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Familial X-Linked Mental Retardation, Verbal Disability, and Marker X Chromosomes

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SUMMARY

Cytogenetic and verbal studies were done on members of four families with non-specific X-linked mental retardation. Cytogenetic analysis was done using media 199 and GTG-banding; one family had a marker X with a fragile site in band Xq27 or 28. Preliminary results indicate variation of culture conditions can effect the frequency of the marker X. A generalized language disability was found which tended to concentrate in the areas of auditory reception, auditory sequential memory, visual closure and grammatic closure. Articulation errors involved the same sounds which are late in normal development and occur most frequently in both the general population and a Down syndrome population.

INTRODUCTION

Renpenning syndrome and non-specific X-linked mental retardation are common terms used to describe a rather heterogeneous subgroup of male mental retardates. The historical development of this syndrome has been traced in recent publications [1, 2]. One of the subgroups in this disorder consists of families having a marker X chromosome [3, 4, 5, 6]. Such a marker has a secondary constriction or fragile site in band Xq27 or 28 and is usually seen in 20%–40% of leukocytes from affected males, although values ranging from 8%–50% have been reported [3, 5, 6, 7]. Thus far, detection of the fragile site in fibroblast cultures has been unsuccessful [4, 5].

A major degree of verbal disability in the affected males is frequently reported in such families [1, 2, 8–13]. Lehrke [13] suggests that one or more major genes on the X chromosome relate specifically to verbal functioning.

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We report here the genetic, cytogenetic, and verbal evaluations of four families having non-specific X-linked mental retardation.

FAMILY HISTORIES

Family A

This large Caucasian family was previously reported by Yarbrough and Howard-Peebles [1]. Retardation is confirmed in six out of seven generations. Further results are reported here on three affected males, IV-18, VII-15, and VII-16.

Family B (fig. 1)

Two brothers and a nephew were in the same institution for the retarded. Table 1 summarizes the history of these three males. Retardation is present in two of five generations in this Caucasian family. The other retarded males in the family were living at home with the exception of III-21. None were available for testing.

Family C (fig. 2)

This family was ascertained when the proband (V-26) was evaluated on an out-patient basis at a state institution for the mentally retarded. Individual III-9 was later admitted to this institution. Individual III-20 died at age 6. The blood sample on III-10 was mailed to the lab.

At 4 years 7 months, V-26 was slightly above the 97th percentile on height, between the 50th and 75th percentile on weight, and slightly above the mean for head circumference. He had poor hand and leg control and walked with an awkward gait.

Psychological evaluation was difficult on individual III-9 (fig. 3*a*) due to a short attention span. Thus, the IQ scores in table 1 were probably underestimates. His epilepsy was well controlled by medication. Other retarded males were not available for testing, as all live at home.

Family D, E0772-9 (fig. 4)

The three probands (fig. 3*b–d*) of this family were in the same state institution for the retarded. III-24 had been a resident earlier but was released to his home; medical records indicate he had a slight articulation disorder. III-21 was born prematurely at about 7 months. Records indicate II-3 and II-4 may have been "slow" intellectually; however, no psychometric testing was possible. III-25 died at 4 months from pneumonia, and III-26 died in the Vietnam War. All other information is in table 1.

CYTOGENETIC STUDIES

Chromosome analysis of leukocyte cultures was done on each available family member including GTG-banding studies as well as routine staining. These studies of Families A (IV-18, VII-15, VII-16), B (II-6, II-11, III-1), and C (III-9, V-26) were completed prior to the report of Sutherland [4, 5] that the culture media used affected the results of marker studies. We routinely used commercially prepared culture media containing MEM with Eagle's salts; the 72-hr cultures were exposed to colcemid (2 μg/5 ml media) for 2 1/2 hr prior to harvest.

