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Molecular studies of parental origin and mosaicism in 45,X conceptuses

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Summary. The present report summarizes molecular studies of parental origin and sex chromosome mosaicism in forty-one 45,X conceptuses, consisting of 29 spontaneous abortions and 12 liveborn individuals with Turner syndrome. Our studies indicate that most 45,X conceptuses have a single, maternally derived X chromosome, regardless of whether the conceptus is liveborn or spontaneously aborted. In studies of mosaicism, our identification of X- and Y-chromosome mosaics among 45,X spontaneous abortions indicates that mosaicism does not ensure survival to term of 45,X fetuses. However, the incidence of sex chromosmome mosaicism is substantially higher in liveborn than in aborted 45,X conceptuses, indicating that the presence of a second cell line increases the likelihood of survival to term.

Introduction

Sex chromosome monosomy is the most commonly identified chromosome abnormality in humans, occurring in approximately 1%–2% of all clinically recognized pregnancies (Hassold 1986). Liveborn 45,X individuals have the characteristic features of Turner syndrome, but survival to term is an extremely rare outcome, as over 99% of 45,X fetuses spontaneously abort (Hook and Warburton 1983).

The reason for this high in utero lethality is unclear, but we previously have suggested that there may be an association between the mechanism of origin of monosomy and likelihood of survival to term (Hassold et al. 1985). Studies of X-chromosome inactivation indicate that in rodents and humans paternally derived and maternally derived X chromosomes are differentially imprinted (Wake et al. 1976; West at al. 1977; Harrison 1989). Thus, it is possible that the parental origin of the single X chromosome in 45,X conceptuses affects the phenotype, including in utero viability. Alternatively, the timing of the error may differ between liveborn and spontaneously aborted 45,X conceptuses. For example, if monosomy originates postfertilization, it may result in a normal/monosomy mosaic capable of survival to term, while a meiotic origin will yield nonmosaic monosomy, a condition possibly incompatible with livebirth.

In the present report, we describe molecular studies of parental origin and mosaicism in forty-one 45,X conceptuses, and compare our observations to those of other recently reported studies of 45,X fetuses and liveborns. The results of our and other studies provide no evidence that the parental origin of the single X chromosome affects the phenotype and, in particular, the viability of 45,X fetuses. Furthermore, our identification of X-chromosome and Y-chromosome mosaics among 45,X spontaneous abortions indicates that sex chromosome mosaicism does not ensure survival to term of 45,X fetuses.

Materials and methods

Study population

The study population consists of 41 conceptuses with sex chromosome monosomy (Table 1). Of these, 29 cases were identified as part of cytogenetic surveys of spontaneous abortions conducted in Honolulu, Hawaii (Hassold et al. 1980), Hamilton, Ontario (Uchida 1990) or Atlanta, Ga. (T. Hassold, unpublished observations). In each case, placental fragments (typically consisting of chorionic villi and material from fetal membranes) were used for both the cytogenetic and DNA marker studies. The remaining 12 cases were liveborns, 5 of whom were referred for clinical features of Turner syndrome and 7 of whom were identified as part of chromosome studies of newborn individuals conducted between 1964–1974 (Robinson et al. 1990). In each case, results of cytogenetic and molecular studies were based on analyses of peripheral blood samples. On cytogenetic analysis, all cases were diagnosed as being nonmosaic for sex chromosome monosomy, with one case (K3034) also being trisomic for chromosome 22.

