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XY Chromosome Nondisjunction in Man Is Associated with Diminished Recombination in the Pseudoautosomal Region

Terry J. Hassold,* Stephanie L. Sherman,* Dorothy Pettay,*,† David C. Page,† and Patricia A. Jacobs‡

*Division of Medical Genetics, Department of Pediatrics, Emory University School of Medicine, Atlanta; †Howard Hughes Research Laboratories, Whitehead Institute for Biomedical Research and Department of Biology, Massachusetts Institute of Technology, Cambridge; and ‡Wessex Regional Genetics Laboratory, Salisbury, United Kingdom

Summary

To assess the possible association between aberrant recombination and XY chromosome nondisjunction, we compared pseudoautosomal region recombination rates in male meiosis resulting in 47,XXY offspring with those resulting in 46,XY and 46,XX offspring. Forty-one paternally derived 47,XXYs and their parents were tested at six polymorphic loci spanning the pseudoautosomal region. We were able to detect crossing-over in only six of 39 cases informative for the telomeric DXYS14/DXYS20 locus. Subsequently, we used the data to generate a genetic linkage map of the pseudoautosomal region and found it to be significantly shorter than the normal male map of the region. From these analyses we conclude that most paternally derived 47,XXYs result from meiosis in which the X and Y chromosomes did not recombine.

Introduction

Trisomy is the most commonly identified chromosome abnormality in man, occurring in approximately 5% of all clinically recognizable pregnancies. Almost all trisomies spontaneously abort, and by the time of birth only two types—namely, trisomy 21 and trisomies involving the sex chromosomes—occur in appreciable frequency (Hassold and Jacobs 1984).

We have been using X-linked DNA polymorphisms to study the parent and meiotic stage of origin of sex-chromosome trisomies, and we recently presented our preliminary observations on 47,XXX and 47,XXY individuals (Jacobs et al. 1988; May et al. 1990). To date, we have studied 39 47,XXX individuals, with 37 resulting from nondisjunction either in maternal meiosis I or maternal meiosis II. This is similar to DNA marker studies of trisomy 13, 16, 18, and 21, in which 85%–95% of cases have been attributed to maternal meiotic errors (Hassold and Takaesu 1989). In contrast, our studies of 47,XXY individuals indicate a high proportion of paternal nondisjunction, as 56 (50%) of 112 cases have inherited both an X and Y chromosome from their father (Jacobs et al. 1988, and unpublished observations). In such instances, the trisomy must have arisen from nondisjunction at paternal meiosis I, since meiosis II or postzygotic mitotic errors would lead to either 47,XXX or 47,XYY offspring.

The relatively large proportion of cases of paternal origin among 47,XXYs suggests that the XY bivalent may be particularly susceptible to nondisjunction. If so, this might be attributable to the meiosis I pairing configuration of the human X and Y chromosomes. In normal male meiosis a single chiasma is formed in the XY pairing, or pseudoautosomal, region (Burgoyne 1982; Goodfellow et al. 1986; Rouyer et al. 1986; Page et al. 1987). Absence or loss of the single chiasma might result in XY univalency or desynapsis and, consequently, in nondisjunction at anaphase I. In contrast, most other human chromosomes are held together by two or more chiasmata in meiosis I (Wallace and Hulten 1985). Thus, for these chromosomes, absence or loss of a single chiasma need not disrupt the normal process of segregation.

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Address for correspondence and reprints: Terry J. Hassold, Ph.D., Division of Medical Genetics, Department of Pediatrics, Emory University School of Medicine, 2040 Ridgewood Drive, Atlanta, GA 30322.

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To test this model, we have compared pseudoautosomal region recombination rates in male meiosis resulting in 47,XXY offspring with those resulting in 46,XY and 46,XX offspring. In the present report, we summarize our observations on 41 paternally derived 47,XXY individuals and demonstrate a strong correlation between failure of recombination of the XY bivalent and subsequent XY chromosome nondisjunction. This provides the second example of an effect of recombination deficiency on human nondisjunction, the first example being the association between reduced recombination and nondisjunction for chromosome 21 (Warren et al. 1987).

