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Extremely Skewed X-Chromosome Inactivation Is Increased in Women with Recurrent Spontaneous Abortion

To the Editor:

Recurrent spontaneous abortion (RSA), defined as three or more consecutive losses at ⩽20 wk gestation (Stirrat 1990), affects 1%–2% of couples trying to have a family (Stray-Pedersen and Lorentzen-Styr 1979; Roman 1984). Although spontaneous abortion occurs quite frequently in humans, affecting ~15% of all clinically recognized pregnancies (Warburton and Fraser 1964; Edmonds et al. 1982; Wilcox et al. 1988), the observed rate of RSA is much higher than the expected rate of 0.3% due to chance alone. This suggests the presence of factors that may predispose particular couples to multiple pregnancy losses. Nearly 60% of RSA cases can be potentially explained by identifiable autoimmune, endocrine, anatomical, or infectious factors or by structural chromosome rearrangements in one partner (Stephenson 1996). However, >40% of RSA is still unexplained. We suggest that a significant proportion of the unexplained cases of RSA may be caused by a genetic mutation or chromosomal abnormality that would not be discovered by routine investigation.

X-chromosome inactivation (XCI) is the process whereby one of the two X chromosomes present in each cell of female mammals is inactivated during early embryogenesis, to achieve dosage compensation with males (Lyon 1961). Generally, in a given cell type in humans, the maternal X chromosome is inactivated approximately equally as often as the paternal X chromosome (Belmont 1996). However, extremely skewed XCI, defined in this letter as >90% inactivation of one allele, is observed in ~2% of newborns and ~4.5% of 28–32-year-old women (Busque et al. 1996). This extremely skewed XCI pattern may be due to a number of possible causes: (1) chance; (2) a mutation in the XIST gene that is found on the X chromosome and is thought to be critical in the inactivation process (Plenge et al. 1997); (3) selection against cells with a growth disadvantage because of a deletion or mutation on one of the X chromosomes (Pegoraro et al. 1997) or to an X-autosome translocation (Gaal and Laszlo 1977); and (4) a reduction in the fetal precursor-cell pool size, as has been suggested to occur in twinning (Bamforth et al. 1996; Goodship et al. 1996). Trisomy mosaicism has also recently been shown to be associated with extremely skewed XCI (Lau et al. 1997). Extremely skewed XCI (>90% inactivation of one allele) was found in the majority (11 of 18) of prenatally detected mosaic cases when the trisomic cell line was of meiotic origin and absent from most fetal tissues (Lau et al. 1997; W.P. Robinson and M.S. Peñahererra, unpublished data). Skewing is hypothesized to result from a reduction in the number of embryonic precursor cells, because of selection against the trisomic cells shortly after XCI.

At least three causes of skewed XCI are expected to be associated with an increased risk of spontaneous abortion: (1) some deletions or mutations on the X chromosome may be lethal to male fetuses carrying the abnormal X chromosome (Pegoraro et al. 1997); (2) X-autosome translocations can lead to RSA, because some gametes may be deleted and/or duplicated for portions of each chromosome that are involved in the rearrangement (Byrne and Ward 1994); and (3) trisomy mosaicism may also be associated with RSA if the germline is affected, since recurrent aneuploidy may result (Kohn and Shohat 1987; Gersdorf et al. 1990; Satge et al. 1996). Although it is impossible to determine how often the germline is mosaic in individuals with a normal phenotype and blood karyotype, one case was reported in which trisomy 16 was found in placenta and oocytes but in no other fetal tissue (Stavropoulos et al. 1998). To evaluate the degree to which mosaicism or other genetic factors associated with extremely skewed XCI may contribute to RSA, we screened women with RSA in order to determine their XCI status and compared them with controls of similar age.

Patients were ascertained through the Recurrent Pregnancy Loss Clinic at British Columbia's Women's Hospital and Health Centre. Between September of 1997 and December of 1998, all new patients with a history of RSA who were seen by the one of the authors (M.D.S.) were offered participation in this study. RSA was defined as three or more consecutive pregnancy losses prior to 20 wk gestation, with each pregnancy documented by a positive result on serum or urinary hCG, ultrasound, or pathology. Ethics approval was obtained from the

University of British Columbia Clinical Research Ethics Board, and the consent form was thoroughly reviewed with each patient. A single tube of peripheral blood was collected from consenting women, and DNA was extracted by use of a standard protocol. Every effort was made to collect these blood samples when samples for other standard blood work were being collected, according to the RSA protocol of Stephenson (1996). Controls were mothers who had donated blood previously, each having had at least one full-term pregnancy.

