Short report

A new folate sensitive fragile site at 1p21.3

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Nineteen rare, heritable fragile sites on human autosomes have been documented.¹ They are classified by their response to tissue culture conditions as folate sensitive, distamycin A (dist A) inducible, or bromodeoxyuridine (BrdU) inducible.¹ We have found a fragile site at 1p21.3 in two family members which meets the criteria for a rare, heritable, folate sensitive fragile site.^{2 3}

Whole blood lymphocyte cultures were established in Eagle's minimal essential medium without folic acid² and RPMI 1640 supplemented with 5% fetal bovine serum. Twenty-four hours before harvest, cultures were further supplemented with 10 mg/l and 300 mg/l thymidine, 0.05 mg/l fluorodeoxyuridine (FUDR), 75 mg/l dist A, 40 mg/l BrdU, or 0.1 mg/l aphidicolin (APC). Cultures were harvested using standard methods after one hour's exposure to 1 mg/l colchicine. Fifty unbanded metaphases were scored in each culture. The location of fragile sites was confirmed by destaining and G banding.

The fragile site was found in a 32 year old woman being investigated for recurrent miscarriages. She had had three first trimester miscarriages, the second two with her present partner whose first wife had three miscarriages before the birth of two normal children. Concurrent studies of her partner showed he was carrying a balanced translocation $t(1;9)(p34.3;q34.3)$. Chromosome analysis of fetal material from the most recent miscarriage showed the karyotype $46,XY,der(9),t(1;9)(p34.3;q34.3)$. This is the most probable cause of the reproductive problems experienced by the couple.

Family studies showed the same fragile site in the woman's physically and mentally normal 75 year old mother. The appearance of the fragile site is shown

in the figure. Lesions at the fragile site had the variety of appearances typical of rare fragile sites, that is, chromosome gaps and breaks, chromatid gaps and breaks, and triradial configurations.

Appearance of the fragile site: (a) chromosome break, (b) triradial configuration, (c) G banded chromosome pairs illustrating the location of the fragile site at 1p21.3.

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Frequency of expression of the fragile site under different conditions of culture.

	MEM-FA		RPMI 1640					
	No addn	10 mg/l thymidine	No addn	300 mg/l thymidine	0.05 mg/l FUdR	0.1 mg/l APC	40 mg/l BrdU	75 mg/l dist A
Daughter	17/50	0/50	2/50	11/50	22/50	—	0/50	0/50
Mother	7/50	—	0/50	4/50	11/50	2/50*	0/50	—
Father	0/50	—	0/50	—	0/50	0/50	0/50	—

*Resolution not sufficient to distinguish between fra(1)(p21.3) and fra(1)(p21.2).

The frequency of expression of the fragile site under various conditions of tissue culture is shown in the table. Fragile site expression was elicited in folic acid free medium, and in medium supplemented with FUdR and high levels of thymidine. Fragile site expression was suppressed in medium RPMI 1640 and by the addition of low levels of thymidine to the folic acid free medium and was not induced by dist A, BrdU, or aphidicolin. The common aphidicolin inducible fragile sites on 1p (p21.2, p22, and p31.2) were present at low levels of expression in the latter culture.

This is the first report of a heritable rare fragile site on chromosome 1. At 1p21.3 it is in close proximity to the common aphidicolin inducible sites at 1p21.2, 1p22, and 1p31.2 (FRA1E, FRA1D, and FRA1C) and could be confused with these. High resolution G banding studies of chromosomes of subjects showing a high level of fragility in this area should be performed. This new fragile site would have gene symbol FRA1M.

A lymphoblastoid cell line has been established in which the fragile site can be elicited by the addition of

FUdR. Fragile sites are useful physical markers in gene mapping as they provide anchor points for a linkage map.⁴ This cell line is available upon request.

Apart from FRAXA, which is associated with the commonest heritable form of mental retardation and which is the only rare, heritable fragile site on a sex chromosome, fragile sites do not appear to have any deleterious effect in heterozygotes. It is important, however, that new sites be documented with family studies so that rare instances of homozygosity could be detected and their clinical significance established.

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