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Heritable Fragile Sites on Human Chromosomes II. Distribution, Phenotypic Effects, and Cytogenetics

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SUMMARY

Individuals and families have been documented in which there are a number of fragile sites on chromosomes. These include sites at 2q11, 10q23, 11q13, 16p124, 16q22, 20p11, and Xq27 or 28. Fragile sites reported in the literature are compiled. The cytogenetics of the sites is discussed. The phenotypic effects of the sites are considered, and it is speculated that homozygosity of the autosomal sites might be deleterious as is hemizygosity of the site on Xq. These sites are used in the previous report which documents the effect of tissue medium components on their expression.

Since Dekaban [1] reported the first fragile site on the long arm of a C-group chromosome in 1965, there have been numerous reports of fragile sites on a variety of chromosomes. Lejeune [2] was the first to show that such sites were heritable when he described a site at 2q1 in a woman and her daughter. Most fragile sites have been regarded as normal variants. One, however, on the end of the long arm of the X chromosome has been shown to be a marker for one form of X-linked mental retardation [3, 4, 5].

Sutherland [6, 7] showed that the expression of fragile sites in lymphocyte culture was dependent upon the composition of the tissue culture medium used. The main factor necessary for expression of these sites is that the culture medium be deficient in folic acid and thymidine. This report documents families and individuals with fragile sites located at 2q11, 10q23, 11q13, 16p124, 16q22, 20p11, and Xq27 or 28. Lymphocytes from individuals in these families were used for the studies reported in the preceeding paper [7].

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MATERIALS AND METHODS

All lymphocyte cultures were set up and harvested as previously described [6]. In some cases Eagle's minimal essential medium (MEM) was used rather than medium 199, and the fetal bovine serum concentration was reduced to 5% in most cultures in the latter part of this study. Some cultures were grown in a special folic acid free MEM (MEM-FA), [7]. Bone marrow was collected directly in either MEM or medium 199 containing 1 μg/ml colchicine and harvested 2 hr later using the same method as for blood lymphocyte cultures (except that the exposure time to .075M KCl was 20 min). Lymphoblastoid cultures were established by the method of Pope et al. [8] except that they were cultured in medium 199 supplemented with 10% fetal bovine serum.

Skin fibroblast cultures were grown in medium 199 and harvested for chromosome studies using a standard trypsin method.

Until 1973 this Cytogenetics Unit used medium 199 for routine diagnostic work, and some families in this report had been detected prior to that time. Since late 1976, all diagnostic lymphocyte cultures have been grown in medium 199 and Ham's F10, and additional families ascertained. Institutionalized retarded males were screened by lymphocyte culture to detect individuals with a fragile site at Xq27 or 28. In routine diagnostic cultures 30 metaphases have been examined. At least 50 metaphases have been examined looking for fragile sites on the X. All data presented on the frequency of fragile sites are based on examination of at least 50 cells.

FAMILY STUDIES

Family F

This family (fig. 1*a*) has a fragile site at 2q1. The propositus was a severely retarded boy referred for chromosome study at 12 years as part of investigation of his retardation. He has no major physical malformations and no satisfactory explanation for his retardation has been found. Cytogenetic results have been described [6]. The chromosomal expressions of the fragile site are shown in figure 2.

Family Ay

This family (fig. 1*b*) has a fragile site on 10q23. The propositus was a 31-year-old retarded schizophrenic male referred for chromosome study as part of an investigation of his severe mental retardation of unknown origin. Cytogenetic results have been previously summarized for the propositus [6]. Different forms resulting from this fragile site are shown in figure 3.

Subject At

This girl has a fragile site at 11q13. At 11 years she was retarded, had epilepsy, and spastic quadriplegia. Her retardation was thought to be due to a combination of prematurity, maternal pre-eclamptic toxemia, and a neonatal convulsion. Initial cytogenetic studies in 1973 showed a fragile site to be present in 20% of cells examined. In 1977 the site was seen in 44% of cells cultured in medium 199. Extensive studies of her parents revealed no evidence of the fragile site. The appearances of this site are shown in figure 4.