Material and Methods

Study Population

For the past 3 years we have been using DNA markers to study the parental origin of the additional sex chromosome in males with a 47,XXY chromosome constitution. To date, we have identified 56 paternally derived cases (Jacobs et al. 1988, and unpublished observations). In 41 of the 56 cases, DNA samples were available from the proband and from both parents, making it possible to study pseudoautosomal region recombination in the trisomy-generating meiosis. The analyses of the 41 families form the basis for the present report.

DNA Studies

DNA was isolated from peripheral blood samples, digested with *Taq*I, and processed for Southern blotting experiments as previously described (Hassold et al. 1988). DNA samples from 47,XXYs of paternal origin and from their parents were hybridized to probes detecting RFLPs at six pseudoautosomal loci: MIC2, DXYS17, DXYS15, DXYS28, DXYS14, and DXYS20. Information on the polymorphisms and the probes used to detect them is provided elsewhere (Kidd et al. 1989).

Genetic Linkage Studies

47,XXY Cases.—We used centromere-gene mapping methods to estimate the amount of pseudoautosomal region recombination in meiosis involved in XY chromosome nondisjunction. For this type of analysis, the estimation of recombination depends both on knowing the parent and meiotic stage of origin of nondisjunction and on identifying genetic markers for which the parent of origin is heterozygous; the markers are then evaluated in the trisomic offspring to determine whether heterozygosity is maintained (nonreduction) or reduced to homozygosity (reduction). Chakravarti et al. (1989) and Morton et al. (1990) have recently discussed the application of this approach to the study of autosomal trisomies and maternally derived sex-chromosome trisomies, respectively. Centromere mapping for sex chromosome trisomies of paternal origin is similar to these approaches, except that the sex-chromosome constitution defines the meiotic stage of origin; that is, 47,XXYs are derived from meiosis I (or premeiotic) errors, and 47,XXXs and 47,XYYs are derived from meiosis II (or mitotic) errors.

Six pseudoautosomal genetic markers were studied in each of the 41 paternally derived 47,XXY offspring and their parents. For each locus at which the father was heterozygous, the 47,XXY offspring was categorized as follows: N = nonreduced or retained heterozygosity (e.g., father [FA]: 12 × mother [MO]:11; XXY:112); R = reduced or loss of heterozygosity (e.g., FA:12 × MO:11; XXY:111); PI = intercross with partial information on heterozygosity (e.g., FA: 12 × MO:12; XXY:112); and – = uninformative (table 1). Data for the two most telomeric loci, DXYS14 and DXYS20, were combined, since no recombinants have been detected in studies of normal individuals (Page et al. 1987).

These data were used to obtain the maximum likelihood estimates of the probability of nonreduction (y) between all pairs of markers by using the program TETRAD (Shahar and Morton 1986) (table 2). For each pair of markers, the estimated probability of nonreduction was based on the number of 47,XXY cases for which (*a*) both markers were nonreduced (N→N), (*b*) both were reduced (R→R), or (*c*) one was nonreduced and the other was reduced (N→R). The first two categories are consistent with no recombination, while the third indicates that recombination has occurred. From these data, recombination fractions (θ_{XXY}) and lod scores (Z_{XXY}) were derived from the estimated probability of nonreduction by assuming, at most, one chiasma within any interval (complete interference). Lod scores were based on the likelihood-ratio $\log_{10}[L(\hat{y})/L(y=2/3)]$ where $y=2/3$ indicates no linkage.

