Clinical features and reproductive patterns in fragile X female heterozygotes

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SUMMARY Clinical findings are presented on 113 fragile X female heterozygotes from 44 families, based on physical examination, behavioural assessment, and reproductive history. In 85% of a subsample of 92 adult females non-verbal IQ score derived from the Block Design test was 85 or less. Verbal ability deficits were much less common. Typical facial characteristics, irregular teeth, and hypermobility of finger joints occurred in approximately 40% of adult females, but facial abnormalities were less common in children. Some physical anomalies and the level of intellectual impairment were, in adult carriers, associated with the presence of fragile X sites. The commoner physical anomalies or typical facial characteristics and intellectual abilities differed significantly between the known female heterozygotes and their 40 presumed normal relatives.

Frequency of miscarriages was increased in fragile X females; in spite of this, a moderate increase in the number of children has been encountered in female carriers with borderline intellectual impairment. This important problem has genetical implications and needs further investigation.

The importance is emphasised of a more detailed clinical examination of the females at risk in fragile X families.

A comprehensive clinical survey of 125 fragile X female carriers, undertaken by Fryns,¹ was an innovation in clinical studies of this condition. We independently performed a similar study of 113 female heterozygotes, encountered in 44 investigated fragile X families, with generally consistent results. Preliminary results of this study have been published.² In this paper we extend two particularly important conclusions from the Fryns study by additional data from our investigation which involved much more precise physical and behavioural measures than in the study of Fryns.¹ These particular conclusions are as follows.

- (1) "... At the present time we strongly recommend careful clinical examination of the female relatives of fra(X) males. This seems to provide valuable and definite information with regard to the carrier status in individual women. . .".
- (2) "... Fragile X carriers have a high fertility which is even higher in the mentally subnormal patients. . .".

Materials and methods

One hundred and thirteen fragile X females from 44 families were ascertained mainly through probands admitted to genetic counselling clinics (25 families), or through retarded sibs screened for fragile X in special institutions or workshops (13 families). The further five families were ascertained through a single retarded male in a special institution (two) or workshop (three) and one family was diagnosed through a slow learning boy, referred for cytogenetic testing by his school teacher.

The standard procedure was to contact families of all the probands, visit them at home, take a detailed family history, and test those affected as well as unaffected male and female relatives who were available and willing to participate in our study. As in the Fryns survey,¹ family investigations of the proband's female or male relatives involved as many family members as possible. That is to say, we proceeded from a proband and his (or her) sibs to their mother, mother's sibs and their parents, and to their more distant relatives, if they were available and possibly affected with this condition. Thus, our sample of female heterozygotes has been as com-

pletely ascertained as is feasible at this time. Fragile X positive subjects or fragile X negative obligate carriers are both listed as carrier females (or female heterozygotes). Their 40 fragile X negative and apparently normal female relatives are also included for comparative purposes. The whole sample of females obtained from fragile X families thus consists of 153 subjects including 91 adult carriers, 22 child carriers, 26 adult 'normal' relatives, and 14 child relatives. In addition, we included data on the number of offspring and miscarriages obtained from a random sample of 107 Australian adult females matched for age, ethnic origin, and socioeconomic status as described by Loesch *et al.*³ This sample was also used to obtain normal data on facial measurements.

The results of the following testing procedures are presented.

(1) Clinical assessment was based on physical examination, especially recording any major or minor abnormalities, and those unusual facial features commonly encountered in fragile X males. In at least 50% of female subjects clinical investigation was performed without previous knowledge of the result of the cytogenetic test. In all females who were not obviously retarded the clinician (DZL) was not aware of the results of their psychological assessment at the time of physical examination. We also report information obtained on the number of offspring and frequency of miscarriages. Moreover, several facial measurements, including bizygomatic, bigonial, nose breadth and height, upper and total face height, jaw length, and ear height and breadth, were performed using sliding and spreading calipers. All the measurements were adjusted for age and size and a detailed description of methods has been given elsewhere.³

