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Reduced recombination and paternal age effect in Klinefelter syndrome

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Summary. The parental origin of the additional sex chromosome was studied in 47 cases with an XXY sex chromosome consitution. In 23 cases (49%), the error occurred during the first paternal meiotic division. Maternal origin of the additional chromosome was found in the remaining 24 cases (51%). Centromeric homo- versus heterozygosity could be determined in 18 out of the 24 maternally derived cases. According to the centromeric status and recombination rate, the nondisjunction was attributable in 9 cases (50%) to an error at the first maternal meiotic division, in 7 cases (39%) to an error at the second maternal meiotic division and in 2 cases (11%) to a nullo-chiasmata nondisjunction at meiosis II or to postzygotic mitotic error. No recombination, and in particular none in the pericentromeric region, was found in any of the 9 cases due to nondisjunction at the first maternal meiotic division. Significantly increased paternal age was found in the paternally derived cases. Maternal age was significantly higher in the maternally derived cases due to a meiotic I error compared with those due to a meiotic II error. There were no significant clinical differences between patients with respect to the origin of the additional X chromosome.

Introduction

About 1 out of 600 males has an additional X chromosome in his karyotype (47,XXY) and hence has the Klinefelter syndrome (Nielsen and Wohler 1991). A minority of 47,XXY patients are clinically and intellectually much more adversely affected than the average Klinefelter male, and several authors have argued that the more severely handicapped cases could be explained by a different origin of the extra sex chromosome. Zang (1984) hypothesized that two copies of the same X chromosome as a result of nondisjunction at the second meiotic division of the mother or at one of the first zygotic divisions might induce a negative dosage effect of some harmful recessive genes on the X chromosome. Jacobs et al. (1989) postulated an "imprinting effect" on the phenotype of the patients depending on the parental origin of the additional chromosome.

Using restriction fragment length polymorphism (RFLP) analysis, Jacobs et al. (1988, 1989) showed in a series of 65 patients that the extra sex chromosome in 47,XXY cases derived in equal proportions from the mothers and from the fathers. In a gross phenotypic analysis, they could not find a distinct difference in phenotype between paternally and maternally derived cases.

Reduced recombination and nondisjunction have been found to be associated with trisomy 21 (Warren et al. 1987; Sherman et al. 1991). Preliminary data from sex chromosome trisomies (XXX and XXY) of maternal origin also suggested reduced recombination in the X tetrads, giving rise to nondisjunction in the first meiotic division, but an excess of recombination in the pericentromeric region (Morton et al. 1990). A more recent report on XY chromosome nondisjunction showed reduced recombination in the pseudoautosomal region (Hassold et al. 1991).

We report here a molecular study of a series of patients with 47,XXY karyotypes in order (a) to determine the parental origin of the extra sex chromosome, the meiotic stage of nondisjunction, and the recombination rate, and (b) to assess whether a correlation exists between origin of the aneuploidy and phenotype of the patients and/or parental ages at conception.

Materials and methods

The probands studied included 45 liveborn patients at different ages who were referred to the Institute of Medical Genetics of the University of Zürich for cytogenetic examination and two prenatally determined fetuses with a 47,XXY karyotype (nos. 23 and 57).

Chromosome examinations were performed from peripheral blood in the liveborns and from chorionic villi in the fetuses.

DNA was extracted from peripheral blood of subjects and parents and from muscle of the fetuses. In five cases (nos. 15, 22, 24, 38, 39) no blood from the father was available. In one of these (38), however, the paternal haplotype was inferred by examining a sister of the proband. Additionally, in one case (19) both parents were deceased, but their haplotypes were inferred by examining two sisters of the proband.

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The parental origin of the additional sex chromosome was determined using two highly polymorphic probes: M27β, which maps in the short arm near the centromere (locus DXS255; Fraser et al. 1989) and F814, which is located in the distal part of the long arm (loci DXS52 and F8; Heilig et al. 1988). The degree of heterozygosity in white Caucasian females has been calculated to be more than 85% for each probe.