Family D

This family (fig. 1*d*) has a fragile site at 16p124. The proposita was a 7-year-old girl with Laurence-Moon-Biedl syndrome and an ill-defined lymphoreticular malignancy. Her parents were nonconsanguineous. An older sister had died at 17 years

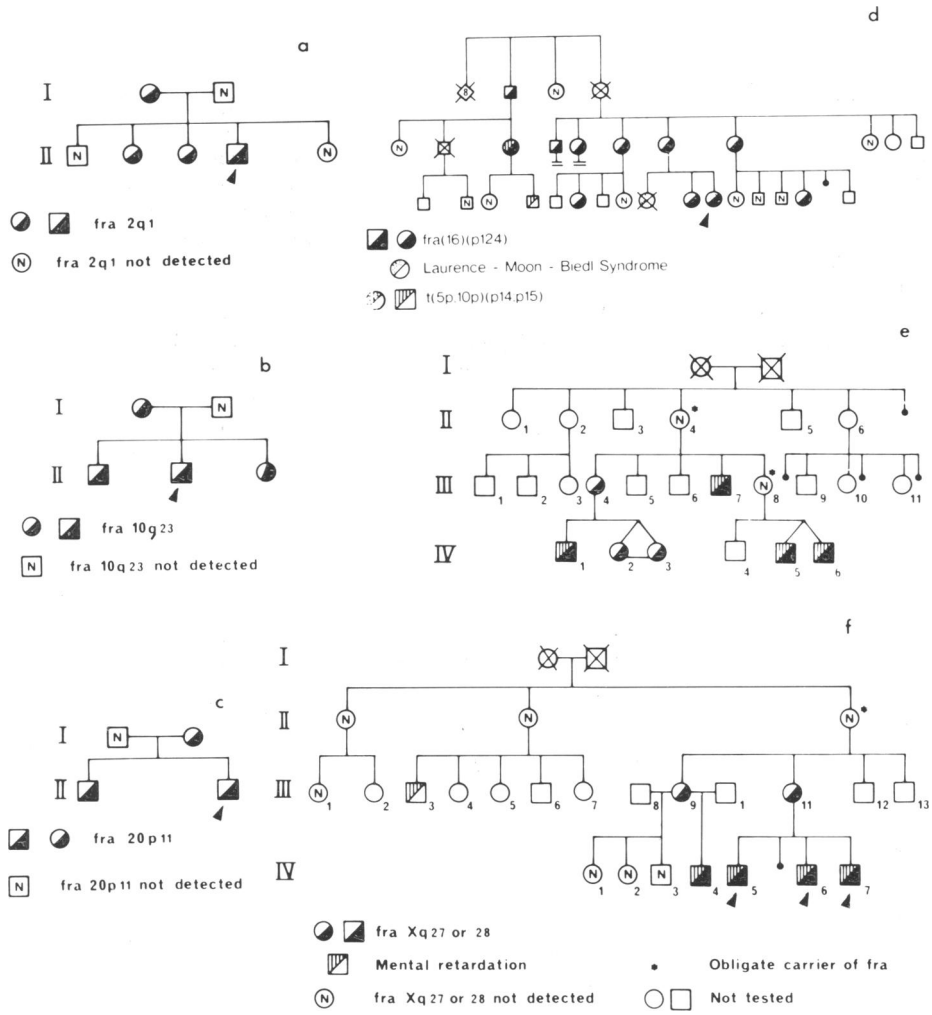

FIG. 1.—Family pedigrees: *a*, Family F; *b*, Family Ay; *c*, Family Mi; *d*, Family D, *e*, Family E; *f*, Family Ma. Note—symbols for *e* and *f* are the same.

from what appeared to be the same condition. The proposita is of normal intelligence and has responded well to standard leukemia remission induction therapy. The appearances of the fragile site are shown in figure 5.

Subject B

This 29-year-old mildly retarded male was detected in an institutional survey. He has fragile sites at 16q22 and Xq27 or 28. The cause of his retardation was unknown; he has no physical abnormalities. Family studies have not yet been carried out. The appearances of his fragile sites are shown in figure 6.