Chromosomally normal individuals.—Information on recombination in the pseudoautosomal region in male meiosis resulting in normal 46,XX and 46,XY offspring was obtained from previous studies by our and other laboratories (Goodfellow et al., 1986; Rouyer et al. 1986; Page et al. 1987). Recombination fractions (θ_{NOR}) and lod scores (Z_{NOR}) were obtained from the

Table 1

Summary of DNA Studies at Five Loci for Each 47,XXY Family

Case	CEN–	MIC2–	DXYS17–	DXYS15–	DXYS28–	DXYS14/20
1	N	–	N	–	–	R
2	N	N	N	N	–	N
3	N	N	N	N	N	N
4	N	–	N	R	R	R
5	N	–	–	R	–	R
6	N	N	N	N	–	N
7	N	N	N	N	–	N
8	N	–	–	–	–	N
9	N	–	N	N	–	N
10	N	–	N	–	N	N
11	N	N	N	N	–	N
12	N	–	N	N	–	N
13	N	–	N	–	–	–
14	N	N	N	N	N	N
15	N	N	NT	–	N	N
16	N	PI	NT	N	N	N
17	N	PI	NT	–	–	N
18	N	PI	NT	N	–	–
19	N	PI	NT	N	N	N
20	N	–	NT	–	–	N
21	N	N	NT	N	–	N
22	N	N	NT	R	–	R
23	N	PI	NT	–	–	N
24	N	–	NT	–	N	N
25	N	–	NT	N	–	N
26	N	N	NT	N	–	N
27	N	–	NT	–	N	N
28	N	–	NT	N	–	N
29	N	–	NT	–	–	N
30	N	–	NT	–	–	N
31	N	–	NT	–	–	N
32	N	N	NT	–	N	N
33	N	–	NT	N	N	N
34	N	PI	NT	N	N	N
35	N	–	NT	–	N	N
36	N	–	NT	N	–	N
37	N	PI	NT	R	R	R
38	N	PI	NT	N	–	N
39	N	–	NT	–	–	N
40	N	–	NT	N	–	N
41	N	–	NT	–	–	R

NOTE.—For each locus for which the father was heterozygous, the trisomic individual was scored.

number of recombinants detected among the total number of meiosis.

Comparison of genetic maps of the pseudoautosomal region derived from 47,XXY cases and from normal offspring.— The order of genetic markers in the pseudoautosomal region has been well established and, from the most centromeric to the most teleomeric, is given as MIC2–DXYS15–DXYS17–DXYS28–DXYS14/DXYS20. Based on this order, the interval distances between adjacent markers were estimated from the recombination fractions and lod scores for all pairwise combination of markers obtained by using the computer program MAP (Morton and Andrews 1989). By this procedure, the total lod score over all pairs of markers was maximized to give the best estimates of interval distances. Map intervals were estimated by assuming various levels of interference, to ensure that the results did not depend on assumptions of interference.

Table 2

Summary of recombination fractions and associated lod scores for All Pairwise Combinations of Genetic Markers

Marker		Evaluation of Heterozygosity (proximal locus→distal locus) (*n*)			47,XXY			Normal	
Proximal	Distal	N→N	R→R	N→R	*Y*	θ	*Z*	θ	*Z*
sex[a]/cen	MIC2	11	0	0	0	0	2.57	.02	11.70[b]
sex[a]/cen	DXYS17	12	0	0	0	0	2.11	.16	9.75[b,c]
sex[a]/cen	DXYS15	20	0	4	.33	.17	.73	.32	1.07[b,c]
sex[a]/cen	DXYS28	12	0	2	.29	.14	.57	.38	2.26[d]
sex[a]/cen	DXYS14/20	33	0	6	.31	.15	1.40	.41	1.90[b,c,d]
MIC2	DXYS17	6	0	0	0	0	1.06	.18	3.35[b]
MIC2	DXYS15	8	0	1	.20	.10	.66	.33	6.07[b]
MIC2	DXYS28	4	0	0	0	0	.72	. . .	. . .
MIC2	DXYS14/20	10	0	1	.16	.08	.99	.36	.54[b]
DXYS17	DXYS15	8	0	1	.22	.11	.52	.27	1.03[b,c]
DXYS17	DXYS28	3	0	1	.50	.25	.03	. . .	. . .
DXYS17	DXYS14/20	9	0	2	.36	.18	.27	.32	2.31[b,c]
DXYS15	DXYS28	6	2	0	0	0	2.01	. . .	. . .
DXYS15	DXYS14/20	19	4	0	0	0	5.25	.12	6.00[b,c]
DXYS28	DXYS14/20	12	2	0	0	0	3.07	.11	23.21[d]

Note.—For the 47,XXY cases, these data were derived from the maximum likelihood estimate of the probability of nonreduction (y) (see text). For the normal 46,XY and 46,XX cases, these data were based on the number of recombinations divided by the total number of meiotic events.