Leukocyte cultures were repeated on members of Families A, B, and C using culture media 199; Family D was originally studied in this media. This medium contained: (1) 81.0% medium 199 (Gibco #320-1150 Grand Island, N.Y.), (2) 0.8% antibiotics, (3) 2.0% PHA-M (Difco #0528-57 Detroit, Mich.), and (4) 16.2% fetal calf serum. Cultures (72-hr) grown in medium 199 were exposed to colcemid (1 μg/5 ml media) for 2 1/2 hr.

As seen in table 2, the marker X was not found in Families A, B, or C, but was present in Family D. The marker was not seen in the obligate carrier mother (II-5) but this may have been due to the poor quality of the preparation. She and her son (III-24) were cultured at the same time from mail-in blood samples, and his culture showed 4% positive cells which is lower than other affected males studied earlier. GTG-banding showed all chromosomes from the 14 people studied had a normal banding pattern; the marker in Family D was confirmed to be an X (fig. 5).

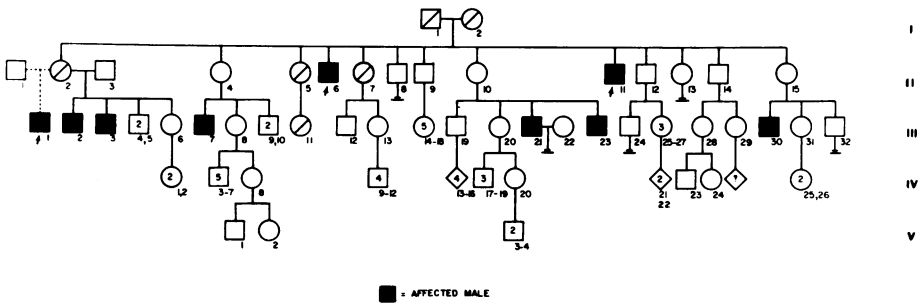

FIG. 1.—Pedigree of Family B

Leukocyte cultures from III-19 (Family D) were originally grown in both medium 199 and commercial medium MEM; scoring of coded slides revealed the marker present in 17% of cells from medium 199 and 3% of cells from medium MEM. Later, at the suggestion of Dr. Patricia A. Jacobs (Hawaii), leukocyte cultures were grown in regular medium 199 and medium 199 with 5% fetal calf serum for 72 hr, and regular medium 199 for 96 hr and coded for analysis. The marker was present in 18%, 27%, and 27%, respectively, in the above preparations. This preliminary data suggest that the frequency of the fragile site increases at lower concentrations of fetal calf serum or under culture conditions where the medium is approaching depletion.

VERBAL EVALUATION

The verbal aspect of this study involved an examination of language function, speech production, hearing ability, and an oral-peripheral examination of the speech mechanism.

Language can be defined as the symbolic formulation of ideas involving a complex combination of semantic and syntactical rules. It provides the underlying framework on which speech is built.

For this study, language functioning was screened using the *Utah Test of Language Development*, and all subjects were found to be deficient in some aspect. The *Illinois Test of Psycholinguistic Abilities* was used as the evaluation instrument. This test utilizes 12 subtests including: auditory reception, visual closure, verbal expression, grammatic closure, manual expression, auditory closure, and auditory sequential memory.

The results revealed that all subjects tested had significant language weaknesses as well as strengths. These weaknesses were concentrated in the areas of auditory reception, auditory sequential memory, grammatic closure, and visual closure. More strengths occurred in non-verbal areas, such as manual expression and visual closure, thus indicating that these individuals process information more successfully through visual and tactile modalities than through auditory. Apparently, while all subjects had language deficiencies, they were due to a general rather than specific disability. Comparison of familial groups revealed that Family D differed from the other three families because they did not demonstrate a weakness in auditory reception, nor a strength in manual expression.

Speech production was examined using the *Goldman-Fristoe Test of Articulation* to evaluate articulation errors. The most frequently occurring errors involved substitution of one sound for another. Four substitution pairs accounted for approximately one-fourth of the substitution errors; these errors were all commonly substituted sounds with the exception of /t/ for /ch/. Most errors of this type occurred at the beginning of a word.