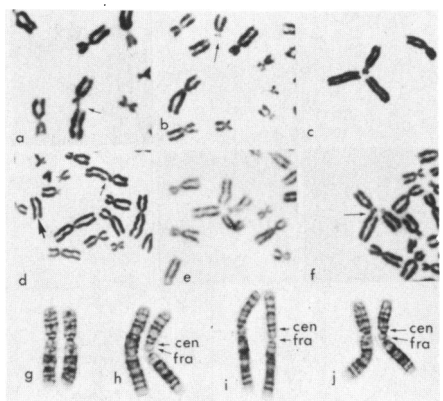

FIG. 2.—Appearances of the fragile site on 2q; *a*, single chromatid break; *b*, chromosome break; *c*, triradial configuration; *d*, single chromatid break (*small arrow*) and acentric fragment (*large arrow*) of $2q_1 \rightarrow 2qter$; *e*, quadriradial configuration; *f*, lesion at the fragile site from a skin fibroblast metaphase; *g–j*, G-banded chromosomes showing the break point for the site at 2q at the distal end of 2q11; *g*, no lesion at fragile site; *h–j*, chromosome gaps at the fragile site.

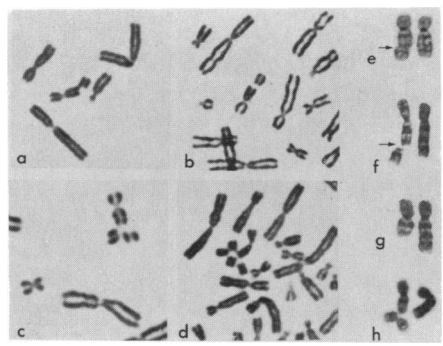

FIG 3.—Appearances of the fragile site on 10q; *a*, single chromatid break; *b*, chromosome break; *c*, triradial configuration; *d*, pentaradial configuration; *e* and *f*, G-banded chromosomes showing break point at the distal end of band 10q23; *g*, G-banded chromosome showing deletion of the chromosome distal to the fragile site; *h*, G-banded triradial configuration.

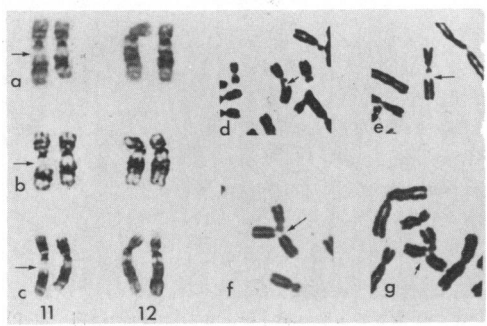

FIG 4.—Appearances of the fragile site at 11q13; *a–c*, G-banded chromosomes 11 and 12 showing the site in the proximal part of 11q13; *d*, single chromatid break at the site; *e*, chromosome break at the site; *f* and *g*, triradial configurations.

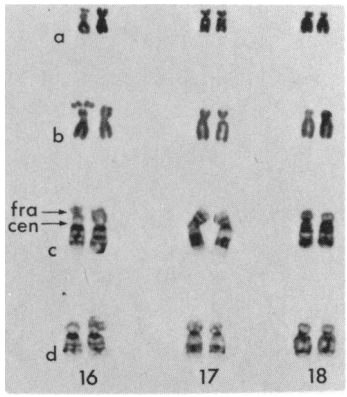

FIG. 5.—E-group chromosomes from cells with a lesion on 16p; *a*, chromosome gap; *b*, triradial configuration; *c*, G-banded chromosomes showing fragile site at band 16p124; *d*, G-banded chromosomes showing deletion of material distal to the fragile site.

Family Mi

This family (fig. 1*c*) has a fragile site on 20p11. The propositus was a profoundly retarded 6-year-old boy who was referred for chromosome studies. His retardation is presently regarded as being due to CNS degeneration of unknown cause despite intensive investigation. Results of cytogenetic studies on the propositus and his normal brother have been recorded [6]. The appearances of the fragile site are shown in figure 7.

