The fragile X syndrome in a large family.

II Psychological investigations

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SUMMARY Intelligence levels and intelligence profiles were investigated in 52 members of a large family with the fragile X syndrome. The mental abilities were evaluated by the three Wechsler intelligence tests (WAIS, WISC-R, and WPPSI). Chromosomal and psychological data were then compared. In 22 non-retarded fra(X) negative family members, a mean IQ of 102 was found (males 97, females 106). Eleven non-retarded carrier females had IQs between 70 and 110 (mean 86.8), which is 20 points below the mean of normal women ($\alpha=0.01$). One non-retarded male with 6% fra(X) positive cells had an IQ of 98. His intelligence profile closely resembled the profile in the non-retarded female carriers. The highest IQ in the group of retarded males was 31. The mentally retarded females scored IQs between 26 and 41. In male and female patients verbal intelligence substantially exceeded performance abilities. There was a considerable gap between the highest IQ in the group of retarded females and the lowest IQ in the group of non-retarded carriers (41 and 71 respectively) and a considerable overlap was found between the IQ levels of the non-retarded carriers and normal women.

In recent years the fragile site on the long arm of the X chromosome has become a well known cause of mental retardation. However, delineation of the mental deficiency in the fra(X) syndrome has not been easy. Even in hemizygous males, difficulties have occurred since different results have been reported by various investigators. Gustavson *et al*,¹ reviewing 53 patients in 26 families, concluded that only 25% of the males were severely retarded, 75% of them having IQs between 50 and 70. Frijns,² on the other hand, with IQ data on 43 out of 157 cases, found IQs below 50 with a mean of 30 in 41 of these males (95%). Only in a minority of published cases have intelligence tests been performed and the level of mental deficiency is often expressed in terms such as mild, moderate, or severe. Without a more exact definition of these terms, the range of mental capacity is not clear.

Intelligence can be measured not only quantitatively but also qualitatively. Since Martin and Bell³ drew attention to sex linked mental retardation, the verbal disability found to accompany it has been emphasised. This has culminated in Lehrke's supposition that X linked genes specifically relate to verbal function.⁴ Most of the reports on verbal

disabilities in these patients, however, date back to the years before the fragile X syndrome had been separated from other X linked conditions⁵⁻⁸ and thus cannot simply be applied to this syndrome. Yet various authors have claimed that they have identified patients with the fragile X only by their peculiar speech.⁹⁻¹⁰ Others found it difficult to analyse the speech in their patients¹⁻¹¹ or regarded the language difficulties as articulation errors common to all patients with mental retardation.¹² This would imply that a general verbal disability rather than a specific speech defect exists. In this connection it should be remembered that the formal qualities of speech have to be distinguished from verbal aspects of intelligence. This verbal capacity constitutes an overall intelligence pattern together with performance abilities. Theobald and Hay¹³ have reported that in the patients with the fra(X) syndrome a verbal intelligence quotient (VIQ) was found far in excess of the performance intelligence quotient (PIQ).

Compared to males, heterozygous females show much greater variability in intellectual level, as expected. However, different investigators used various different test methods which prevents comparison of the results. Also, intelligence tests in females have been performed only in a minority of published cases. The mental capacities of carrier

women are frequently qualified as "apparently normal", "borderline", "dull", or sometimes as "severely retarded". This does not facilitate the investigation of differences between normally functioning carriers and normal women nor among the carriers themselves. As severely retarded patients are more easily detected than 'borderline' cases, it is likely that ascertainment bias has not always been avoided. These problems also make difficult the comparison between the cytogenetic expression (reflected by the percentage of fragile sites) and the phenotypic expression reflected by the various aspects of intelligence.

Recently we had the opportunity to investigate the intelligence levels and intelligence profiles of males and females in a large kindred. By the investigation of a large number of subjects belonging to the same pedigree (and therefore ascertained without bias) by one investigator using identical methods, a comparison of their intellectual status could be made without the problems mentioned above. The cytogenetic and clinical data, together with the pedigree, are presented in the preceding paper in this issue.¹⁴