(2) Psychological assessment was based on the Peabody Picture Vocabulary Test (PPVT) and the Block Design test (BD). PPVT is a vocabulary test and BD a measure of non-verbal ability⁴ and their use with fragile X is justified in Loesch *et al.*⁵ and Theobald *et al.*⁶ as is the classification of the degree of retardation for each test separately rather than based on an overall IQ score. Fryns¹ gives no indication of the form of psychological assessment used with their sample of female carriers and refers only to overall IQ scores. But evidence is increasing⁵⁻⁷ that fragile X males and females are characterised mainly by non-verbal deficits, so that overall IQ scores may overestimate their competence. Although our intellectual assessment is more extensive than just these two tests,⁶ PPVT and BD are sufficient measures of verbal and non-verbal ability respectively⁴ in the present context. Here the major concern is the relationship of ability measures to

physical features and to reproduction rather than the psychological profile of female carriers. Thus tests are needed which encompass the range of abilities and the two psychological studies of such carriers^{6,7} indicate vocabulary (PPVT) and BD are respectively among the best and worst features of their cognitive profile. Two forms of the Block Design test were used, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) version for the very few with mental age <6.5, and the British Ability Scales version (BAS) for the others. All results were standardised using the published test norms and for the purposes of comparison converted to the equivalent of IQ scores with mean 100.

Cytogenetic tests in our female subjects and their relatives were performed at the Murdoch Institute, Royal Children's Hospital, Melbourne, or at the Cytogenetics Unit, Department of Histopathology, Adelaide Children's Hospital. In Melbourne, lymphocytes were cultured in Hepes buffered medium 199 with 13% fetal calf serum. Scoring of the fragile X was from G banded slides only.⁸ In Adelaide, at least two methods of fragile X induction were used, one being culture in MEM-FA and the other being the use of either trimethoprim or FUDR in RPMI 1640⁹ and at least 50 metaphases were examined for each type of induction.

Results

CLINICAL CHARACTERISTICS OF THE CARRIER FEMALES

The level of intellectual performance and the presence or absence of fragile X positive cells are presented in table 1, separately for adults and children. Using Fryns's cut off of IQ 85 or less, subnormal intelligence as assessed by the PPVT score occurred in 47.5% of both adult females and children, which is somewhat higher than Fryns's 34% assessed by overall IQ scores. However, PPVT correlates only 0.7 with general IQ. An unprecedentedly high proportion (85%) of subjects with lowered non-verbal IQ (not specifically assessed in Fryns's study) is consistent with the disparity between levels of verbal and non-verbal performance, especially in adult females, noted before.⁵⁻⁷ Considering the fact that the fragile X chromosome could be shown in not more than 57% of adult females, the results of non-verbal assessment appear to be a more important indication of carrier status than cytogenetic tests. The appreciable difference in percentage of fragile X positive subjects between adults and children is clearly related to ascertainment bias, as previously postulated by Turner and Jacobs¹⁰: children can only be classified as fragile X if they are fragile X positive or if they have a

TABLE 1 Fragile X females: cytological and intellectual characteristics.

	91 adults (mean age=41.3, SD=11.0)			22 children (mean age=11.0, SD=4.0)		
	No	Mean	SD	No	Mean	SD
Percentage of fra(X) cells						
PPVT	90	9.4	13.8	22	14.4	10.1
BD	80	82.9	31.3	20	83.6	32.1
	81	62.3	30.8	19	69.5	32.3
Fragile X positive (%)		56.7			95.5	
Range of IQ scores (%)						
	PPVT			PPVT		
	BD			BD		
<85	52.5			50.0		
<85 >70	13.8			30.0		
Below normal						
<70 >45	23.8			15.0		
Retarded						
<45	10.0			5.0		
	47.6			20.0		
	33.8			50.0		
	85.0			36.8		
	60.0			10.5		
	15.0			31.6		
	25.0			31.6		
	25.0			26.3		
	35.0			68.4		

PPVT=Peabody Picture Vocabulary Test, BD=Block Design.

carrier father. We also found a much stronger relationship between the degree of impairment in non-verbal abilities, assessed by the BD test, and the presence or absence of fragile X cells ($\chi^2_3=11.38$ in adult females and 12.00 in children, both $p<0.01$) than between verbal performance and fragile X manifestation ($\chi^2_3=7.85$, $p<0.05$ and 3.45, $p>0.05$ respectively).

The occurrence of the commonest minor malformations or unusual features in our sample of fragile X females is summarised in table 2, separately for adults and children. For comparison, frequencies are given for their apparently non-fragile X female relatives. The frequency of 'typical' facial manifestations (fig 1), contrasting with normal facial appearance, is fairly close to that reported by Fryns¹ (37.4% and 28%, respectively). The somewhat lower proportion of females with the facial manifestations reported in the Fryns study may be partly attributed to the fact that we separated adult women from children among whom, as table 2 indicates, these features are less frequent. The difference between affected children and adults presumably relates to changes in facial appearance during growth and maturation and should be accounted for in considering carrier status in young girls. We have encountered similar differences in frequencies of several, especially facial, characteristics, between fragile X adults and children in the male sample from the same families (unpublished data).