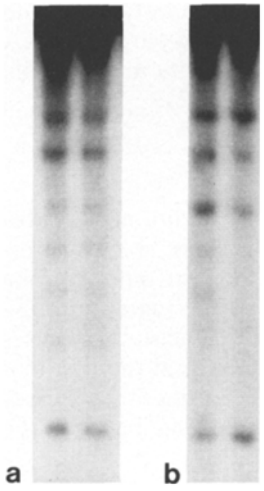

Fig. 1a, b. Autoradiographs of Southern blots showing *Xba*I restriction fragment length polymorphisms (RFLPs) on the X chromosome detected by the centromeric probe pBAMX7 in two maternally derived cases. **a** Case 4; the proband (on the right) has inherited all the maternal bands, which indicates an error at the first meiotic division. **b** Case 6; the proband (on the right) shows some but not all of the maternal bands; this represents a reduction of maternal heterozygosity to homozygosity in the proband and therefore an error in the second meiotic division

Paternity was tested in all cases with both parents available using the minisatellite probe 33.15 (Jeffreys et al. 1985).

The cases in whom the additional X chromosome was maternally derived were studied with the centromeric probe pBAMX7 (DXZ1; Willard et al. 1986). According to the α satellite restriction pattern with *Xba*I, they were classified into: M-I cases (considered to be due to nondisjunction at maternal meiosis I) when the proband showed the same polymorphic bands as the mother; and M-II cases (considered to be due to nondisjunction at maternal meiosis II) when some but not all of the maternal bands were present in the proband, i.e. when reduction of the maternal heterozygosity at some loci to homozygosity in the proband had occurred (Fig. 1).

Recombination was tested in the paternally derived cases using a pseudoautosomal probe, 602 (DXYS17; Rouyer et al. 1986). A reduction of the paternal heterozygosity to homozygosity in the proband implies recombination between the X and Y chromosomes.

In the maternally derived cases, the recombination rate was investigated using a battery of probes detecting RFLPs on the X chromosome: dic56 (DXS143), L782 (DXS85), 602 (DXYS17), pSE3.21 (DXS16), pPA4B (DXS207), pXG-16 (DXS92), XJ1.1 (DXS206), L1.28 (DXS7), p58.1 (DXS14), p8 (DXS1), psptPGK (PGK1), pDP34 (DXYS1), p19.2 (DXS3), p212.9 (DXS178), p22.33 (DXS11), p43.15 (DXS42), 6A1 (DXS10), c11 (DXS144E), F9-P1 (F9), 4D-8 (DXS98), VK21A (DXS296), U6.2 (DXS304), 1A1 (DXS374) and F814 (F8 and DXS52) (for references see Mandel et al. 1989). Reduction of maternal heterozygosity to homozygosity in the proband at some loci and nonreduction at some others implies recombination between the two maternal X chromosomes. Recombination in the M-II cases also excludes a postzygotic nondisjunction as mechanism of formation. Pericentromeric recombination was investigated by combining the results obtained with the centromeric probe pBAMX7 (DXZ1) with those of the pericentromeric probe M27β (DXS255).

In order to determine whether the parental origin of the additional sex chromosome affects the phenotype, we used a questionnaire to obtain information about clinical features of the patients. This questionnaire was filled out by the patient's physician and

Table 1. Analysis of the clinical data of 47,XXY liveborns with respect to the origin of the single X. P, Present; NP, not present

Clinical features	Counts[a]	Origin paternal		Origin maternal	
		P	NP	P (MI/MII)	NP (MI/MII)
Eunuchoid habitus	27	5	6	9 (3/5)	7 (3/3)
Leg varicosis	25	2	8	4 (2/2)	11 (5/6)
Scoliosis	26	4	7	3 (2/1)	12 (6/6)
Muscular hypotonia	24	1	9	5 (2/2)	9 (3/5)
Epilepsy	26	1	10	1 (0/1)	14 (5/7)
EEG abnormalities	11	2	2	4 (3/1)	3 (1/2)
Immunologic disorder	18	1	7	0 (0/0)	10 (4/5)
Diabetes	22	1	8	1 (0/1)	12 (5/5)
Small penis	24	1	7	6 (4/2)	10 (1/7)
Hypospadias	24	1	8	0 (0/0)	15 (5/8)
Small testes	30	12	2	16 (5/9)	0 (0/0)
Cryptorchidism	25	1	8	4 (2/1)	12 (4/7)
Gynaecomastia	24	4	5	9 (4/4)	6 (1/4)
Delayed speech development	32	12	4	8 (4/3)	8 (3/4)
Delayed motor development	31	11	5	6 (3/2)	9 (4/4)
School problems	30	12	2	14 (4/8)	2 (2/0)
Psychological problems	24	4	6	8 (4/3)	6 (2/4)
Psychiatric problems	24	2	9	2 (1/1)	11 (4/6)
Less successful[b]	24	8	3	11 (3/7)	2 (2/0)