The mean number of consecutive spontaneous abortions per patient was 4.1, with a range of 3–11. Patients' ages were 19–45 years, with a mean of 33.6 years. For the control group, the age at which the blood was drawn was available for 86 of the 111 individuals informative at the androgen-receptor (AR) locus; the controls' ages were 20–49 years, with a mean age of 35.0 years. Results of karyotype analysis using standard Giemsa banding at 550-band resolution, in patients with RSA, their reproductive partners, and prior spontaneous abortions were taken from patients' charts; a total of 49 aborted pregnancies from patients with RSA who were informative for XCI status underwent karyotype analysis.

The degree of skewed XCI was estimated by an assay based on a methylation-sensitive *Hpa*II restriction site located near the human AR gene. This site is known to be methylated on the inactive X chromosome and to be unmethylated on the active X chromosome (Allen et al. 1992). When *Hpa*II was used to digest the genomic DNA prior to PCR, the AR allele was amplified only from the inactive X chromosome, since the sequence to be amplified on the active X chromosome was cleaved by the restriction enzyme. A trinucleotide CAG-repeat polymorphism located within the amplified region was used to distinguish between the two X chromosomes. For each patient, two PCR reactions were performed—one with genomic DNA digested with *Hpa*II and one without *Hpa*II. The second reaction served as an internal control to establish a baseline level of amplification of each allele, specific to the individual. This measure corrected for any preferential amplification of one allele over the other, in a given patient. Genomic DNA from males was used as a digestion control, since their X chromosome is always active (unmethylated) and therefore should have been completely digested by *Hpa*II and should have yielded no amplification product. Products were separated by PAGE and were visualized by silver staining. Quantification of the resulting bands was performed as detailed elsewhere (Lau et al. 1997). The analysis was repeated for any patient in whom skewing was >70%, in order to verify the result. Thus, the degree of skewing reported in these cases was an average of two or three independent tests; the mean difference between two estimates of skewing for the same patient was four percentage points.

XCI status was informative in 76 of the 98 patients with RSA and in 111 of the 137 female controls. This frequency may be less than that in other reports because some heterozygous cases were considered to be uninformative if the two bands were too close to resolve adequately for densitometric analysis. Extremely skewed XCI, defined as >90% amplification of one allele, was found in 14 (18%) of the 76 informative females with RSA and in just 6 (5%) of the 111 controls ($P < .001$; χ^2 test) (see table 1). The mean rate of skewing in the control group was similar to the 4.5% rate of skewing observed by Busque et al. (1996) in women 28–32 years of age. This rate was not significantly altered if controls for whom no age data were available were excluded.

These results show that factors associated with extremely skewed XCI account for a significant proportion (i.e., as much as 18%) of couples with RSA. Similar results have been reported, by Lanasa et al. (1999), for women who have experienced two or more spontaneous abortions. What is the explanation for extreme skewing in these patients with RSA? A pattern of extremely skewed XCI is commonly seen in females who carry balanced translocations involving one X chromosome and an autosome. The normal X chromosome is usually preferentially inactivated, presumably to maintain a balanced chromosomal complement in each cell (Gaal and Laszlo 1977). Theoretically, X-chromosome rearrangements could also lead to recurrent pregnancy loss. However, in a study that reported karyotype results in 1,142 couples with recurrent abortion there was not a single rearrangement involving the X chromosome (Portnoi et al. 1988). Thus, this is too rare a finding to account for the significant number of patients with RSA whom we observed to have extremely skewed XCI. Furthermore, in our study, all 14 of the patients with RSA who had extreme skewing had normal results on karyotype analysis—that is, 46,XX (see table 2).

Extremely skewed XCI may also result from a mutation on one of the two X chromosomes because of selective advantage of those cells that have the normal X chromosome active. In such cases, any male conceptus inheriting the abnormal X chromosome would most likely be aborted, because of the presence of only the defective copy of the locus in question. One such family has been reported in which 100% of the females exhib-

Table 1

Proportion of Females with RSA Who Showed Extremely Skewed XCI Compared with Control Females

	No. (%) Observed With	
Group	<90% Skewing	>90% Skewing
Females with RSA	62 (82)	14 (18)
Control females	105 (95)	6 (5)

Note.—For comparison by χ^2, $P < .001$.