The second most frequently occurring error type was errors of omission; these usually occurred in the medial and final positions in words. This corresponds with the placement of errors by Down syndrome patients [14] as well as intellectually normal children [15]. When a comparison of articulation errors was made between Family D and Families A, B, and C, no significant differences were noted.

Articulation errors for these subjects can be compared with the most frequent misarticulations

TABLE 1

SUMMARY OF DATA BY FAMILY

	FAMILY B			FAMILY C		FAMILY D			
	II-6	II-11	III-1	V-26	III-9	III-18	III-19	III-21	III-24
Year of birth	1890	1906	1905	1970	1923	1943	1944	1939	1945
Gross neurological disorder	None	None	None	(Text)	grand mal epilepsy	None	None	None	None
Physical malformation	None	None	None	(Text)	None	None	None	None	None
IQ:									
-WAIS (Full scale-verbal-performance)	63-61-64	60-59-67	57-55-65	...	...	...	...	44-53-39	45-?-?
-Peabody Picture Vocabulary Test	...	...	...	...	43	...	...	...	...
-Leiter International Performance Scale	...	...	...	...	45	...	...	...	...
-Columbia Mental Maturity Scale	...	...	...	73	...	...	...	...	...
-Pictorial Test of Intelligence	...	...	...	76	...	...	...	...	...
-Slosson Intelligence Test	...	...	...	...	...	23	21	...	...
Biochemical screening tests*	Normal	...	...	...	Normal	Normal	...	...	...

* Blood and urinary amino acids, Guthrie test (blood) and urine spot tests (for protein, reducing sugars, glucose, phenylpyruvate and related metabolites, disulfides, ketoacids and ketone bodies and acid mucopolysaccharides).