DNA studies

DNA samples were extracted from fetal tissue or blood samples and processed for Southern hybridization studies as previously de-

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Table 1. Summary of cytogenetic and molecular observations on 41 conceptuses with sex chromosome monosomy. +, Positive; −, negative; n.t., not tested

Identification no.	Cytogenetic analysis	(No. of cells analyzed, if known)	Parental age		Parental origin of single X chromosome[b]	Results of molecular studies of mosaicism	
			Father	Mother		Y chromosome	X chromosome
Spontaneous abortions							
K3034[a]	46,X,+22	(9)	37	36	Maternal	−	−
K3090[a]	45,X	(10)	25	20	Maternal	−	−
K3231[a]	45,X	(11)	34	24	Maternal	−	−
K3253[a]	45,X	(11)	49	40	Maternal	−	−
K3261[a]	45,X	(6)	32	27	Maternal	−	−
K3281[a]	45,X	(11)	33	23	Maternal	−	−
K3340[a]	45,X	(4)	34	33	Maternal	−	−
Y37.0	45,X	(16)	37	35	Maternal/mosaic	+	−
Y39.0	45,X	(16)	28	28	Paternal	−	n.t.
Y42.0	45,X	(16)	32	27	Maternal	−	−
Y44.0	45,X	(16)	26	20	Maternal	−	−
Y85.0	45,X		32	28	Paternal/mosaic	−	+
S28.0	45,X	(15)	29	35	Maternal/mosaic	−	+
S137.0	45,X	(6)	33	31	Maternal	−	−
S186.0	45,X	(7)	30	28	Maternal/mosaic	+	−
S237.0	45,X	(4)	36	30	Maternal	−	−
S260.0	45,X	(8)	?	30	Maternal	−	−
S278.0	45,X	(8)	29	28	Maternal	−	−
S289.0	45,X	(7)	27	26	Maternal/mosaic	+	−
S327.0	45,X	(3)	37	36	Maternal	−	−
S360.0	45,X	(4)	27	29	Maternal	−	−
S409.0	45,X	(9)	29	27	Maternal	−	−
S417.0	45,X	(7)	42	31	Maternal/mosaic	+	−
S445.0	45,X	(7)	31	28	Paternal	−	−
S465.0	45,X	(3)	28	29	Maternal	−	−
S485.0	45,X	(4)	32	31	Maternal	−	−
S493.0	45,X	(5)	35	34	Maternal	−	−
S495.0	45,X	(10)	31	30	Maternal	−	−
Y101.0	45,X	(15)	36	34	Maternal	−	n.t.
Liveborns							
Y8.0	45,X	(20)	24	22	Maternal/mosaic	−	+
Y29.0	45,X		?	24	Maternal	−	−
Y34.0	45,X		40	40	Paternal	−	−
Y58.0	45,X	(72)	23	22	Maternal	−	−
Y59.0	45,X	(60)	22	21	Maternal	−	−
Y60.0	45,X	(20)	31	30	Maternal	−	−
Y63.0	45,X	(80)	41	37	Maternal/mosaic	−	+
Y67.0	45,X	(50)	31	23	Maternal	−	n.t.
Y102.0	45,X	(15)	25	21	Maternal	−	−
Y102.3	45,X	(15)	26	23	Paternal	−	n.t.
Y130.0	45,X	(15)	35	33	Maternal	−	−
Y165.0	45,X	(6)	?	21	Maternal	−	−

[a] Partial information on these cases has been presented previously (Hassold et al. 1988)
[b] Analyses of single copy loci for parental origin determinations were done independently of mosaicism studies; thus, in some cases an apparent nonmosaic 45,X was subsequently observed to carry a second cell line

scribed (Hassold et al. 1988). For determinations of parental origin of the single X chromosome, we used a total of 21 probes detecting polymorphisms at the following X-chromosome loci: DXS1, 3, 7, 14, 15, 16, 41, 42, 43, 51, 52, 84, 86, 89, 144, 207, 255, 278, DXYS1X, OTC, and TIMP. Information on the polymorphisms and physical locations of the loci is provided elsewhere (Kidd et al. 1989).