We also included those individual features which largely contribute to the characteristic facial appearance in fragile X subjects, such as long, prominent chin, long and narrow face, bulbous nose, and abnormalities of size and shape of the ears. Some of these apparently subjective features have been verified by the measurements. Jaw length was strikingly increased in fragile X females as compared with the normal sample, and the upper face height was considerably decreased. The impression of an oblong face with long chin and prominent nose may thus be attributed to the combination of these two deviations. In addition, nose breadth was somewhat increased, but the difference was only marginally significant. The average ear height was unchanged, but the average ear breadth was decreased. Clearly these two particular measurements averaged across the group are diagnostically less valid than simple inspection, which revealed the presence of abnormally large but also of abnormally small ears in nearly 40% of fragile X females (table 2). A more comprehensive discussion of the deviation in body measurements and their diagnostic significance has been given elsewhere.³

Table 2 also gives frequencies of some other minor malformations such as malpositioned teeth,

high arched or narrow palate or both, hypermobility of finger joints, and dysmorphic features of fingers. Speech impediment occurred mainly in the form of faltering articulation. Frequencies of some of these traits reach 40% and exceed more than 10 times their estimated population incidence.^{11 12} Compared with their 'normal' relatives, the frequencies of typical facial features, dysmorphic ears, hypermobility of finger joints, and speech impediment are also appreciably higher in fragile X females, especially the adults. This is in spite of the fact that some proportion of the apparently normal female relatives, especially children, must be undetected fragile X.¹³ At the same time, facial features and anomalies of the ear occurred significantly more often in those female carriers with fragile X present than in fragile X negative carriers (table 2), but the fact that in nearly half of the subjects the investigator was aware of cytogenetic results may have influenced the interpretation of physical features.

The degree of relationship between unusual physical characteristics and the level of intellectual performance (table 3) may be somewhat over-

estimated by a similar process. However, in our study this would have applied only to rare instances of obvious mental retardation.

Our data also include the relationships between various aspects of physical expression of fragile X based on the χ^2 test. The occurrence of typical features of the face, such as long chin and long, narrow face, were associated with high arched and narrow palate. Another observed association was between abnormal palate and malpositioned teeth. The association between speech impediment and malpositioned teeth (within the teeth-speech-palate cluster) indicates that faltering articulation such as is encountered in some females may be determined by changes in the oral bone structures. Hypermobility of finger joints was not associated with any of the above traits. Nevertheless, significant occurrence of any of these traits still represents independent information to a considerable extent, especially as the strength of the associations may have been overestimated by the previously discussed possibility of interpreting some physical features in the context of presence of the other. This implies that the

TABLE 2 Percentage frequencies of some physical characteristics in fragile X females and in their female relatives. Adults and children are considered separately.

Variables	Adults		Children	
	Fragile X	Relatives	Fragile X	Relatives
<i>Skull</i>	N=90	26	20	14
Flat occiput	12.1°	7.1°	14.0*	0.0*
<i>Face</i>	N=90	26	21	14
'With typical features'	37.4°‡	3.6°	14.3°	7.1°
<i>Specific features</i>				
Long, prominent chin	38.2°	14.3°	10.0*	14.3*
Long face and/or narrow face	32.6°	7.1°	10.0*	0.0*
Long nose	38.4°	10.7°	0.0*	0.0*
Very asymmetrical face	30.0°	10.7°	15.0*	7.1°
<i>Ears</i>	N=91	26	21	14
Large, microtic, abnormally shaped	38.5†	25.0	28.6	7.1
<i>Teeth</i>	N=54	26	21	14
Malpositioned	40.7	21.4	52.0	21.4
<i>Palate</i>	N=69	21	21	14
High arched, narrow, or both (cleft in 1 case included)	40.5	29.1	38.1	21.4
<i>Limbs</i>	N=90	21	21	14
Hypermobility of finger joints	40.0*	14.3°	52.4*	28.6*
Dysmorphic features of fingers‡	32.1	25.0	9.6	28.5
Flat feet	19.1	17.9	19.0	14.3
<i>Epilepsy</i>	N=91	26	20	14
	7.8	0.0	5.0	0.0
<i>Speech impediment</i>	N=87	26	20	14
	24.1°	3.8°	10.0°	0.0*

Underlined values are significant ($p < 0.05$) differences in frequency as compared with 'normal' relatives.