Material and methods

To evaluate mental ability the Wechsler intelligence tests were chosen for various reasons. The Wechsler Adult Intelligence Scale (WAIS), the Wechsler Intelligence Scale for Children-revised (WISC-R), and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) are based on the same definition of intelligence and show a comparable approach to mental capacity. Together they constitute a continuous scale for mental evaluation of persons from four to 75 years of age. The WPPSI is also suitable for investigating the mentally disabled older than six years.¹⁵ The tests are widely known and amply evaluated, which also applies to the Dutch and Flemish versions of the tests. Due to cultural and educational circumstances, these versions differ in some respects from the original tests but are fundamentally the same. The tests consist of a number of subtests to evaluate specific aspects of intelligence. Verbal aspects (VIQ) are measured by six of these subtests, the remaining five subtests assessing mainly performance qualities (PIQ). Combining the VIQ and PIQ scores leads to an overall intelligence score (IQ). The subtests in the three Wechsler tests, though not constituted on identical formulae, are reasonably comparable. The clustered subtest results compose an intelligence profile (table 1).

The decision as to which of the Wechsler tests should be used was based on previous education,

TABLE 1 *The subtests named in the original version of the WAIS and the corresponding subtests in the Dutch/Flemish versions of the three Wechsler tests.*

WAIS	WAIS	WISC-R	WPPSI
Information	Informatie	Kennisvragen	Informatie
Comprehension	Begrijpen	Inzicht	Begrijpen
Arithmetic	Rekenen	Rekenopgaven	Rekenen
Similarities	Overeenkomsten	Overeenkomsten	Overeenkomsten
Digit span	Cijferreeksen	Cijferreeksen	Zinnen
Vocabulary	Woordenschat	Woorden	Woordenschat
Digit symbol	Substitutie	Codes	Dierenhuis
Picture completion	Onvolledige tekeningen	Onvolledige tekeningen	Onvolledige tekeningen
Block design	Blokpatronen	Blokpatronen	Blokpatronen
Picture arrangement	Plaattjes ordenen	Doolhoven (beeldverhalan)	Doolhoven
Object assembly	Figuurleggen	Legpuzzels	Geometrische figuren

present age, and residential setting. For persons institutionalised on grounds of mental retardation the WPPSI was chosen. This test is also capable of measuring low levels of intelligence. Subjects who had not received primary education and who were looked after at home were subjected to a number of WISC-R questions not contained in the WPPSI. If these were not suitably answered, then the WPPSI was selected. Adults who had received primary education and were functioning normally in their daily life were tested with the WAIS. The WISC-R was used to test two girls of eight and nine years in accordance with their age and once as a check when a retarded woman (IV.65) scored rather high with the WPPSI. However, she failed most of the WISC-R questions.

Calculation and evaluation of the results of the test items and of the subtests was performed according to the guidelines relating to the respective Wechsler tests. The WAIS test does not differentiate IQs below 45. Mental capacities below this level have to be evaluated with the WPPSI which was originally designed for children under 76 months of age. WPPSI scores were therefore converted into final scores corresponding to the actual age of the subject tested. The level of intellectual capacity was defined according to the

TABLE 2 *Classification of subtypes of mental deficiency (American Association on Mental Deficiency—AAMD)*.*

AAMD intellectual levels	IQ range	Mental age expectancy	Educational classification	AAMD levels of adaptive behaviour
Borderline	69–80	13	Slow learner	I
Mild	52–68	8–12	Educable	II
Moderate	36–51	3–7	Trainable	III
Severe	20–35	0–3		

*From Cleland CC. *Mental retardation. A developmental approach*. New Jersey: Prentice-Hall. 1978.

classification of the American Association on Mental Deficiency. This is based on IQ levels, but also gives the corresponding mental age, which facilitates the comparison of intellectual capacities between persons of the same age (table 2).

All persons were investigated at the place where they lived. The psychological assessments were done under standard conditions and performed by one investigator (TV). The cytogenetic data were not known to her until the end of the procedure.

TABLE 3 Results of cytogenetic and psychological investigations in 52 members of the kindred.