For evaluation of Y chromosome mosaicism, DNA samples were digested with *Taq*I or *Eco*RI. Following electrophoresis and Southern transfer, the membranes were hybridized with the fol-

Table 2. The parental origin of the single X chromosome in putative nonmosaic 45,X spontaneous abortions, therapeutic abortions, and liveborns

Population	Study	Origin of the X chromosome	
		Paternal	Maternal
Liveborns	Jacobs et al. (1990)	9	20
	Mathur et al. (1991)	7	18
	Loughlin et al. (1991)	0	12
	Villamar et al. (1990)	0	3
	Hassold et al. (1988) and present study	3	12
		19 (23%)	65 (77%)
Therapeutic abortions	Cockwell et al. (1991)	2	5
		2 (29%)	5 (71%)
Spontaneous abortions	Cockwell et al. (1991)	0	1
	Hassold et al. (1988) and present study	8	38
		8 (17%)	39 (83%)

lowing Y chromosome detecting probes: pDP97 (DYZ3), which detects alphoid sequences at the centromere of the Y chromosome; pDP105 (DYZ4), which detects repeated sequences on Yp and Yq in intervals 3 and 6, respectively, of the Y-chromosome deletion map (Cantrell et al. 1989); pDP34 (DXYS1Y), which detects a single Y-linked *Taq*I fragment on Yp in deletion interval 4A; CRIS232 (DYS136), which detects two Y-linked *Taq*I fragments on Yq in deletion interval 6; and pDP230 (DXYS20), which detects a complex polymorphism in the pseudoautosomal region. The probes were used at high stringency (i.e., hybridization at 42°C, with the final wash in 0.1 SSC at 65°C), and the 45,X samples were routinely compared to a control panel of mixtures of normal male: female DNA samples in ratios 1:1, 1:9, and 1:90. Using this approach, we were able to detect Y-chromosome sequences at the 1% level using the probes pDP97 and pDP105. However, the sensitivity for the remaining probes was much lower and, for these loci, we could not confidently exclude even high-level mosaicism.

For evaluation of X-chromosome mosaicism, DNA samples of the 45,X conceptus and the parent of origin were digested with *Hind*III and, in a separate experiment, with *Xba*I. Following electrophoresis and Southern transfer, the membranes were hybridized with pBamX9 (DXZ1), which detects a complex polymorphism at the centromere of the X chromosome (Willard et al. 1986). We considered the 45,X conceptus to be a mosaic if we were able to identify a fragment(s) not present in the parent of origin in both the *Hind*III- and *Xba*I-digested samples; failure to identify any additional fragments was consistent with the 45,X being nonmosaic for the tissue under investigation. To determine the sensitivity of this assay, DNA samples from two individuals with different X-centromere restriction fragment patterns were mixed in the proportions 1:1, 1:9, and 1:90, digested with *Hind*III or *Xba*I and processed as above. We were always able to identify fragments from both individuals in the 1:1 mixture and usually in the 1:9 mixtures; thus, the assay should allow us to detect a 10%–50% level of mosaicism, but probably not a level of mosaicism lower than 10%.

Results

Detailed information on the 41 cases is presented in Table 1 and summaries of the studies of parental origin and mosaicism are presented in Tables 2 and 3, respectively.

Parental origin studies

We were able to determine unambiguously the parental source of the single X chromosome in each of 31 cases for which blood samples were available from both parents; in most of these (25/31 = 81%) the determinations were based on results at multiple loci.

Two other cases (Y102.0, Y102.3) were sisters and came from a family in which blood samples were available only from the mother and the two affected girls. One of the girls (Y102.3) must have received her father's X chromosome because, at two loci, she had a single allele not observed in the mother. The other girl (Y102.0) did not have these paternal alleles, and she and her mother shared an allele at all loci studied; therefore, she presumably had a single, maternally derived X chromosome.

In the remaining 8 cases (S28, S260, S289, S417, Y34, Y58, Y59, Y165) a blood sample was available from only one of the two parents. In each of these, the proband and the available parent shared an allele at each of 5–11 loci studied, consistent with that parent having contributed the single X chromosome. If we assume the parental origin to be known in these 8 cases as well, we were then able to specify the parental source of the X chromosome in each of the 41 cases.