*Significant difference in frequency if fragile X adults and children combined are compared with all non-fragile X female relatives.

†Significant difference between fragile X positive and fragile X negative subsamples (adults only, as only one case in the sample of carrier children was fragile X negative).

‡Includes clinodactyly of fifth fingers, syndactyly, brachydactyly, arachnodactyly, shortening of fifth metacarpal bone, or other rare minor anomalies.

FIG 1 Several examples of adult female heterozygotes 'with typical facial features'. (a) Fragile X negative obligate carrier aged 47 (PPVT score 60, BD score 83). (b) Her daughter aged 23, reported as a 'slow learner'. 35% of fragile X positive cells, PPVT score 60, BD score 46. In addition to more noticeable facial features than in the mother, she has large ears, very short fingers, and flat feet. No children. (c) Fragile X positive (14%) carrier aged 46. PPVT score 70, BD score 41. She has speech impediment and repaired cleft palate. Four children. (d) Fragile X positive (4%) carrier aged 30, PPVT 100, BD 76. No children.

occurrence of several fragile X typical but normally rare features more or less multiplicatively increases the likelihood of a given subject being a carrier.

REPRODUCTION AND INTELLECTUAL STATUS

One third of our female heterozygotes reported at least one miscarriage, and the frequency of miscarriages per total number of pregnancies was 41% in younger women and 40% in older women. This is clearly a considerable excess as compared with the normal frequency in Australia of no more than 20% (R J Pepperell, 1987, personal communication). Moreover, the average proportion of women experiencing one or more miscarriages in this sample

was significantly higher than in the random sample of normal females included in this study (0.34 ± 0.08 and 0.14 ± 0.01 , respectively). It is unlikely that this estimate in our fragile X sample is biased by including a relatively more fertile subsample of 36 mothers of probands. This is because the average frequency of miscarriages was no higher in this subsample than in the remaining heterozygous females.

However, in spite of the higher incidence of miscarriages, the average number of female offspring (excluding probands) in the total sample of female heterozygotes is significantly higher than that in the random sample (1.03 ± 0.12 and 0.69 ± 0.09

TABLE 3 Relationships between level of verbal (PPVT test, first row) and non-verbal (BD test, second row) IQ and physical features in 91 fragile X adult females (included are only those variables with significant differences between categories).

Physical features	Level of performance				ΣN	Probability (based on χ^2 test)
	Moderate or lower IQ<50	Mild IQ 55-70	Borderline IQ 70-85	Normal IQ>85		
Face 'with typical features'	87.5	68.4	63.6	21.9	79	0.000
	64.2	55.0	20.0	25.0	80	0.012
Bulbous nose	62.5	38.9	27.3	17.1	78	0.043
	48.1	30.0	10.0	16.7	79	0.027
Abnormal size or shape of ears	87.5	42.1	27.3	26.8	79	0.010
	46.4	50.0	20.0	25.0	80	0.127
Flat feet	50.0	5.3	9.1	17.5	78	0.000
	14.8	20.0	10.0	25.0	79	0.584
Speech impediment	60.0	33.3	45.5	9.8	75	0.001
	48.0	21.1	10.0	0.0	76	0.023

respectively), but the average number of male offspring (without probands) is not higher (0.78 ± 0.11 compared with 0.75 ± 0.10 in the normal sample). Information concerning the sex of aborted fetuses would be important in explaining the observed differences between the number of daughters and sons born alive to female heterozygotes. These estimates may be somewhat biased through including mothers of probands as well as their heterozygous relatives in our fragile X sample. On the other hand, excluding these mothers would bias our estimate in the opposite direction, since our fragile X sample covers the whole range of clinical expression in female heterozygotes. This is because family investigation of relatives of the mothers of probands involved as many members of each family as possible, especially those suspected of having the

fragile X condition. Moreover, several types of ascertainment led to the families included in our sample as explained in previous sections.

More specific and less biased information can be obtained from the distribution of the average number of children born to female heterozygotes in each of the four categories of intellectual performance, both verbal (PPVT) and non-verbal (BD), as presented in table 4. This estimate is not affected by inclusion of mothers of probands among the other heterozygotes, since the distribution of normal to mild categories of intellectual performance does not differ between those two subsamples. The results indicate that, although the number of offspring sharply (and significantly) falls with a decrease in intellectual performance, there is nevertheless a slight increase, consistent on both

FIG 2 Fragile X negative obligate carrier aged 41 (PPVT score 90, BD score 83), classified as having normal facial appearance.