[a] In studies of normal meioses, sex was defined as the most centromeric marker. In the present study, the most proximal marker is designated as "sex/cen," since the 47,XXY individual received both his father's X and Y centromeres.

[b] Source of linkage information: Goodfellow et al. (1986).

[c] Source of linkage information: Rouyer et al. (1986).

[d] Source of linkage information: Page et al. (1987).

To determine whether there were a difference between the genetic maps derived from normal and trisomy-generating meiosis, the likelihood of the maps estimated with a fixed 47,XXY:normal map-distance ratio (k) of 1($L_k = 1$) was compared with that in which the ratio was estimated ($L_{\hat{k}}$). Significance was tested as $\chi^2_1 = 2\ln L_{\hat{k}} - 2\ln L_{k=1}$. When a significant result was obtained, a second test was performed to determine whether this map-distance ratio was constant or varied between map intervals. To test this hypothesis, the likelihood obtained by estimating each interval separately for each genetic map was compared with the likelihood of the two maps estimated using a constant ratio, k, as described above. In this case, the df's equal $2n - (n+1)$, where n is the number of intervals being estimated.

Results

The 41 paternally derived 47,XXY individuals were scored as being nonreduced (N) or reduced (R) at each of the pseudoautosomal loci. These results are summarized in table 1, and an example is provided in figure 1. All 41 individuals were scored as N at the centromere (sex/cen), since they had inherited both their father's X and Y chromosomes. Six of the 41 cases (individuals 1, 4, 5, 22, 37, and 41) were reduced at one or more of the pseudoautosomal loci, consistent with crossing-over in the region. However, in the remaining 35 cases heterozygosity was maintained at all informative loci, and in 33 cases this included the telomeric DXYS14/DXYS20 locus. Assuming a meiosis I error and complete interference, we should detect a single exchange in the pseudoautosomal region in 50%, or 19.5, of the 39 cases informative for DXYS14/DXYS20. Thus, our observation of nonreduction in 33 of 39 cases represents a highly significant difference from expectation ($\chi^2_1 = 18.7$; $P < .001$).

To further test these observations, we compared the genetic map of the pseudoautosomal region that was based on meiosis involved in XY chromosome nondisjunction with that which was based on normal meiotic