However, subsequent studies of mosaicism (see below) indicated that 8 of the 41 cases were mosaic for a second sex chromosome, leaving 33 apparent nonmosaic cases. Of the 33, 29 (88%) had a single, maternally derived X chromosome and 4 (12%) a single paternal X. There was no obvious effect of parental origin on the likelihood of survival to term of these cases, as 21/23 of the nonmosaic spontaneous abortions and 8/10 of the nonmosaic liveborns had an X^{Mat}. There also was no obvious difference in maternal age among the different categories of 45,X conceptuses; the mean maternal age for the 8 mosaics were 30.3 ± 5.2 years, for the 4 paternally derived nonmosaics 29.8 ± 7.3 years, and for the 28 maternally derived nonmosaics (including K3034, the

Table 3. Molecular studies of sex chromosome mosaicism in conceptuses diagnosed as nonmosaic 45,Xs on cytogenetic analysis

Population	Study	Cases positive (+) for presence of second sex chromosome	
		Y chromosome +/ total studied	X chromosome +/ total studied
Liveborns	Hassold et al. (1988)	0/5	–
	Jacobs et al. (1990)	0/31	–
	Mathur et al. (1991)	0/25	–
	Loughlin et al. (1991)	0/12	–
	Ostrer et al. (1989)	0/11	–
	Present study	0/13	2/10
		0/97 = 0%	2/10 = 20%
Therapeutic abortions	Cockwell et al. (1991)	0/9	–
		0/9 = 0%	
Spontaneous abortions	Cockwell et al. (1991)	0/1	–
	Hassold et al. (1988)	1/25	–
	Present study[a]	4/29	2/27
		5/55 = 9.1%	2/27 = 7.4%

[a] Data on 7 spontaneous abortions originally reported in Hassold et al. (1988) and subsequently re-examined for this study are considered part of the present data set only

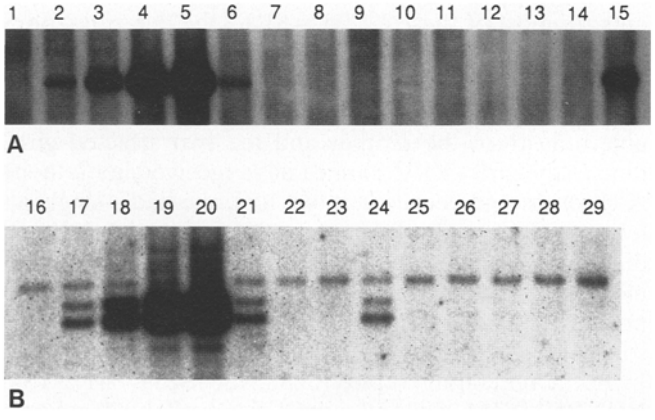

Fig. 1A, B. Evaluation of Y-chromosome mosaicism using *Eco*RI-digested DNA samples probed with pDP97 **(A)** and pDP105 **(B).** *Lanes 1–5* and *16–20* are control samples consisting of mixtures of normal male: female DNA samples corresponding to 0%, 1%, 10%, 50%, and 100% male DNA. Four lanes from cases gave clear positive results, and these represent three different 45,X abortuses *(lanes 6* and *21,* S186; *lane 15,* Y37; and *lane 24,* S417). Additionally, *lanes 10* (S289) and *14* (S417) gave faint, detectable signals on longer film exposure

case with the 46,X,+22 chromosome constitution), 27.8 ± 5.3 years.

Studies of mosaicism

We evaluated Y and X chromosome mosaicism in all cases, regardless of the results of the parental origin studies. We identified four cases, all spontaneous abortions that were positive for Y chromosome material (see Fig. 1 for examples). In each of the four, Y-chromosome hybridization was observed with probes detecting repeated sequences at the centromere (pDP97) and proximal long and short arms (pDP105), but no signal was detected with any of the other Y-linked probes. Apparent X-chromosome mosaicism was detected in two of the spontaneous abortions and in two of the liveborn individuals (see Fig. 2 for examples). In one case (Y85.0) the presence of a cell line containing two X chromosomes was apparent at several of the X-linked RFLPs used in our parental origin studies. However, in the remaining three cases the determination of mosaicism was based solely on analysis of the centromeric region.