TABLE 4 Percentages of fragile X females by number of children in each of the four categories of verbal and non-verbal performance. Underlined are high proportions of females in borderline and mildly retarded categories having more than two children.

	No of children							
	0		1-2		>2		Total No	
	PPVT	BD	PPVT	BD	PPVT	BD	PPVT	BD
Moderate or lower IQ<55	87.5	53.6	0.0	10.7	12.5	35.7	8	28
Mild IQ 55-70	52.6	25.0	10.5	20.0	36.8	55.0	19	20
Borderline IQ 70-85	9.1	5.0	18.2	35.0	72.7	60.0	11	20
Normal range IQ>85	9.5	7.7	35.7	38.5	54.8	53.9	42	13
Totals	22	22	19	19	39	40	81	81

χ^2_6 (PPVT)=34.42 ($p<0.0001$).

χ^2_6 (BD)=21.46 ($p<0.01$).

TABLE 5 Percentage of fragile X females in each of the four categories of intellectual performance on verbal (PPVT) and non-verbal (BD) tests in relation to age categories.

	Age categories			Totals
	18-30	31-40	>40	
PPVT				
<Moderate	16.7	13.0	3.0	8
Mild	45.8	4.3	21.2	19
Borderline	12.5	8.7	18.2	11
Normal	25.0	73.9	57.6	42
Totals	24	23	33	80 $\chi^2_6=18.10$ ($p=0.006$)
BD				
<Moderate	54.2	17.4	32.4	28
Mild	29.2	31.7	23.5	20
Borderline	4.2	39.1	29.4	20
Normal	12.5	21.7	14.7	12
Totals	24	23	34	81 $\chi^2_6=12.01$ ($p=0.062$)

tests, in the number of children from the mothers in the borderline category; in non-verbal abilities the increase also applies to the mild category.

In order to verify whether this is a genuine increase or simply related to a higher proportion of women in the postreproductive age in borderline and mild categories, we have assessed the distribution of age in relation to intellectual status (table 5). Although the distribution is not random, the proportion of older women (>40 years) is not increased in borderline or mild categories. This rules out the possibility that the observed increase in the total number of children born to carriers with a lesser degree of intellectual impairment can be attributed to the specific age distribution in our sample.

These results are remarkably consistent with the higher reproduction rate in carriers of borderline intelligence observed by Fryns,¹ although he does not specify the properties of his sample. We have shown, moreover, that this higher rate is not related

merely to the age distribution in different intelligence categories, and applies particularly to the non-verbal ability, where there is increased reproduction in mild as well as in borderline categories.

Discussion

The purely descriptive approach is not fully adequate for the investigation and clinical diagnosis of the fragile X condition and objective data on phenotypic abnormality should be used instead of relying solely on clinical impressions. In particular, we have shown the greater validity of continuous variables such as anthropometric measurements in the diagnosis of fragile X female carriers,³ but there is a tendency in clinical practice to discard this approach as too inconvenient or incomprehensible.

Where results obtained from measurements are inconclusive as regards carrier diagnosis, or are

unavailable, the best possible use should be made of binary traits, by means of careful clinical examination of fragile X negative females from the affected families. Typical features or minor malformations can then be compared with their frequencies in non-fragile X populations and used in estimating carrier probabilities, following the method explained by Overall and Klett.¹⁴ On the other hand, the evident discrepancy between verbal as compared with non-verbal intelligence, which is not uncommon even in apparently normal female carriers, is diagnostically important, since it is far more informative than the presence or absence of fragile X cells.

The problem of a presumed high fertility in fragile X female carriers, combined with increased frequency of miscarriages, needs further investigation. Our findings and those of Fryns¹ are indicative of a moderately increased number of offspring in those carriers of borderline intelligence but not obviously affected, partly compensating for a gene loss in affected fragile X subjects.¹⁵ Moreover, our preliminary results of comparison between fragile X and normal females indicate that the former may be on average slightly more fertile but they need to be confirmed by an unbiased estimate. This increased fertility may be relevant to a fourfold increase in twinning in the offspring of fragile X females¹ or to the enlargement of ovaries observed in some carrier females¹⁶ or both. On the other hand, increased fertility in heterozygotes would imply that the true mutation rate is lower than estimated previously on the basis of the assumption of unchanged fertility in heterozygotes.^{13 17}

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