[a] Number of questionnaires received in which this question was answered
[b] Less successful at school and/or work than siblings

included questions about length and weight at birth, physical abnormalities, mental development, educational level and present profession. The data were compared with those of brothers and sisters. Table 1 presents a list of clinical features whose presence or absence in the individual patient was noted.

Clinical data and parental ages were analysed with respect to the parental origin of the additional sex chromosome.

Results

Cytogenetic examinations

The karyotype was considered to be non-mosaic 47,XXY in 46 cases based on an examination of 10 to 20 metaphase spreads per case. One case of double aneuploidy 48,XXY,+21 was also included in the examination. This case has been reported in detail previously (Lorda-Sanchez et al. 1991).

Parental origin

The parental origin of the additional sex chromosome could be determined in all 47 families using the probes M27β and/or F814 (Table 2). In 23 of the 47 cases (49%) the additional sex chromosome was paternal in origin. A maternally derived additional X chromosome was found in 24 cases (51%).

In three (22, 24, 27) out of the five cases for whom paternal DNA was not available, investigations showed that alleles not present in the mother were found in the probands; therefore, the additional X was of paternal origin. In the remaining two cases, all markers were consistent with maternal origin of the two X chromosomes of the proband. The analysis of the DNA of the proband and of two sisters in the case for whom no parental DNA was available (19) was also consistent with a maternally derived additional X chromosome (Fig. 2).

Meiotic stage of nondisjunction

Among the 24 patients in whom the additional X chromosome was maternally derived, we were able to determine the centromeric status using the centromeric probe pBAMX7 in 18 cases: in 9 cases all the maternal polymorphic bands were present in the proband; these cases therefore were compatible with an error at the first maternal meiosis (M-I cases) (Fig. 1a); in the other 9 cases the absence of some maternal polymorphic bands in the

Table 2. Status of informative markers (loci ordered from Xpter to Xqter) for maternally derived XXY cases. R, Reduction to homozygosity; N, non-reduction to homozygosity; a blank is either an untyped or an uninformative locus

Locus	Probe	Location	Case number																							
			3	4	5	6	7	8	9	10	11	15	19	23	28	29	30	33	35	38	39	41	44	48	51	52
			Meiotic origin																							
			I	I		II	I	II	II[a]	II[a]	I				I	I	I	II		II	I	II	II	I	I	
DXS143	dic56	p22.2			R										N				R							
DXS85	L782	p22.2–22.3							R																N	
DXYS17	602	p22.32		N						R			N					N					N			N
DXS207	PA4B	p.22.2	N					R		R						N		N					R		N	
DXS9	RC8	p22.2							R																	
DXS92	pXG-16	p22.1	N							R																
DXS206	XJ1.1	p21.1								R								N		N		N				
DXS7	L1.28	p11.3	R						R									N		N						
DXS255	M27B	p11.22	R	N	N	N	N	R	R	R	N	N	R	N	N	N	N	R	N	R	N	R	N	N	N	R
DXS14	p58.1	p11.21						R																		
DXZ1	pBamx7	Cen	R	N		R	N	R	R	R	N				N	N	N	R		R	N	R	R	N	N	
DXS1	p8	q11–12.2						R	R																	
PGK1	sptPGK	q13																				N				
DXYS1	pDP34	q21.31	R					R										R		R						N
DXS178	p212.9	q22	R																			N				
DXS144e	c11	q26		N														R				R				
F9	F9-P1	q26.3–27.1	N						R	R										N		R				
DXS98	4D-8	q27.2						N												N		R				
DXS374	1A1	q28								R								R								
DXS296	VK21A	q27.2–28				N		R	R	N	N										R	N				
DXS304	U6.2	q28	N					N	R		N	N		N			N			N						
F8c	F814	q28															N		R							
DXS52	F814	q28		N	N	N	N		R	R	N	N	N	N		N	N	R	N	N	N	N		N	N	R

[a] The lack of any informative loci showing non-reduction indicates that these cases may be due to a mitotic duplication event rather than a meiotic II error

proband was indicative of a nondisjunction at the second stage of the maternal meiosis (M-II cases) (Fig. 1b).