Discussion

The purpose of the present study was to investigate two possible reasons for the high in utero lethality of the 45,X condition: (1) that the effect might be due to differential selection against $45,X^{Mat}$ and $45,X^{Pat}$ cases and (2) that sex chromosome mosaicism might be restricted to, or more likely to involve, liveborn than spontaneously aborted 45,X conceptuses.

A summary of molecular studies of parental origin in 138 putative nonmosaic 45,X conceptuses, including 32 from the present study, is presented in Table 2. Overall, the number of X^{Mat} and X^{Pat} cases is 109 (79%) and 29 (21%), respectively, and there is no evidence for significant differences among the three ascertainment categories. Thus, there is little reason to believe that the parental origin of the single X chromosome affects the in utero viability of 45,X fetuses. This conclusion is consistent with recent clinical studies of Turner syndrome, which have reported no obvious differences in the phenotypes of liveborn X^{Mat} and X^{Pat} individuals (Mathur et al. 1991). Thus, despite the fact that X-chromosome in-

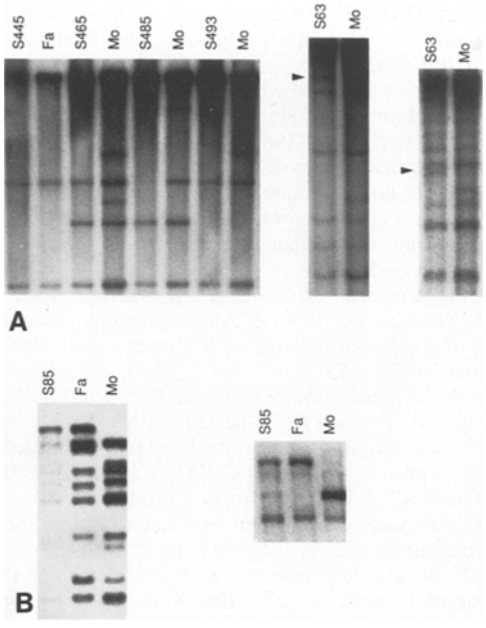

Fig. 2A, B. Evaluation of X-chromosome mosaicism. **A** DNA samples from 45,X conceptuses and the parent contributing the single X chromosome were digested with *Xba*I or *Hin*dIII and probed with pBamX9, which detects alphoid sequences at the centromere of the X chromosome. In the *left* panel (*Xba*I digest), none of four 45,X conceptuses has restriction fragments not seen in the parent of origin; thus there is no evidence for X-chromosome mosaicism in these cases. However, the *center* (*Xba*I digest) and *right panels* (*Hin*dIII digest) show that, for S63, fragments are present which are not inherited from the mother *(mo)*; these are indicated by the *arrowheads*. Thus, we conclude that this case is mosaic for a second X chromosome or at least for the centromeric region of the X. **B** Analysis of Y85 and parents at two polymorphic markers, DXYS20 *(left)* located in the pseudoautosomal region and DXS42 *(right)* located on Xq. In both examples, a prominent, paternally derived allele and a fainter, maternally derived allele are evident. *Fa* father

activation preferentially involves the paternal X chromosome in rodent and human extraembryonic tissues, the available data provide no evidence for an X-chromosome imprinting effect in the development of 45,X fetuses, at least not those that survive long enough to be clinically recognized pregnancies.