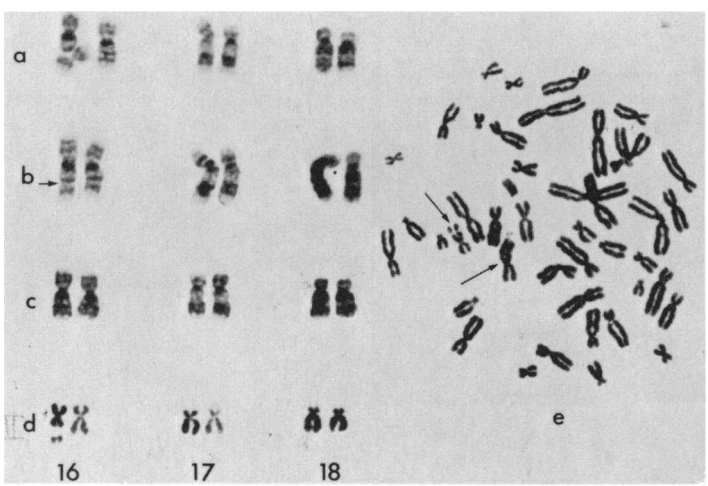

FIG. 6.—E-group chromosomes from cells with a lesion at the proximal end of band 16q22; *a*, G-banded triradial configuration; *b*, G-banded chromosome showing lesion (*arrow*) at 16q22; *c*, C-banded chromosomes from a metaphase not showing a lesion; *d*, unbanded chromosomes showing chromosome break at the fragile site; *e*, metaphase showing lesions at fragile sites at 16q22 and Xq27 or 28.

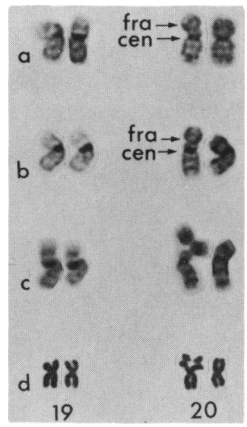

FIG. 7.—Appearance of the fragile site on 20p; *a–c*, G-banded chromosomes showing the site at band 20p11; *d*, unbanded F-group chromosomes showing triradial configuration resulting from the fragile site.

Family Ma

This family (fig. 1*f*) has a fragile site at Xq27 or 28. The propositi were three mildly retarded boys who are their parents only children. They were ascertained as part of a search for families with possible X-linked mental retardation. Cytogenetic data on this family have been given in [6] and are shown in more detail in table 1. Appearances of the fragile site are shown in figure 8.

Family E

This family (fig. 1*e*) also has a fragile site at Xq27 or 28. The propositi were mildly retarded twin boys. They were referred for chromosome study because the family was thought to be one in which there was X-linked mental retardation. The appearance of the fragile site is identical to that in family Ma. Cytogenetic data are shown in table 1.

DISTRIBUTION OF FRAGILE SITES

The fragile site at 2q1 was the first to be shown to be heritable [2]. Since then there have been numerous reports of individuals and families with this site which have recently been reviewed [9]. Conen and Erkman [10] recorded a child with Down syndrome and leukemia who showed breakage in the short arm of chromosome 2 near the centromere in a number of cells. Parental chromosomes were not studied; a fragile site at this location must therefore await confirmation. Similarly, Tartaglia et al. [11] reported a patient with congenital erythroid hypoplasia who had an achromatic lesion in the middle of one arm of chromosome 1. The lesion appeared to affect only one chromatid, and the published karyotypes show its position to vary. Parental chromosomes were not studied. It is unlikely that they had a patient with a heritable fragile site as previously defined [7]; Bühler et al. [12] were also of this opinion.

Brøgger [13] reported a mentally retarded boy with a gap in the middle of one arm of chromosome 3 which appeared to be fragile. This appeared to affect one chromatid

TABLE 1

FREQUENCY OF FRAGILE SITE AT Xq27 OR 28 IN LYMPHOCYTE METAPHASES

Subject	Culture medium	Proportion of cells with fragile sites
Family Ma:		
II 2	199	0/30
II 3	199	0/100
	MEM-FA	0/100
III 9	199	7/50
	MEM-FA	30/200
III 10	199	5/50
IV 4	199	18/50
	MEM-FA	51/100
IV 5	199	7/50
IV 6	199	1/50
IV 7	199 (1st culture)	8/50
	199 (2nd culture)	5/50
	MEM-FA	15/50
Family E:		
II 4	199	0/50
III 4	199	1/40
III 7	199	5/50
III 8	199	0/50
IV 1	199	4/50
IV 2	199	8/100
IV 3	199	9/50
IV 5	199 (1st culture)	10/50
	199 (2nd culture)	16/50
IV 6	199 (1st culture)	0/50
	199 (2nd culture)	10/50

more often than both and in some cells was present on both number 3 chromosomes. Parental chromosomes were normal. It is unlikely that this report concerned a heritable fragile site.

A number of C-group chromosomes with fragile sites reported prior to chromosome banding have been reviewed by Giraud et al. [4]. They were the first to specifically identify such C-group chromosomes and reported fragile sites at 10q242 and 12q13. The present report of a site at 10q23 probably involves the site Giraud et al. [4] reported to be at 10q242. They used R-banding, whereas G-banding has been used in this report suggesting that the site is near the distal end of band 10q23. Savage [14] has drawn attention to discrepancies in breakpoint localization when different banding methods are employed.