All paternally derived cases are necessarily due to first meiotic nondisjunction.

Recombination

Out of 17 cases with an additional paternally derived sex chromosome who were tested for recombination using the probe 602 (DXYS17), 10 were informative. No reduction of paternal heterozygosity to homozygosity in the proband was found in any of them. Thus, no case showed evidence of recombination in the pseudoautosomal region between the paternal X and Y chromosomes, although the recombination fraction in normal individuals is only 0.20 and reduction from heterozygosity to homozygosity would only be expected to occur in approximately two out of ten cases.

Using a battery of probes on the X chromosome, none of the nine M-I cases showed reduction of any maternal heterozygous locus. Thus, no recombination, even in the pericentromeric region, was observed. In a proportion of these cases, however, the number of informative loci was too low definitely to exclude recombination (Table 2).

Among the nine M-II cases, non-reduction for at least one locus was detected in seven cases (Table 2). This observation implies that at least one recombination occurred prior to meiotic nondisjunction and excludes a postzygotic error as the mechanism of formation. Two cases (nos. 9 and 10) showed reduction in all informative markers (Table 2). The high number of informative loci (nine in each case) as well as their distribution along both arms of the X chromosome allows an almost definitive exclusion of recombination in these two cases. Thus, they might both result from either a maternal meiotic II error following a nullo-chiasmata prophase or a postzygotic mitotic error.

Two out of the nine informative M-II cases showed non-reduction of the maternal heterozygosity at the DXS255 locus, indicating that a recombination had occurred between the DXZ1 and DXS255 loci. Pericentromeric recombination was therefore found in two out of the nine M-II cases (22%), but in none of the nine cases due to first meiotic nondisjunction (Table 3).

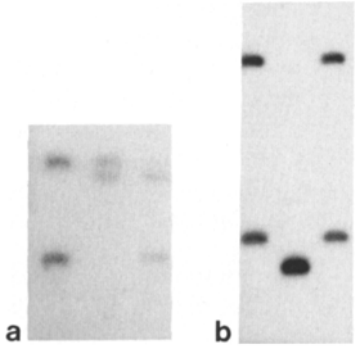

Fig. 2a, b. Southern blot analysis of patient no. 19 *(lane 2)* and two sisters *(lanes 1, 3)* to determine the parental origin of the X chromosomes using two high polymorphic probes on the X. **a** F814 (DXS52); both sisters show a common allele, which, assuming a common father, corresponds to the paternal X chromosome and two different alleles corresponding to the maternal ones. The proband has inherited two alleles, which correlate with the maternal alleles of both sisters, respectively. Both X chromosomes of the patient are therefore maternally derived. **b** M27β (DXS255); the proband shows a double dosage of one allele, which is different from both alleles present in the sisters. Since both sisters have to possess the paternal X allele and one of the two maternal alleles, the allele of the proband should correspond to the other maternal X chromosome. A reduction of the maternal heterozygosity to homozygosity in the proband at this locus has to have occurred

Table 3. Recombination between the centromere and DXS255 and DXS52

			Frequency expected[a]	Frequency observed		Significance[b]
				Present data	Morton et al. (1990)	
	DXS255	cen				
MI	N	N	0.9	9	14	
Errors	R	N	0.1	0	9	$P < 0.05$
MII	R	R	0.8	7	8	
Errors	N	N	0.2	2	3	NS
	cen	DXS52				
MI	N	N	0.67	8	13	
Errors	N	R	0.33	0	15	$P < 0.01$
MII	R	R	0.33	3	2	
Errors	R	N	0.67	3	5	NS

