	All Robertsonian translocations	All non-Robertsonian rearrangements	Total
Spontaneous abortions	22.32×10^{-4}	23.02×10^{-4}	45.34×10^{-4}
Live births	0.63×10^{-4}	1.99×10^{-4}	2.62×10^{-4}
All recognized conceptions.....	3.88×10^{-4}	5.14×10^{-4}	9.03×10^{-4}

whom the mutation occurred. Among the 19 structural rearrangements ascertained in the Hawaiian spontaneous abortion survey, eight were mutants, and six of these involved one or more chromosomes with a pronounced heteromorphic band. By comparing the parental and fetal heteromorphisms, it was possible to determine the parental origin of four of the six mutants. In one (a 13/13 Robertsonian translocation), the mutation was clearly paternal in origin, while in three (two 13/14 Robertsonian translocations and one structurally abnormal chromosome 9), it was clearly maternal in origin.

The mean paternal age of the eight de novo mutants ascertained in the Hawaiian abortion survey was 26.13 years, and the maternal age was 25.75 years. This compares with a paternal age of 32.48 ± 7.89 years and a maternal age of 27.70 ± 6.17 years for the series as a whole. These data are in agreement with those published previously in finding no association between increased parental age and the origin of structurally abnormal chromosomes [17].

DISCUSSION

The calculated mutation rate for all detectable structural chromosome abnormalities that survive long enough to give rise to a recognized pregnancy is of the order of .001 per gamete per generation, a figure not dissimilar to the estimate of .002 previously suggested by Jacobs et al. [17]. The rate of .001 must be an underestimate for at least two reasons. First, it has been computed on the assumption that 15% of all clinically recognized conceptions terminate as spontaneous abortions. However, carefully monitored studies of human pregnancy suggest that 25% is a more accurate figure [18]. Using this estimate, the mutation rate for chromosome structural rearrangements becomes .0013. Second, in many surveys from which the calculations in this paper are derived, the original observations were made on nonbanded preparations. Thus, the estimates are largely restricted to structural rearrangements detectable by nonbanded techniques, and, for this reason, all the mutation rates, except those for Robertsonian translocations, must be underestimates.

The five pairs of human acrocentric chromosomes can give rise to 15 different types of Robertsonian translocations, five involving homologous and 10 involving nonhomologous chromosomes. The frequencies of the various types are very different, the translocation involving a chromosome 13 and a chromosome 14 being by far the most common among both the balanced and unbalanced rearrangements, with a mutation rate of 1.5×10^{-4}. While there may well be multiple sites in the

TABLE 7

13/14 ROBERTSONIAN TRANSLOCATIONS

POPULATION	NO. EXAMINED	BALANCED/UNBALANCED		13/14 TOTAL	13/14 DE NOVO	13/14 FAMILIAL Pat	13/14 FAMILIAL Mat	13/14 FAMILIAL ?
Spontaneous abortions	3,030	Balanced		0	0	0	0	0
		Unbalanced		13	4	0	6	3
Live births	59,452	Balanced	Max	39	2	12	13	12
			Min	30	1	12	11	6
		Unbalanced	Max	3	1	0	1	1
			Min	0	0	0	0	0

%:		
Spontaneous abortions		0.429
Live births	Max:	0.071
	Min:	0.050
Gametic mutation rate:		
Spontaneous abortions		8.58×10^{-4}
Live births	Max:	0.37×10^{-4}
	Min:	0.10×10^{-4}
All recognized conceptions	Max:	1.60×10^{-4}
	Min:	1.37×10^{-4}

short arms, centromeres, and proximal parts of the long arms of the acrocentric chromosomes in which breakage and exchange would lead to a Robertsonian translocation, a mutation rate of 1.5×10^{-4} seems a remarkably high figure for a single type of two-break arrangement. The reason for the high mutation rate of human Robertsonian translocations in general, and for the 13/14 translocation in particular, is obscure.

Clearly, the great majority of de novo chromosome rearrangements in our species result in conceptions with unbalanced karyotypes that are subsequently spontaneously aborted. Thus, in any attempt to monitor the population for the effects of mutagenic agents that are known or suspected of causing chromosome breakage, spontaneous abortuses are the most obvious and rewarding population to study.

ACKNOWLEDGMENTS

I would like to thank Drs. André and Joelle Boué, Dr. Koso Ohama, Dr. Hiroyuki Takahara, Dr. Dorothy Warburton, and Dr. Terry Hassold for generously allowing me to use their unpublished observations on spontaneous abortuses.

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