Table 3 provides a summary of our and other laboratories' molecular studies of mosaicism in 158 45,X conceptuses diagnosed as nonmosaic on cytogenetic analysis. Previous studies have evaluated only Y-chromosome mosaicism, and, therefore, the estimates of X-chromosome mosaicism are based solely on the present study. The frequency of Y-chromosome mosaicism is significantly elevated among spontaneous abortions by comparison with liveborns ($\chi_1^2 = 9.19$, $P < 0.01$), while the frequency of X chromosome mosaicism is elevated, although not significantly so, among the liveborn cases. Overall, the estimated frequency of sex chromosome mosaicism is 20% for the liveborns and 16.5% for the spontaneous abortions, with none of the nine therapeutic abortions being identified as mosaics.

The high frequency of mosaicism among the spontaneous abortions is somewhat surprising. In previous DNA studies of sex chromosome monosomy (Hassold et al. 1988) we identified one Y-chromosome mosaic among 25 spontaneous abortions, while in the present series 6 of 29 abortuses were mosaic for either an X or Y chromosome. Combining the results from the two series, the estimated incidence of mosaicism among spontaneously aborted 45,X conceptuses is over 15%. Furthermore, this is likely an underestimate, since (1) in some cases, the level of mosaicism may have been too low to be detected by our assays, (2) mosaicism may have been present in tissues other than the ones we studied, and (3) in our initial studies (Hassold et al. 1988) we made no systematic attempt to detect X-chromosome mosaicism.

Thus, our results might be taken as evidence that mosaicism is as common in spontaneously aborted as in liveborn 45,X conceptuses. However, this would be an incorrect interpretation, since it does not take into account the differences in selection of liveborn/aborted 45,X cases for the molecular studies of mosaicism. That is, in the studies summarized in Table 3, cases had been prescreened cytogenetically to exclude any obvious mosaics; therefore, the data of Table 3 represent the subset of liveborn or aborted 45,Xs that are nonmosaic on cytogenetic analysis. Among spontaneous abortions, the incidence of cytogenetically detectable sex chromosome mosaicism among 45,X fetuses is only 1%–2% (Hassold et al. 1988), meaning that the fetuses reported in Table 3 are representative of all 45,X spontaneous abortions. However, this is not the case for the liveborn 45,X category. The reported incidence of cytogenetically detectable mosaicism among all newborn infants with a 45,X cell line is about 80% (Hook and Hamerton 1977) despite the fact that the studies upon which this value is based typically analyzed only two to five metaphases. Among liveborn individuals with clinical features of Turner syndrome, the incidence of detectable mosaicism is lower, but still approaches 50% (Hook and Warburton 1983). Thus, the liveborn individuals reported in Table 3 comprise a subset of perhaps 20%–50% of all 45,X liveborns, with the remainder being mosaics. By combining these estimates with those from the molecular studies of mosaicism, we can calculate that at least 60%–80% of 45,X liveborns have a second cell line, compared with only 15%–20% of 45,X spontaneous abortions. Thus, sex chromosome mosaicism is probably at least 3–5 times as common among liveborn as among spontaneously aborted 45,X conceptuses. This implies that the presence of a second cell line confers a selective advantage to otherwise 45,X fetuses and increases their likelihood of surviving to term. This conclusion is consistent with previous reports, based on cytogenetic analyses, which have compared the incidence of nonmosaic and mosaic 45,Xs at different points in pre- and postnatal life (e.g., Hook and Warburton 1983; Hook et al. 1989).

However, our data also make it clear that mosaicism per se does not ensure survival to term, as we have identified seven sex chromosome mosaics in a relatively small series of 45,X spontaneous abortions. It is, of course, possible that the mosaicism associated with 45,X spontaneous abortions differs qualitatively or quantitatively from the mosaicism associated with 45,X live-

borns. For example, there may be differences in tissue-specific distribution of mosaicism between the two categories; the mosaicism associated with the abortions may more often involve a structurally abnormal sex chromosome; or the proportion of cells with two sex chromosomes may be lower among aborted mosaics than among liveborn mosaics. Nevertheless, our identification of mosaics among 45,X spontaneous abortions indicates that mosaicism is not the only factor associated with survival to term of sex chromosome monosomic fetuses.

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