There have been reports of abnormal fragility in the C-band heterochromatin of chromosome 9 [15, 16, 17]. The karyotypes published by Fraccaro et al. [16] suggest that chromosome 11 or 12 is more likely to be involved. Two other reports are more convincing about identification of chromosome 9, although in the absence of banding, this remains uncertain. Neither case showed multiradial chromosomes resulting from the fragility in chromosome 9. Further study is necessary before the possibility of a fragile site in or adjacent to the C-band on chromosome 9 can be confirmed. The fragile site at 11q13 is the first recorded at this location. There are few positively identified paracentric fragile sites on C-group chromosomes. Giraud et al. [4] recorded two cases

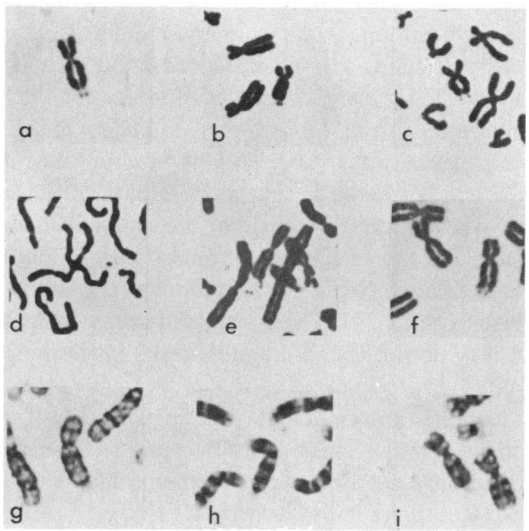

FIG. 8.—Appearances of the fragile site on Xq; *a–c*, usual "satellited" appearance in metaphase chromosomes; *d*, appearance in prophase; *e* and *f*, "double satellited" appearance equivalent to triradial configuration; *g–i*, G-banded chromosomes show the fragile site on the very distal end of Xq.

involving chromosome 12, and McCreanor (personal communication, 1977) has studied a family in which such a fragile site is segregating. This site at 12q13 is the only well established fragile site which has not been available for study in this laboratory. There is only one previous report [18] concerning a site on 16p in a man who also appeared to have a translocation involving chromosome 18; his parents were not studied. The present report shows that a fragile site on 16p is certainly heritable. A large kindred in which a chromosome with a fragile site at 16q22 was segregating without apparent phenotypic effect has been documented [19]. A further six individuals, of whom two were father and son, with this fragile site have been recorded [4]. Drets et al. [20] recorded a family in which several members had one chromosome 16 replaced in a proportion of their cells by what appeared to be a chromosome 16 with a greatly lengthened long arm, and a fragile site near its mid-point. This fragile site is certainly heritable, but without chromosome banding its origin and location remain unknown.

The site on 20p11 has not been previously described. Apart from the family in this report, another unrelated and less well-documented family is known with the same site.

The site on the distal end of Xq was first described by Lubs [3], shown to be heritable, and its association with mental retardation recorded. Harvey et al. [5] confirmed this site as a marker for one form of X-linked mental retardation. The two families recorded here further document this association. Other retarded males with this site, such as subject B, have been detected, and other families not included in this report are known.

The well-documented and potential fragile sites are summarized in figure 9. Chromosome 17 is not included in this summary and requires further discussion. This chromosome undoubtedly contains a heritable constriction on the short arm which gives rise to its so-called satellited appearance in some families [21, 22]. It has also been reported in homozygous form in a normal woman [23]. This chromosome behaves differently in several ways from all the fragile sites which have been examined. It appears not to be fragile in that the satellites do not appear to separate from the chromosome as a minute fragment, nor are double satellited chromosomes (equivalent to the triradials of the fragile site chromosomes) produced. This satellited appearance is not dependent upon conditions of culture as are all the other fragile sites studied (except for that at 16q22 [7]). These satellited chromosomes are undoubtedly heritable variants, but they do not have a fragile site as this term applies to the other chromosomes discussed [7].

