Letters to the Editor

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No Evidence for Parent of Origin Influencing Premature Ovarian Failure in Fragile X Premutation Carriers

To the Editor:

We were interested to read, in the February edition of the *Journal,* an article by Hundscheid et al. (2000) that reported an imprinting effect on the fragile X premutation, such that paternally inherited premutations are more likely to give rise to premature ovarian failure (POF). We were impressed by the rigorous design of the study, which ensured that all women were interviewed personally and that adherence to strict criteria for the definition of POF was maintained. However, we were very surprised by the results of the study, in light of the results of our own study of a similar cohort of women from Wessex, United Kingdom.

We interviewed 352 women from families with the fragile X premutation about their reproductive and menstrual histories; of these women, 116 carried premutation-sized (51–200-repeat) alleles and were from 62 families (Murray et al., in press). These families have been investigated extensively during the past 15 years, and, therefore, we have almost complete ascertainment of "at-risk" individuals. All premutation and full-mutation carriers and their unaffected first- and second-degree relatives were invited to participate in the study and were interviewed either in person or via the telephone. Women who were using the contraceptive pill were excluded from the analysis, and those women who were still menstruating or who had undergone a hysterectomy were taken as censored values. We used Kaplan-Meier survival analysis to demonstrate that the premutation group had a mean age at menopause of 47.87 years, compared with 52.96 years for the full-mutation and normal groups combined (Murray et al., in press). It was apparent, from inspection of our data, that there were no parent-of-origin differences. In a separate study of women ascertained through the presence of POF, six pedigrees were illustrated (Murray et al. 1998); we could determine the origin of the premutation in only four women with POF (who were from two families), and the origin was maternal in each case.

However, the study by Hundscheid et al. (2000) prompted us to reevaluate our data and to analyze them in a similar fashion. Our population of 116 premutation carriers was comprised of 40 carriers with maternal transmissions, 51 carriers with paternal transmissions, and 25 carriers for whom we were not able to determine the origin of transmission. The results of survival analysis comparing maternal and paternal premutations demonstrated no significant shift in age at menopause between the two groups ($\chi^2_1 = 0.0143$; $P = .91$). POF was defined as spontaneous cessation of menses for >1 year, before age 40 years—a definition that is essentially the same as that in the study by Hundscheid et al. Similar to table 1 in the study by Hundscheid et al., table 1 in our study shows that we have only considered females that were of age ⩾40 years at the time of the interview; POF is not significantly more common in either group (two-tailed Fisher's exact test; $P = .669$).

The results of analyses of 116 female premutation carriers from families with fragile X do not provide any evidence with which to support the suggestion that there is imprinting of the *FMR1* gene. We can provide no explanation for the discrepancy between our data and the material presented in the report by Hundscheid et al. (2000). In both studies, survival analysis was used to estimate the distribution of age at menopause in an uncensored cohort, since any method that excludes premenopausal subjects underestimates the mean. Survival analysis extracts full and unbiased information from all relationships to probands, which have different frequencies of paternally inherited fragile X premutations (PIP) and maternally

Table 1

Origin of Premutation in Women of Age ⩾40 Years at the Time of the Interview

Classification	No. of Premutations of Origin		Total
	PIP	MIP	
Age at Menopause:			
<40 years	2	5	7
⩾40 years	6	10	16
Proved ovarian function[a]	4	3	7
Total	12	18	30

[a] Not menopausal, with follicular-phase FSH level <40 U/liter.

inherited fragile X premutations (MIP). Daughters of normal transmitting males all have PIP, sisters of probands never have PIP, mothers of probands have a ratio of nearly 3:1, and so forth (Morton and Macpherson 1992). Neither the present study nor the study by Hundscheid et al. categorizes relationship, which presumably accounts for the observed difference in frequencies; however, this is irrelevant if survival analysis is used correctly. In both studies, all subjects were interviewed and hearsay evidence was rejected. In an unspecified proportion of cases, Hundscheid et al. obtained age at menopause from medical records, whereas we accepted the subject's recall. Our definitions of POF, spontaneous menopause, unnatural menopause, menstrual history, and medication are indistinguishable from those of Hundscheid et al. We based our classification of MIP and PIP on several microsatellites in the FRAXA region, classifying 25 cases as being of unknown origin, according to conservative criteria. Hundscheid et al. did not specify whether markers were tested, how their classification was made, or how many subjects were unclassifiable. Regardless of whether this is consequential, the fact remains that we observed a significant difference between women with MIP and control individuals (log-rank $\chi^2_1 = 8.52$; $P = .0035$), whereas Hundscheid et al. did not. We are unable to explain this difference.

It would be very interesting to know whether other investigators find parent-of-origin differences in the frequency of POF in premutation carriers. As in all recent studies, the protocol should include interviews of all available female relatives, with rigorous definition of menopausal variables and mode of origin and with correct use of survival analysis. Only then will studies by different groups pass from debate to discovery.

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Premature Ovarian Failure Is Associated with Maternally and Paternally Inherited Premutation in Brazilian Families with Fragile X

To the Editor:

Strong evidence has been produced that indicates FMR1 premutation as a risk factor for premature ovarian failure (POF) (Cronister et al. 1991; Schwartz et al. 1994; Vianna-Morgante et al. 1996, 1999; Murray et al. 1998; Uzzielli et al. 1999). The most extensive survey was a collaborative study engaging nine centers in different countries that showed that 16% of women with premutation suffered POF compared with 0.4% of their noncarrier relatives (Allingham-Hawkins et al. 1999). In a recent study of Dutch families with fragile X, Hundscheid et al. (2000) disclosed a parent-of-origin effect of the premutation such that POF occurred with a significant frequency only in women who inherited the premutation from their fathers.

We investigated parental origin of the premutation and occurrence of POF in 113 female carriers in families with fragile X, ascertained through mentally retarded patients. In these families, women aged ⩾25 years who had been tested for the fragile X mutation were interviewed personally by one of us (A.M.V.-M.) about their menstrual, gynecological, and reproductive histories, after appropriate informed consent. Those who had undergone hysterectomy or oophorectomy were not included in the study. POF was defined as spontaneous cessation of menstruation at age <40 years, for at least 1 year. Part of the present sample was included in our previous study of the frequency of POF in fragile X carriers (Vianna-Morgante et al. 1999). Parental origin of the premutation could be determined in 59/113 women: 27 of the premutations were maternally inherited (MIP) and 32 were paternally inherited (PIP). The 27 women with a MIP belonged to 21 sibships (average 1.29 daughters, range 1–3 daughters), and the 32 women with a PIP belonged to 19 sibships (average 1.68