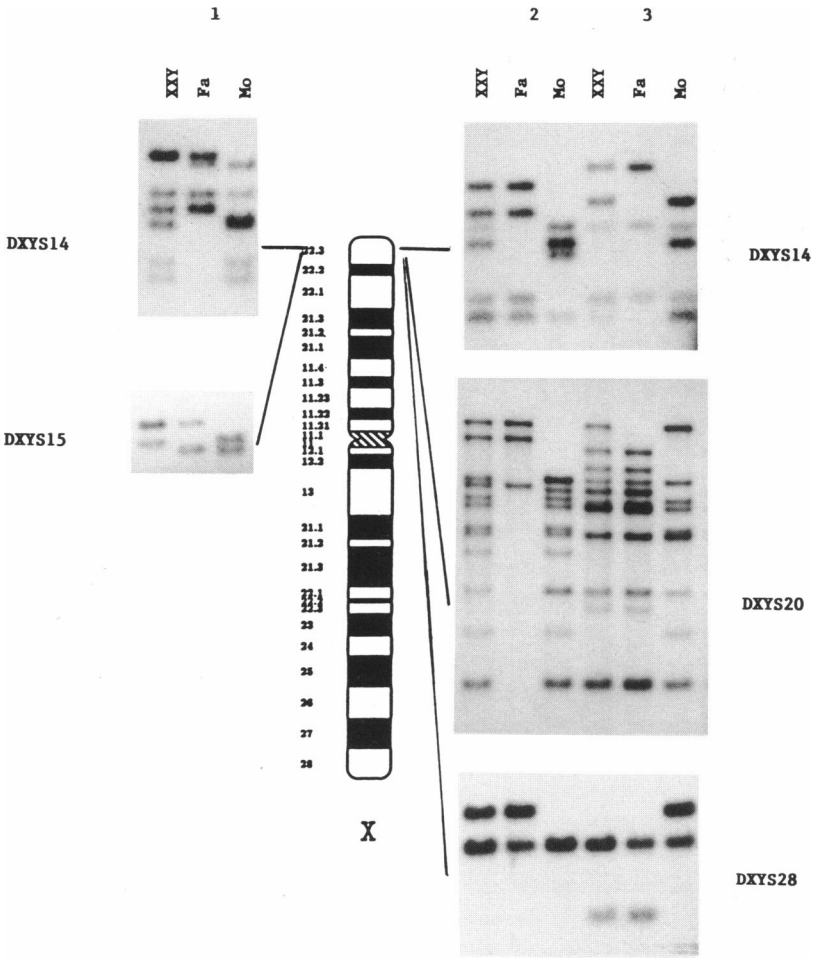

Figure 1 Analysis of recombination in pseudoautosomal region in three paternally derived 47,XXY individuals. Pseudoautosomal loci are ordered, proximal to distal, on the basis of results of previous linkage studies. In the 47,XXY individual in family 1, paternal heterozygosity has been reduced to homozygosity at DXYS15, since the affected individual has received a single maternal allele and, by dosage, two copies of one of the father's alleles. Similarly, at DXYS14 (a locus recognizing a complex polymorphism with multiple restriction fragments) paternal heterozygosity has been reduced to homozygosity, since the 47,XXY has received some but not all of the paternal fragments. Taken together, these observations demonstrate the occurrence of either a single or an odd number of exchanges in the pseudoautosomal region proximal to DXYS15 in the trisomy-producing meiosis. In the 47,XXY individuals of families 2 and 3, paternal heterozygosity is maintained at all three loci. That is, at DXYS28 the affected individuals have received a single copy of each of the paternal alleles, in addition to a single maternal allele; at DXYS14 and DXYS20, loci recognizing complex polymorphisms, the 47,XXY individuals have inherited all possible paternal fragments. Taken together, these observations are consistent with no crossing-over between the X and Y chromosomes in the paternal meiosis leading to the two trisomies.

events. The estimated recombination fractions and associated lod scores are summarized in table 2 for both sets of data. Using these data and assuming complete interference, we identified a highly significant difference in the lengths of the two genetic maps. The trisomic map was less than one-third the length of the normal map ($\chi^2_1 = 17.3$; $P < .001$), and this reduction in recombination was clearly independent of assumptions of interference (tables 3 and 4). Subsequently, we compared the maps to determine whether the reduction in recombination was restricted to specific regions, but we found no evidence for such an effect (table 3).

Discussion

Our results provide strong evidence that failure to recombine is an important correlate of XY chromo-

Table 3

Results of Comparison of Genetic Maps when k Is Assumed to be Constant and When, for Each Map Interval, k Is Assumed to Vary (k_i)

Interference[a]	k	χ^2_1 (H_0:$k = 1$; H_1:$k = \hat{k}$)	$\chi^2_{\hat{k}}$ (H_0:$k = \hat{k}$; H_1:$k = k_i$)
Complete (p = 0)	.29	17.3*	2.4
Intermediate (p = .35)	.24	18.5*	2.4
Null (p = 1)	.18	19.2*	1.9

[a] Interference parameter used in Rao function (Rao et al. 1977).
* $P < .005$.

some nondisjunction. That is, we observed pseudoautosomal region recombination in only six of 39 paternally derived 47,XXYs informative at the most telomeric loci, while in normal male meiosis a single obligatory exchange apparently occurs between the X and Y chromosomes (Goodfellow et al. 1986; Rouyer et al. 1986; Page et al. 1987). Assuming that our assay will detect recombination in one-half of cases in which a single crossover actually occurred, we can estimate the proportion of cases in which pseudoautosomal region recombination occurred by doubling the number of known recombinants. Thus, in our series we estimate 2 × 6 = 12 (31%) of 39 cases to be recombinants, compared with an expected value of 100%.