There is virtually nothing known about the frequency of fragile sites in the population. Most neonatal surveys aimed at establishing frequencies of chromosome abnormalities and variants have not used culture medium suitable for the demonstration of fragile sites. Furthermore, such surveys have been based on the examination of a very small number of cells, usually two, per individual. Consequently, even if fragile sites were expressed, they would not always be detected. The only fragile site detected in a neonatal survey [24] was one in a C-group chromosome (probably an 11 or 12) in one infant out of 3,543 studied. None of the infants in this survey had any phenotypic abnormality.

Fragile sites have not been reported in other species, possibly due to the relatively few individuals usually studied. White [25] reported a type of fragile site in a meiotic study of an undescribed species of morabine grasshopper. Breakage occurred at a specific locus during first premetaphase in all cells examined from a single individual but not in the remaining members of the species studied. Fragile sites in man have not been studied in meiosis.

CYTOGENETICS

The cytogenetics of fragile sites has been discussed in some detail [26, 27, 28]. The most striking appearance of the sites is the multiradial configurations. These were

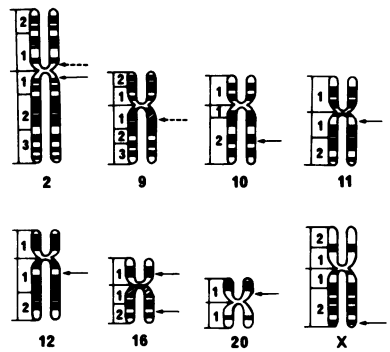

FIG. 9.—Known fragile sites. *Solid arrows* indicate well established fragile sites, and *broken arrows* indicate sites for which definitive evidence is lacking.

originally claimed by Lejeune [2] to be the result of selective endoreduplication. Others [26, 27] have suggested that they could be due to nondisjunction of an acentric chromatid following breakage at the site. This suggestion has been confirmed [28, 29] using BrdU incorporation and differential sister chromatid staining. The term "branched chromosomes" has been used to refer to such multiradials [27].

Lubs [3] studied DNA replication by autoradiography in a female with a site at Xq27 or 28 and found that the X with the fragile site did not appear to be selectively inactivated. Fraccaro et al. [30] similarly studied a site at 2q1 and noted that in most cells there was no detectable asynchrony in DNA synthesis between homologs. In one cell they found a triradial with the whole section distal to the fragile site late labeling and despiralized. Nöel et al. [28] recorded a number of such chromosomes with despiralization distal to the fragile site. Such chromosomes have been seen occasionally in the present study but not at the frequency recorded by Nöel et al. [28].

TISSUE OF ORIGIN OF CHROMOSOMES

Fragile sites in the present study were found almost exclusively in blood lymphocyte cultures. There was limited opportunity to examine bone marrow chromosomes. Bone marrow from a male with a site at Xq27 or 28 did not show a single fragile site in 200 metaphases. Blood lymphocytes cultured at the same time expressed the site in 10% of cells in medium 199, and 30% in MEM-FA. Similarly, bone marrow from a carrier of a site at 16p12 showed no evidence of the site in 60 metaphases, but it was present in 46% of metaphases from blood lymphocytes collected at the same time and cultured in medium 199. Magenis et al. [19] found the site on 16q in two of 41 metaphases from bone marrow. Dr. H. R. McCreanor (personal communication, 1977) found the site on 2q in 36 out of 168 bone marrow metaphases. Other reports do not mention the study of bone marrow chromosomes.

Skin fibroblast cultures were established from individuals with the following fragile sites: 2q1, 10q23, 11q13, 16q22, 20p11 and Xq27 or 28. Fragile sites were rarely identified in these fibroblast cultures even when grown in medium 199, as shown in table 2. Fraccaro et al. [16] could not detect a fragile site at 2q1 in fibroblast cultures, and Magenis et al. [19] could not detect the site on 16q in 165 metaphases from fibroblast culture. Ferguson-Smith [26] found the site at 2q1 in fibroblast culture but at

TABLE 2

FREQUENCY OF FRAGILE SITES IN SKIN FIBROBLAST CULTURES, MEDIUM 199

Site	Proportion of cells with fragile sites
2q1	2/50
10q23	0/50
11q13	2/50
16q22 (Subject B)	0/100
20p11	1/50
Xq27 or 28 (Family Ma)	0/50
Xq27 or 28 (Family E)	0/50
Xq27 or 28 (Subject B)	0/100

a lower frequency than in lymphocyte cultures. Dekaban [1] presented data on skin fibroblast culture which suggested that the site was not present in this material. The reasons why some authors can detect fragile sites in fibroblast cultures and others cannot remain unknown. However, in view of the strong dependence of their expression in lymphocyte cultures on the culture conditions, this is not surprising.