[a] Expected frequencies of recombinant or non-recombinant classes within the meiotic I and meiotic II origin groups are calculated assuming a distance of 10.6 cM for DXS255 to the centromere and 105.9 cM from the centromere to DXS55 (Morton et al. 1990), and following the procedure of Shahar and Morton (1986)

[b] Significance values are for the present data compared with Morton et al. (1990) using Fisher's exact test

Table 4. Mean parental ages at birth. * $P = 0.05$; ** $P = 0.02$ (Student's t-test)

Origin of additional sex chromosome	Paternal age (cases)	Maternal age (cases)
Paternal	35.7* ± 6.5 (20)	29.6 ± 5.5 (21)
Maternal	31.6* ± 7.6 (22)	29.3 ± 8.1 (24)
M-I	30.1 ± 5.7 (8)	31** ± 7.3 (9)
M-II	27.9 ± 5.6 (9)	24** ± 3.6 (9)
Total	33.5 ± 7.3 (42)	29.5 ± 7.0 (45)

Parental ages

The parental ages at birth of the present cases are summarized in Table 4. The mean paternal age is statistically significantly higher ($P = 0.05$, Student's t-test) in the paternally derived as compared with the maternally derived cases. No difference in the mean maternal age was found between the maternally and the paternally derived cases.

There was, however, a significant difference ($P = 0.02$, Student's t-test) in mean maternal ages at birth of the probands between the maternally derived cases due to a nondisjunction during the first maternal meiotic division (M-I cases) and those due to a nondisjunction at the second maternal meiotic division (M-II cases).

Clinical analysis

We received clinical information on 32 of the 45 liveborns investigated, although not all questions were answered in all questionnaires. The results are presented in part in Table 1. No obvious difference could be found for any clinical feature between liveborns with a maternally versus paternally derived additional X chromosome.

A comparison between the maternally derived M-I and M-II cases and paternally originating cases showed minor differences in prevalence of some clinical features in one or the other group (for example small penis or gynaecomastia were present more frequently in M-I patients), but the small number of subjects does not allow a statistical analysis.

The two patients (nos. 9 and 10) showing reduction at all informative loci are only mildly affected, and the diagnosis of Klinefelter syndrome was made as late as the ages of 35 and 52 years respectively.

Discussion

The results concerning the parental origin of the 47 cases investigated in this study confirm those obtained by the only previous study of parental origin of the additional sex chromosome in 47,XXY cases using RFLPs (Jakobs et al. 1988, 1989): approximately 50% of 47,XXY cases are the result of a nondisjunction at the first paternal meiotic division, while an error in a maternal meiotic division is responsible for the remaining 50%. This high paternal contribution to the additional chromosomes contrasts with the proportion of paternally derived 47,XXX cases (May et al. 1990) and autosomal trisomies (Hassold and Takaesu 1989). This difference might be due to more frequent pairing and disjunction difficulties between the X and Y chromosomes due to their incomplete homology. A study of sperm chromosomes of normal males has found a significantly increased frequency of sex chromosomal hyperhaploidy over autosomal hyper- and hypohaploidy (Martin et al. 1991). However, no difference was found in that study between hyperhaploidy of the Y versus the X chromosome.

In patients with a paternally derived additional sex chromosome, no recombination was found in any of the ten patients informative for both the centromeric probe and DXYS17 (20% recombination is observed in normal meiosis). This is consistent with a recent report of an association between reduced recombination in the pseudoautosomal region and XY chromosome nondisjunction (Hassold et al. 1991).

We also failed to observe recombination in any of the nine maternally derived cases considered to be the result of an M-I nondisjunction. These results contrast sharply with the 72% of recombined M-I cases found in the previous study by Jacobs et al. (1989). A difference in the number of informative markers between studies cannot completely explain this discrepancy. Summarizing the data of 65 XXY or XXX cases with two maternally derived X chromosomes, including those of the study of Jacobs et al. (1989), Morton et al. (1990) found reduced recombination in the X tetrads giving rise to nondisjunction in the first meiotic division, but an excess of recombination in the pericentromeric region: DXS255 was reduced in 9 of 23 M-I cases informative with DXZ1 (Table 3). In 6 of these 9 cases, reduction was found with all informative loci except for DXZ1. These results differ from ours at a statistically significant level ($P < 0.05$). We also see significantly less recombination between the centromere and the distal Xq locus DXS52 than reported in Morton et al. (1990) ($P < 0.01$) (Table 3). Both data sets agree with each other and with the normal rate of recombination with regard to chromosomes determined to be M-II errors.