Pedigree No	Age	% fra(X)	IQ	VIQ-PIQ values	Subtests
A. NORMAL FRA(X) NEGATIVE MALES (n=10)					
IV.46H*	70	-	85	0	5 3 3 4 4 4 2 5 5 4 3
IV.47	56	-	96	+ 8	4 4 5 7 5 7 1 5 6 4 6
IV.56	71	-	97	- 8	6 4 3 7 3 5 2 7 6 5 7
IV.57	56	-	101	-19	3 5 4 6 4 5 3 6 8 6 9
IV.58H	82	-	66	- 8	2 0 2 1 4 1 0 4 4 4 1
IV.62	53	-	100	-32	4 2 6 5 4 2 4 7 8 7 9
V.68	17	1	114	-15	6 5 6 6 7 6 5 7 9 9 7
V.74H	55	-	97	- 4	5 3 6 5 5 5 4 6 5 5 6
VI.121	20	-	102	- 8	5 5 4 4 5 3 6 7 5 10 7
VI.110	23	-	114	- 8	5 4 6 6 6 9 7 7 4 7 4
B. NORMAL FRA(X) NEGATIVE FEMALES (n=12)					
IV.60	66	-	113	- 6	5 5 6 8 6 8 3 7 8 7 9
IV.61	59	-	103	-20	4 0 5 7 7 5 3 6 8 7 9
V.60	37	-	100	+ 7	6 5 5 6 6 6 5 5 5 4 5
V.78	39	-	112	- 9	7 5 4 7 6 7 6 7 7 6 8
V.80	42	2	115	- 7	6 6 8 8 5 6 5 10 8 5 7
V.81	38	2	131	-21	7 5 10 8 6 8 10 8 8 10 10
V.82	30	2	103	- 9	6 5 3 8 2 7 5 7 5 5 8
VI.111	21	-	98	- 6	5 4 6 6 4 4 5 5 6 5 6
VI.131	9	-	105	-28	8 7 13 8 8 8 12 13 14 10 15
VI.151	27	-	95	-11	5 3 3 6 4 5 5 7 5 5 5
VI.171	22	-	98	-10	4 4 5 5 5 5 3 5 6 7 7
VI.181	19	-	108	-16	5 5 5 6 4 7 7 6 7 4 10
C. NORMAL FRA(X) POSITIVE MALE					
IV.10	62	6	98	+10	6 4 6 4 5 6 5 6 5 5 4
D. NON-RETARDED CARRIER FEMALES (n=10)					
IV.4	71	8	71	+ 7	3 2 5 3 0 4 1 5 2 2 1
IV.46	66	9	70	+13	2 4 2 3 5 2 0 1 1 4 3
IV.50	49	0	89	-18	5 3 3 3 5 1 4 4 4 6 8
IV.58	74	20	77	+ 6	3 3 3 1 7 3 1 5 3 2 3
IV.59	68	18	81	+12	5 5 3 2 6 3 1 1 4 4 4
V.54	43	4	111	+10	7 7 4 9 7 7 3 10 3 5 7
V.55	41	4	103	-27	5 5 4 4 5 3 6 7 5 10 7
V.72	26	3	98	- 3	5 5 4 6 4 6 7 2 5 8 4
V.74	53	8	90	-12	5 1 3 5 5 4 5 7 5 5 3
VI.132	8	8	78	-24	4 3 7 6 5 4 6 11 9 8 11
E. MENTALLY RETARDED MALES (n=14)					
IV.2	74	28	+	-	0 0 0 0 0 0 0 0 0 0 0
IV.7	66	19	+	-	0 0 0 0 0 0 0 0 0 0 0
IV.8	64	19	+	-	0 0 0 0 0 0 0 0 0 0 0
IV.9	63	30	19	-	1 1 2 1 1 3 2 1 2 2 1
IV.11	59	40	19	-	1 1 2 1 2 2 2 1 2 2 1
IV.12	58	28	19	-	1 1 1 2 1 2 2 1 2 2 1
IV.55	64	9	24	+17	9 5 3 6 4 9 2 2 2 3 2
IV.63	52	9	22	+ 6	4 3 3 4 1 5 2 3 2 3 4
V.57	29	16	19	-	2 2 1 6 1 5 0 1 2 1 1
V.58	37	26	+	-	0 0 0 0 0 0 0 0 0 0 0
V.63	30	42	19	-	2 1 2 1 1 3 2 1 2 2 1
V.66	30	18	24	+15	8 3 4 6 1 9 2 6 4 2 1
V.67	26	34	31	- 4	11 6 4 6 4 7 10 7 6 9 6
V.79	27	14	26	+22	8 7 4 8 1 10 2 7 3 3 1
F. MENTALLY RETARDED FEMALES (n=5)					
V.56	38	20	27	+19	10 5 4 7 9 11 8 5 4 3 3
V.61	31	14	32	+14	14 9 5 6 2 10 12 7 6 3 6
V.62	23	24	41	+11	11 6 6 11 11 13 12 11 0 3 0
V.65	20	22	33	+24	14 7 8 9 6 12 5 5 9 5 8
V.70	30	6	26	+ 7	5 3 5 6 0 9 2 7 5 3 6

*H indicates husbands of female family members.