Transformed lymphocyte cultures were established from individuals with fragile sites at 2q, and Xq27 or 28. No expression of the fragile site was seen in either case in 50 cells examined. No other authors have examined such cultures from individuals with fragile sites.

PHENOTYPIC EFFECTS OF FRAGILE SITES

No abnormal phenotype is associated with the autosomal fragile sites. Many of these sites were detected in abnormal individuals, but probably this only reflects the type of person undergoing chromosome analysis. Williams and Howell [9] suggested that breakage at the fragile site in vivo could give rise to a variety of aneuploid cell lines leading to abnormal development. While this appears possible, there is little evidence that fragile sites are expressed in vivo; indeed, they may be artefacts of tissue culture. The variety of phenotypic abnormalities associatied with the sites suggests that they are without phenotypic effect in the heterozygote. By analogy with mutant reciprocal translocations which can be associated with phenotypic abnormality [31], when a fragile site newly arises it might produce an abnormal phenotype. There is no reliable evidence in the literature regarding fragile sites which are new mutants. Several authors found no fragile sites in the parents of their index cases, but because of the previously unknown dependence of these sites on culture conditions, such findings cannot be regarded as definite evidence of mutation. The retarded girl described in this report with a fragile site at 11q13 appears to be a mutant, although paternity has not been checked, and the cause of her mental retardation is largely conjectural.

The fragile site on Xq is undoubtedly a marker for one form of X-linked mental retardation. This was first shown by Lubs [3] for one family and subsequently by Harvey et al. [5] in four more families; this group has since detected several additional such families (Weiner, personal communication, 1977). Giraud et al. [4] described a number of retarded males with this fragile site. Two families are documented in the present report, and several others are currently being studied as a result of screening 203 institutionalized retarded males for fragile sites. Among these, five (two are brothers) with fragile sites at Xq27 or 28 were identified. This condition is apparantly not rare, but because the appearance of the fragile site is not spectacular, and in some instances is expressed in only a small proportion of metaphases, and because lymphocytes must be cultured in specific types of culture medium, it has gone largely unrecognized. The nature of the association between the fragile site and the mental retardation remains obscure. Not all families with X-linked mental retardation show the fragile site. It may be that demonstration of the site in some families is more difficult than in others. Even in those retarded males studied, the proportion of metaphases in which the site is expressed ranged from less than 5% up to more than 30%. There is, however, no reason why X-linked mental retardation could not be a group of different conditions, only one of which is associated with the fragile site.

The fragile site on Xq is associated with mental retardation in the hemizygote but not the heterozygote. This would allow the speculation that homozygosity for the autosomal folic acid sensitive fragile sites would lead to an abnormal phenotype. Such homozygosity has not been reported, although a normal female homozygous for a "satellited" chromosome 17 has been recorded. Rare autosomal recessive disorders should be reexamined chromosomally as some may be due to homozygosity for fragile sites.