Using conventional gel techniques, the interpretation of results using the α-satellite probe has proved difficult (Mahtani and Willard 1990): many visible bands are nonpolymorphic, and the frequency of resolvable polymorphic bands depends on the enzyme and gel running time. If the number of visible polymorphic bands is small, as is often the case, then the probability is relatively high that a nonreduction is observed, when reduced bands are present but partially or totally hidden. Thus, M-II cases could mistakenly be interpreted as M-I cases, but not vice versa. While Jacobs et al. (1989) observed only 5 reduced (M-II) cases out of 23 cases informative for the centromeric probe, we found 9 M-II cases out of 18 informative ones. Errors in the assignment of the meiotic stage of nondisjunction (M-II mistaken for M-I) can explain the difference in M-I and M-II rates in both studies, as well as the differences in pericentromeric recombination in M-I cases. Further investigations using

the centromeric α-satellite probe with appropriate technique (pulse-field gel analysis; Mahtani and Willard 1990) are required to determine the potential for error in assignment of centromeric status, and thus how recombination, particularly in the pericentromeric region, may contribute to nondisjunction of the sex chromosomes.

The low rate of cases with additional chromosomes of paternal origin in the majority of the trisomies makes an investigation of a potential paternal age effect difficult. The high proportion of paternally derived 47,XXY cases allows such a study. Jacobs et al. (1989) found no paternal age effect, but increased mean maternal age in the 47,XXY cases with a maternally derived extra X chromosome; the latter appeared to be confined to those cases resulting from a maternal meiotic I nondisjunction. In the present study, however, a significant increase in mean paternal age for paternally derived versus maternally derived cases, but no difference in mean maternal age between cases of both origins, were found. Nevertheless, the mean maternal age in cases assumed to be due to maternal meiosis I nondisjunction is significantly increased compared with those cases assumed to be due to maternal meiosis II nondisjunction. These data support the idea that the overall increased mean maternal age in 47,XXY cases is confined to instances due to a maternal meiosis I nondisjunction.

The degree of mental deficiency, as well as other phenotypic traits, is quite variable in patients with the Klinefelter syndrome. A minority are of normal intelligence, and again a minority display distinct mental impairment. Zang (1984) explained these differences by hypothesizing homozygosity for harmful X chromosomal recessive genes in the more severely retarded Klinefelter patients, in whom twice the same X chromosome would be present as a result of nondisjunction during the second meiotic division of the mother or during one of the first postzygotic divisions. The negative dosage effect of these genes could be exerted either before onset of X-inactivation or later, due to incomplete inactivation. An imprinting effect, which implies differences in the phenotype depending on the parental origin of the additional chromosome, was also postulated as a possible explanation of the phenotypic variability of Klinefelter patients. However, analysis of clinical features in a series of patients whose extra chromosomes were traced back to one of the parents failed to confirm such as assumption (Jacobs et al. 1988). In the present study, no differences were found in the severity of the clinical findings (physical abnormalities as well as mental deficiency) between cases of different parental origin (see Table 1). In contrast to Zang's hypothesis, both cases in this study in whom reduction of the maternal heterozygosity to homozygosity in the patient was found at all informative loci are even less severely affected than the majority of cases. It is possible that mosaicism with a normal cell line exists in other tissues as these cases are compatible with a mitotic origin of the extra chromosome. No mosaicism was found in lymphocytes based on an examination of 11 (case 9) and 23 (case 10) metaphases.

The present data, therefore, do not support either an imprinting effect or a homozygosity effect to explain the phenotypic variability in patients with the Klinefelter syndrome. Perhaps differences in X-inactivation or possible autosomal controlling genes may influence the phenotypic variability. It is also possible that mosaicism exists in some tissues due to loss of one of the extra chromosomes.

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