In making this estimate, we have assumed that multiple exchanges do not occur within the pseudoautosomal region; indeed, we found no evidence for double or triple crossovers in our study group. It is, of course, formally possible that such events occurred and went undetected in some proportion of our cases. For example, our assay will not detect two-strand double crossovers if both recombinant or both nonrecombinant strands segregate together at meiosis II; nor will it detect four-strand double crossovers if complementary recombinant strands segregate together at meiosis II. However, these cases must be rare, since they require nonrandom events at both meiosis I and meiosis II. We have also discounted as unlikely the possibility that a single exchange occurs between the X and Y chromosomes but that the chiasma is not resolved prior to anaphase I and that, at anaphase II, the recombinant X and Y products segregate together. This mechanism also would lead to an apparent reduction of recombination, but, like the models for multiple exchanges, it requires that nonrandom events occur at both meiosis I and meiosis II. Thus, it seems more reasonable to conclude that most paternally derived 47,XXYs involve meiosis with nonrecombinant X and Y chromosomes.

If this interpretation is correct, it implies the occurrence of one of two abnormal meiotic events—namely, (1) meiosis in which the X and Y fail to pair and consequently to recombine, or (2) meiosis in which pairing occurs but pseudoautosomal region recombination does not. In either case the likelihood of nondisjunction should be increased.

Table 4

Comparison of Genetic Maps When k_i Is Assumed

Interference[a]	Pseudoautosomal Genetic Map (cM)					Total Length (cM)
	SEX/CEN	MIC2	DXYS17	DXYS15	DXYS28	DXYS14/20	
Complete (p = 1):							
47,XXY	0	0	13.0	0	0		13.0
Normal	1.9	12.8	19.2	.9	9.3		44.2
Intermediate (p = .35):							
47,XXY	0	0	13.0	0	0		13.0
Normal	2.0	14.7	23.5	1.4	10.3		52.0
Null (p = 1):							
47,XXY	0	0	15.1	0	0		15.1
Normal	2.1	19.1	42.2	3.1	11.7		78.2

[a] Interference parameter used in Rao function (Rao et al. 1977).

Our assay cannot distinguish between these two processes, and there is little direct evidence from mammals that bears on this question. In both mice and humans, chromosome abnormalities which impair XY pairing are associated with spermatogenic breakdown and male sterility (De Boer and de Jong 1989; Speed 1989). This suggests that the consequence of XY pairing failure is germ-cell death rather than increased nondisjunction. However, this interpretation is based on studies of pairing in individuals in which most germ cells are abnormal. We do not know what effect, if any, the chance occurrence of XY pairing failure has on gametic survival in an otherwise normal testis. Therefore, our observations still may be attributable to abnormalities in formation or maintenance of pairing, with the recombination deficiency simply being a by-product of this abnormal event.

Our interpretations must be applied cautiously to other human trisomies, since, whereas our observations pertain to paternal nondisjunction, most nondisjunction is maternal in origin. There is evidence for an association between reduced recombination and maternal trisomy 21 (Warren et al. 1987; Sherman et al. 1990), but additional data are needed to understand the importance of recombinational errors to human trisomy in general. Nevertheless, our data clearly demonstrate an association between failure to recombine and most cases of XY chromosome nondisjunction. Therefore, at least for this abnormality, it is unnecessary to invoke nondisjunctional processes which act at metaphase/anaphase I to disrupt chromosome segregation (e.g., see Backer and Allen 1987). Future studies of paternal sex-chromosome nondisjunction can instead focus on the reasons why the X and Y chromosomes fail to recombine.

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