Table 2

Karyotype Data on Female Patients with RSA and on Their Male Reproductive Partners

Gender and Karyotype	No.
Females:	
46,XX[a]	86
46,XX,t(2;12)(q13;q24.31)	1
46,XX,t(8;12)(q22;q22)	1
46,XX,inv(2)(p11.2q13)	1
46,XX/45,X[b]	1
NA	8
Total	98
Males:	
46,XY	81
NA	17
Total	98

[a] All 14 patients with RSA who had extremely skewed XCI also had a 46,XX karyotype.

[b] A 45,X karyotype was found in 4/100 lymphocytes, and further examination showed a 46,XX karyotype in 30/30 skin fibroblast cells.

iting extremely skewed XCI showed the presence of an X chromosome with an inherited deletion (Pegoraro et al. 1997). The women in this family had a spontaneous-abortion rate more than twice that in their female relatives who did not have the deletion or skewing. They also had a greater proportion of live-born females than of live-born males. There is currently no efficient method that can screen for mutations on the X chromosome that affect viability. However, it would be expected that, if this were the cause of RSA in our group of patients with extremely skewed XCI, then a high rate of 46,XY karyotypes should be seen among their spontaneous abortions. Of the karyotyped spontaneous-abortion specimens that were euploid, 1 of the 2 abortuses from patients with skewing was male, compared with 14 males among the 25 normal abortuses from patients with RSA and without skewing (table 3).

It should be noted that, although the frequency of pregnancy loss would be higher in carriers of an X-chromosome mutation or deletion than in the general population, in theory only 25% of the conceptuses (i.e., one-half of the males) would be at risk of being aborted because of the mutation; this is because all of the females and half of the males should be protected from the mutation, by the presence of the normal X chromosome. If it is assumed that the population rate of abortion due to independent causes is 15%, then the joint probability of pregnancy loss would be ~36%. Thus, only a small number (i.e., ~5%) of women with such an X-chromosome mutation might be expected to have three or more consecutive spontaneous abortions and no live births. Thus, an X-chromosome mutation might be relatively more common among women with either only a few losses or several losses combined with some live births than it is among women who experience a larger number of losses and no successful full-term pregnancies. It is therefore interesting to note that the mean number of spontaneous abortions (4.1) in the 14 patients who had skewed XCI was equal to that of the entire group with RSA.

Finally, a factor that may be associated with both extremely skewed XCI and RSA is aneuploidy mosaicism. Although aneuploidy is the leading cause of random spontaneous abortion, accounting for ~50% of karyotyped losses (Boue et al. 1975; Hassold and Jacobs 1984), it is difficult to evaluate whether recurrence of the same aneuploidy occurs more often than would be expected by chance, since karyotype information on each loss is lacking in most RSA cases. Nonetheless, many cases of gonadal mosaicism for a trisomy have been reported, many of which are ascertained by the multiple recurrence of Down syndrome (Kohn and Shohat 1987; Nielsen et al. 1988; Gersdorf et al. 1990; Sachs et al. 1990; Pangalos et al. 1992; Tseng et al. 1994; Satge et al. 1996), and mosaicism is found in the lymphocytes of one of the two parents in 4% of families with Down syndrome (Uchida and Freeman 1985). However, even if germline mosaicism were a cause of RSA, we would not necessarily expect the same trisomy to recur, since it has been shown that the presence of an unpaired chromosome in mouse oocytes can cause both disruption of meiosis and missegregation of other chromosomes (Hunt et al. 1995). There is also evidence from rare cases of fertile 45,X women that the same effect occurs in humans (Warburton 1989). In our study, seven of nine spontaneous-abortion specimens from the group of women with extremely skewed XCI were found to be aneuploid, whereas, among the women with nonskewed XCI, just 15 (27%) of 40 spontaneous-abortion specimens were aneuploid ($P = .03$; see table 3). Although both skewed XCI and aneuploidy increase with maternal age (Hassold and Jacobs 1984; Busque et al. 1996), the mean age of the patients with extremely skewed XCI

