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.

ANNA MURRAY,[1] SARAH ENNIS,[2] AND NEWTON MORTON[2]

[1]*Wessex Regional Genetics Laboratory, Salisbury District Hospital, Salisbury, Wiltshire, United Kingdom; and* [2]*Human Genetics Research Division, Southampton University Hospitals Trust, Southampton, United Kingdom*

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Address for correspondence and reprints: Dr. Anna Murray, Wessex Regional Genetics Laboratory, Salisbury District Hospital, Salisbury, Wiltshire, United Kingdom SP2 8BJ. E-mail: a.murray@dial.pipex.com


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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

**Table 1**

**Characteristics of Women Carrying an FMR1 PIP or MIP and Their Noncarrier Relatives**

| Characteristic (Age Group) | Data for Premutation Carriers | | Data for Noncarriers |
|---|---|---|---|
| | PIP ($n$ = 32) | MIP ($n$ = 27) | ($n$ = 50) |
| Mean age, years | 39.18 ± 7.03 | 39.84 ± 12.89 | 39.20 ± 12.35 |
| Mean age at menopause, years | 36.50 ± 9.85 ($n$ = 13) | 34.67 ± 11.96 ($n$ = 9) | 50.67 ± 5.07 ($n$ = 9) |
| POF (⩾40 years) | 5/15 | 2/10 | 0/50 |
| POF (<40 years) | 4/17 | 3/17 | 0/50 |
| POF (all ages) | 9/32 | 5/27 | 0/50 |

daughters, range 1–5 daughters). Age at examination did not differ between the two groups (medians: MIP, 36.83; PIP, 38.875; $P$ = .5328 [Mann-Whitney test]). Among women with a MIP, five had experienced POF, and it occurred in nine women with a PIP, a difference that was not statistically significant ($P$ = .5411 [Fisher's exact test]). Age at menopause in the two groups did not differ either (medians: MIP, 38 [$n$ = 9]; PIP, 35 [$n$ = 13]; $P$ = 1.0 [Mann-Whitney test]) but were significantly lower than age at menopause among 50 of their relatives who carried normal alleles (median age: 51 years [$n$ = 9]; $P$ = .0014 [Kruskal Wallis test]). These results are summarized in table 1.

In conclusion, our data do not support the hypothesis of a parent-of-origin effect of the FMR1 premutation on ovarian function such that only the paternally inherited premutation is significantly associated with POF. The association of POF with PIP and MIP in one pedigree as shown by Vianna-Morgante et al. (1996) further denies an effect confined to paternally inherited premutation. The finding of a possible genomic imprinting effect, reported by Hundscheid et al. (2000), may be peculiar to the Dutch population. Otherwise the difference between theirs and the present survey may be the result of an undiagnosed ascertainment bias. Data on other populations are urgently needed, if only considering their implications for genetic counseling.

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Angela M. Vianna-Morgante
and Silvia S. Costa

*Departamento de Biologia*
*Instituto de Biociências*
*Universidade de São Paulo*
*São Paulo*

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Address for correspondence and reprints: Dr. Angela M. Vianna-Morgante, Departamento de Biologia, IB, Universidade de São Paulo, C. P. 11461, 05422-970 São Paulo, SP, Brazil. E-mail: avmorgan@ib.usp.br


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