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REFERENCES

1. DEKABAN A: Persisting clone of cells with an abnormal chromosome in a woman previously irradiated. *J Nucl Med* 6:740–746, 1965
2. LEJEUNE J, DUTRILLAUX B, LAFOURCADE J, BERGER R, ABONYI D, RETHORÉ MO: Endoréduplication sélective du bras long du chromosome 2 chez une femme et sa fille. *C R Acad Sci (Paris)* 266:24–26, 1968
3. LUBS HA: A marker X chromosome. *Am J Hum Genet* 21:231–244, 1969
4. GIRAUD F, AYME S, MATTEI JF, MATTEI MG: Constitutional chromosomal breakage. *Hum Genet* 34:125–136, 1976
5. HARVEY J, JUDGE C, WIENER S: Familial X-linked mental retardation with an X chromosome abnormality. *J Med Genet* 14:46–50, 1977
6. SUTHERLAND GR: Fragile sites on human chromosomes: Demonstration of their dependence on the type of tissue culture medium. *Science* 197:265–266, 1977
7. SUTHERLAND GR: Heritable fragile sites on human chromosomes I. Effect of composition of culture medium on expression. *Am J Hum Genet* 31:125–135, 1979
8. POPE JH, HORNE MK, SCOTT W: Transformation of foetal human leukocytes *in vitro* by filtrates of a human leukaemic cell line containing Herpes-like virus. *Int J Cancer* 3:857–866, 1968
9. WILLIAMS AJ, HOWELL RT: A fragile secondary constriction on chromosome 2 in a severely mentally retarded patient. *J Ment Defic Res* 21:227–230, 1976
10. CONEN PE, ERKMAN B: Combined mongolism and leukaemia. *Am J Dis Child* 112:429–443, 1966
11. TARTAGLIA AP, PROPP S, AMAROSE AP, PROPP RD, HALL CA: Chromosome abnormality and hypocalcaemia in congenital erythroid hypoplasia (Blackfan-Diamond syndrome). *Am J Med* 41:990–999, 1966
12. BÜHLER EM, LUCHSINGER U, BÜHLER UK, MÉHES K, STADLER GR: Non-condensation of one segment of a chromosome no. 2 in a male with otherwise normal karyotype (and severe hypospadias). *Humangenetik* 9:97–194, 1970
13. BRØGGER A: Virus som arsak til kromosomaberrasjoner hos menneske. *Tidsskr Nor Laegeforen* 88:1741–1747, 1968
14. SAVAGE JRK: Assignment of aberration breakpoints in banded chromosomes. *Nature* 270:513–514, 1977
15. SCHMID W, VISCHER D: Spontaneous fragility of an abnormally wide secondary constriction region in a human chromosome no. 9. *Humangenetik* 7:22–27, 1969
16. FRACCARO M, HANSSON K, LINDSTEN J, TIEPOLO L: Specific instability of the paracentric region of chromosome number 9 in a normal woman and her mongoloid son. *Ann Génét* 14:149–152, 1971
17. REEVES BR, LAWLER SD: Preferential breakage of sensitive regions of human chromosomes. *Humangenetik* 8:295–301, 1970
18. DAY EJ, MARSHALL R, MACDONALD PAC, DAVIDSON WM: Deleted chromosome 18 with

paternal mosaicism. *Lancet* 2:1307, 1967
19. MAGENIS RE, HECHT F, LOVRIEN EW: Heritable fragile site on chromosome 16: probable localization of haptoglobin locus in man. *Science* 170:85–87, 1970
20. DRETS ME, CARDOSO JH, DELFINO AH, CARRAU J: Familial normal/partial trisomy 16 with selective endoreduplication in malformed proband. *Cytogenetics* 9:333–350, 1970
21. EMERIT I, DEGROUCHY J, VERNANT P, CORONE P: Chromosomal abnormalities and congenital heart disease. *Circulation* 36:886–905, 1967
22. SCHMID E, BAUCHINGER M: Structural polymorphism in chromosome 17. *Nature* 221:387–388, 1969
23. BERG JM, FAUNCH JA, PENDREY MJ, PENROSE LS, RIDLER MAC, SHAPIRO A: A homozygous chromosomal variant. *Lancet* 1:531, 1969
24. GERALD PS, WALZER S: Chromosome studies of normal newborn infants, in *Human Population Cytogenetics*, edited by JACOBS PA, PRICE WH, LAW P, Edinburgh Univ Press 1970, pp 143–151
25. WHITE MJD: A case of spontaneous chromosome breakage at a specific locus occurring at meiosis. *Aust J Zool* 14:1027–1034
26. FERGUSON-SMITH MA: Inherited constriction fragility of chromosome 2. *Ann Génét* 16:29–34, 1973
27. FORD CE, MADAN K: Branched Chromosomes. An alternative to the hypothesis of selective endoreduplication, in *Chromosome Identification, Nobel Symposium 23*, edited by CASPERSSON T, ZECH L, New York and London, Academic Press, 1973, pp 98–103
28. NOËL B, QUACK B, MOTTET J, NANTOIS Y, DUTRILLAUX B: Selective endoreduplication or branched chromosome? *Exp Cell Res* 104:423–426, 1977
29. FERGUSON-SMITH MA: Human chromosome polymorphism. *Rec Adel Child Hosp* 1:278–286, 1977
30. FRACCARO M, LINDSTEN J, TIEPOLO L, RICCI N: Instability of the paracentric region and selective reduplication of chromosome 2 in man. *Chromosomes Today* 3:138–146, 1972
31. JACOBS PA: Correlation between euploid structural chromosome rearrangements and mental subnormality in humans. *Nature* 249:164–165, 1974