Table 3

Karyotypes of Spontaneous Abortions among Female Patients with RSA Who Have Extremely Skewed XCI, versus Those Who Do Not Have Such Skewing

Type of Abortus Karyotyped	No. of Abortuses From Patients Who Have	
	<90% Skewing	>90% Skewing
46,XY	14	1
46,XX	11	1
Aneuploid	15[a]	7[a]
Total	40	9

[a] $P = .03$ (by Fisher's exact test comparing proportion of abnormal karyotypes in the two groups).

was lower (32.4 years) than that of the group without skewing (33.9 years). Thus, age cannot explain the higher rate of aneuploidy in the spontaneous-abortion specimens from patients with extremely skewed XCI.

It is estimated that 1%–2% of first-trimester pregnancies assessed by chorionic-villus sampling are mosaic (Vejerslev and Mikkelsen 1989). Although the abnormal cell line is often assumed to be confined to the placenta, this is difficult to prove. Even when mosaicism is found in amniotic fluid, the aneuploidy is frequently absent from fetal/newborn blood (Hsu et al. 1997), and trisomy mosaicism for most chromosomes is unlikely to be detected by routine blood karyotyping. Although analysis of skin fibroblasts may detect a greater proportion of mosaic cases, it is still possible for trisomic cells to be found in oocytes even when no other fetal tissues are affected (Stavropoulos et al. 1998). Alternatively, we can look at indirect indicators, such as skewed XCI, to provide clues as to whether an individual may be the product of a pregnancy associated with mosaicism.

Pregnancy loss is a devastating issue for many couples, and identification of an etiology is very important for counseling couples with RSA as to their treatment options. Clearly, genetic factors associated with extremely skewed XCI are important in at least some patients with RSA and, most likely, involve either an X-linked mutation or germline mosaicism. Further review of the medical histories and pedigrees may provide clues as to which etiology is involved in a particular case. A larger epidemiological study documenting the outcome of all pregnancies and including karyotype data from the spontaneous abortions is also necessary to clarify the mechanism involved and, subsequently, to improve counseling of patients with RSA, in regard to future pregnancy outcomes.

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Demonstration of the Recurrence of Marfan-like Skeletal and Cardiovascular Manifestations Due to Germline Mosaicism for an *FBN1* Mutation

To the Editor:

Marfan syndrome (MFS [MIM 154700]) is a dominantly inherited disease of connective tissue. Cardinal manifestations involve the eye (lens dislocation and myopia), skeleton (dolichostenomelia, arachnodactyly, anterior chest deformity, spinal curvature, and joint laxity) and cardiovascular system (aortic root dilation and dissection, mitral valve prolapse, and mitral and aortic valve regurgitation). Striae distensae and inguinal hernia are frequent findings in the integument, and pneumothorax and dural ectasia occur in some patients (Pyeritz and McKusick 1979; First International Symposium on the Marfan Syndrome 1989). If untreated, the syndrome shortens life expectancy mainly because of cardiovascular complications. The disorder is characterized by considerable variation in the distribution and severity of organ system involvement between families, leading to the definition of diagnostic criteria listed first in the Berlin nosology (Beighton et al. 1988) and subsequently revised in the Ghent nosology (de Paepe et al. 1996). In 1986, Sakai and colleagues identified a 350-kD glycoprotein called "fibrillin," which represents the major structural component of connective tissue microfibrils. By using an anti-fibrillin antibody, Godfrey, Hollister, and their colleagues demonstrated a reduction of microfibrils in immunofluorescence studies of cultured dermal fibroblasts in patients with MFS (Godfrey et al. 1990; Hollister et al. 1990). Subsequent studies of fibrillin synthesis, secretion, and incorporation into the extracellular matrix showed abnormalities in most but not all MFS fibroblast strains (Milewicz et al 1992; Collod et al. 1994). Finally, mutations in the *FBN1* gene, encoding fibrillin, have been demonstrated to result in MFS or associated phenotypes (Dietz et al. 1991; Hayward et al. 1994; Kainulainen et al. 1994; Lonnqvist et al. 1994; Sood et al. 1996). The *FBN1* gene is ~200 kb in size, with a coding sequence fragmented into 65 exons (Corson et al. 1993; Pereira et al. 1993; Biery et al. 1999) located on chromosome 15q21.1 (Magenis et al. 1991).