†Undifferentiated low IQ.

Performance of the test by one person took two hours on average. All mentally retarded males and females were asked for their cooperation: 14 out of 17 men and five out of seven women were willing to participate. Further psychological assessments were performed in 34 out of 42 other family members who were cytogenetically investigated at that time. Five persons refused and three were not accessible. In three generations, 11 non-retarded males, 12 non-retarded fra(X) negative females, and 11 normally functioning fra(X) positive carrier females were tested. One of the non-retarded males showed the fragile site Xq27 consistently in 6% of peripheral blood cells. We considered persons as being retarded if they were not able to finish primary

education and to maintain themselves independently.

Results

The chromosomal and psychological data on members of the kindred are grouped according to the presence or absence of the fragile X chromosome and the social and intellectual level of the persons involved (table 3). The Mann-Whitney U test was used to establish the significance of the differences found between the various groups (table 4).

NON-RETARDED FRA(X) NEGATIVE MEN AND WOMEN (n=22)

Ten men and 12 women who were fra(X) negative

FIG 1 Mean intelligence profiles in (a) normal females and normal males, (b) non-retarded carriers and fra(X) positive non-retarded male, (c) retarded females and retarded males. The mean values of VIQ and PIQ are indicated by a horizontal line. The sequence of the subtests is given in table 3.

TABLE 4 Significance of the differences found between various subpopulations (Mann-Whitney U test).

	IQ scores	VIQ-PIQ
1 Normal females—normal males	NS	NS
2 Normal females—carrier females	$\alpha=0.01$	NS
3 Normal females—retarded females	$\alpha=0.001$	$\alpha=0.001$
4 Carrier females—retarded females	$\alpha=0.001$	$\alpha=0.025$
5 Normal males—retarded males	$\alpha=0.001$	$\alpha=0.001$
6 Retarded males—carrier females	$\alpha=0.001$	NS
7 Retarded males—retarded females	$\alpha=0.025$	NS

and non-retarded according to our criteria were investigated. The men scored IQs between 66 and 114 (mean 97.2). The two men with the lowest scores (IV.46 and IV.58) showed some mental deterioration that could be attributed to their advanced age. The women scored IQs between 95 and 131 (mean 106.4) and in their group one case with some deterioration was found (IV.60). In normal subjects the performance capacities measured by the WAIS were considerably better than the verbal capacities, which resulted in negative VIQ minus PIQ values. The observed values corresponded with the expected ones. The intelligence profiles obtained from both subgroups are presented in fig 1a. The differences between the male and female subgroups were not significant for IQ levels or VIQ-PIQ values.

A NON-RETARDED MAN WITH FRA(X)

One non-retarded man (IV.10) expressed the fragile site in 6% of his cells. He had received primary and secondary education, was a foreman in a factory, and lived independently. Eight of his brothers had been institutionalised because of mental retardation. One of them had died. The remaining seven brothers expressed the marker in 19 to 40% of their cells (mean 27.1%). Reinvestigation of the non-retarded man produced a consistent result of 6% fra(X) positive cells. His IQ score was 98 and the VIQ minus PIQ value was +10. His intelligence profile is presented in fig 1b.

NON-RETARDED CARRIER FEMALES (n=11)

Eleven women expressing the fra(X) or recognised as obligate carriers were self-reliant and had finished primary school. The fragile site was found in 0 to 20% of their cells (mean 8.2%). They scored IQs between 70 and 110 with a mean value of 86.8 which is 20 points below the mean in normal women. The difference is significant at a 0.01 level (Wilcoxon's test). The VIQ-PIQ values were predominantly positive but the difference from the normal women was not significant. The intelligence profile of the group is presented in fig 1b.

MENTALLY RETARDED FRA(X) POSITIVE MALES AND FEMALES (n=19)

Fourteen retarded men and five retarded women were investigated. In the males the highest IQ score was 31. Nine elderly institutionalised males showed an undifferentiated low IQ. Many years of institutionalisation may have contributed to the low scores. The women scored IQs between 26 and 41 (mean 32). Congenital progressive hearing loss may have contributed to the low score of V.70. The severity of her deafness seriously impaired her communication in daily life as well as during the test procedure. Without her handicap she might have been assigned to another group.

A clear distinction was found between the mental capacities of male and female patients, which was significant at the 0.025 level. The mutual intelligence profiles, however, showed some resemblances. VIQ-PIQ values were positive in all male and female patients and the differences between the subgroups were not significant. The mean intelligence profiles are presented in fig 1c.

Discussion

Severe to profound mental retardation (table 2) was found in the male patients in this kindred. The female patients belonged to the severely retarded group except for one woman who scored just one point above the line. The difference between male and female IQ levels was significant at the 0.001 level, but the significance disappeared if the nine males with long term institutionalisation and undifferentiated low IQ scores were omitted from the study ($\alpha=0.05$). In most reports, a greater variability of mental deficiency in males has been mentioned. Frijns *et al*¹⁶ found that three out of 21 males from 18 families were mildly retarded (14%), though in another of his studies² only two out of 43 males from 83 families (5%) scored an IQ of 54, one of them having an XXY karyotype. Chudley *et al*¹⁷ reported seven mildly retarded males in 37 patients from eight families (19%) and Kähkönen *et al*¹⁸ reported mild retardation in 23% of their 150 patients. From our study and recent reports it appears that the vast majority of fra(X) positive males are moderately to severely retarded. Some profoundly retarded patients in this kindred answered questions with a single word which by repetition resembled a short sentence. We did not consider this to be specific for the fra(X) syndrome but merely to be a reflection of the severity of the retardation.

In both the male and female subgroups, verbal intelligence exceeded performance capacity in contrast to what is found in normal people, who mostly

show better performance than verbal capacity.¹⁹ Discrepancies of more than 10 points between VIQ and PIQ are considered to be significant at the 0.05 level and discrepancies of more than 13 points significant at the 0.01 level.²⁰ No significant differences in mean VIQ-PIQ values were found between male and female patients. The highest value in males was +22 and in females +19. The finding that verbal capacity in these patients exceeded performance capacity confirms the results of Theobald and Hay.¹³ At the international workshop on the fragile X and X linked mental retardation,²¹ Chudley reported not to have found significant differences between verbal and performance IQs in his patients, but excluded IQ values below table norms. As the WAIS does not differentiate IQs below 45 and the majority of the patients belong to this group, this may explain the difference. Other reports about verbal expression¹¹ or language capacities¹² do not systemically compare VIQ and PIQs or consistently distinguish the formal qualities of speech and the verbal aspects of intelligence.

None of the retarded patients showed psychiatric disorders but five out of 14 males (36%) had a history of at least one seizure.

In our study, a considerable gap appeared between IQ values of the retarded and non-retarded carrier females, the highest score in the retarded group being 41 and the lowest score of the normally functioning carriers being 70. The difference between the mean IQ values of both groups (32 and 86.6) is highly significant ($\alpha=0.001$). On the other hand a considerable overlap in IQ level between non-retarded carriers and normal women was found, although the mean IQ of the carriers lay 20 points below the mean of normal women (106.4), which is significant at a 0.01 level. VIQ-PIQ values did not significantly differ, though in carriers they were more often positive than in normal women. Fifty percent of the carriers showed values between +6 and +13, while only one normal woman was positive (+7). The difference cannot be attributed to the test method as both groups were tested with the WAIS.

The non-retarded man with 6% fra(X) scored values comparable with the female carriers: his IQ was 98 and his VIQ-PIQ was +10. The cytogenetic expression in this patient was considerably lower than in his retarded brothers who showed a mean of 27%. Similar differences in cytogenetic expression exist between non-retarded and retarded females with the fra(X). Fig 2 shows the relationship between the cytogenetic expression and intelligence levels in females. A negative correlation ($r=-0.58$) is shown and would be even more pronounced if we assume that V.70 would have achieved a much

FIG 2 Relationship between the frequency of expression of the fragile site and intelligence levels in females.

higher score but for her deafness. Yet the correlation has only general validity. In individual cases it does not allow prediction of IQ by the percentage of fra(X). This is demonstrated by IV.58 and IV.59, who showed quite high percentages (20% and 18% respectively) but scored IQs just below the mean of non-retarded carriers. So long as it is not known what determines the frequency of expression, prediction of the mental state of a (prenatally) detected carrier must wait. If a general statement is required, it can only be based on our knowledge about that proportion of carriers which is, on average, mentally deficient. In this kindred, 30% of the carriers were severely retarded, which is in agreement with the percentages previously reported.

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