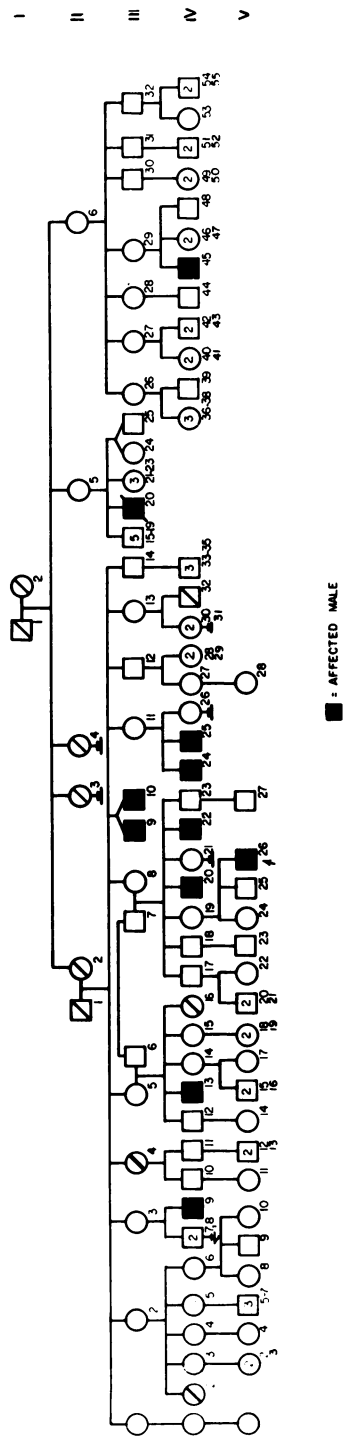

FIG. 2.—Pedigree of Family C

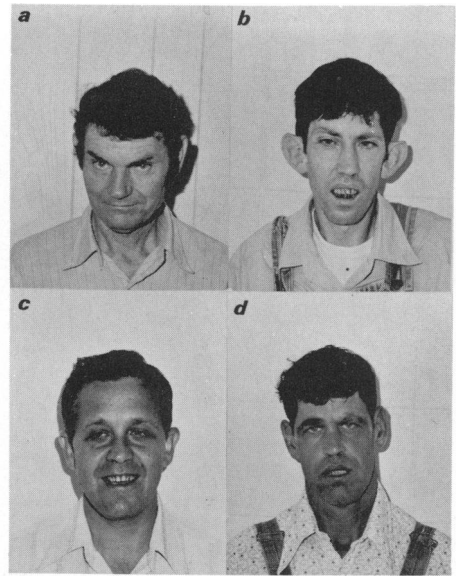

FIG. 3.—*(a)* Family C, III-9; *(b)* Family D, III-18; *(c)* Family D, III-19; *(d)* Family D, III-21.

exhibited by intellectually normal children [15] and by a retarded population (Down syndrome) [14]. All three groups agreed with one another, and the errors correspond closely with late sound development [16]. Thus, misarticulations for the present study could be the result of delayed development and does not demonstrate a distinctive pattern; however, the result does support the idea that errors made by the retarded do not differ significantly from errors made by non-retarded children with defective articulation.

An oral-peripheral examination was done to identify any anatomical or functional abnormality of the speech mechanism. None of the subjects had any structural abnormality. However, it was revealed that seven of them had difficulty with tongue control. The other four could not follow the examiner's instructions, so no results were obtained. It is possible that poor tongue control contributed to the articulation problems of this group.

A pure tone hearing screening test revealed 10 of the subjects had normal hearing ability; the other one had a bilateral sensorineural hearing loss, which was judged to be due to the aging process.

DISCUSSION

It is now possible to divide the families having non-specific X-linked mental retardation into two major groups (i.e., those having a marker X and those not having

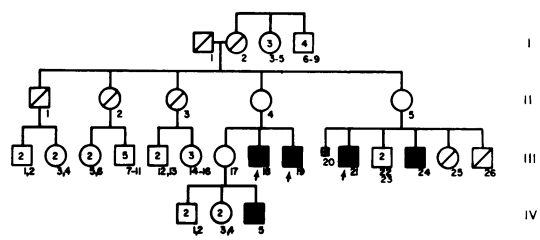

FIG. 4.—Pedigree of Family D

TABLE 2

MARKER X STUDIES USING MEDIA 199

FAMILY	SUBJECT	SEX	MARKER* (−)	MARKER* (+)	% (+)
A	IV-18	M	X	...	0
	VII-15	M	X	...	0
	VII-16	M	X	...	0
B	II-6	M	X	...	0
	II-11	M	X	...	0
	III-1	M	X	...	0
C	III-9	M	X	...	0
	III-10	M	X	...	0
D	III-18	M	...	X	20
	III-19	M	...	X	17
	III-21	M	...	X	28
	III-24†	M	...	X	4
	II-5†	F	X	...	0

* 100 cells per person were scored.
† Technical quality of cultures was poor.

such a marker) based on cytogenetic evaluation of media 199 leukocyte preparations. Families with the marker can be appropriately counseled, and prenatal diagnosis may be possible in the future [4, 5].

It has been suggested [6, 10, 11] that the risk of a carrier female having a retarded son is significantly greater than 50%. This is not the case in our families, as 45 of 88 sons (51%) were affected.

It has been hypothesized [2, 13] that males from these families will have a lower verbal IQ than performance IQ. Wechsler Adult Intelligence Scale (WAIS) scores were available on four members; three showed a higher performance score (Family B, II-6, II-11, and III-1), and one had a higher verbal score (Family D, III-21). The subjects in this study had a generalized language disability which tended to concentrate in the areas of auditory reception, auditory sequential memory, visual closure, and grammatic closure. Speech production examination revealed none of the subjects had normal articulation. The articulation errors involved the same errors which are late in normal development and occur most frequently in both the general population and in another retarded population (Down syndrome). These errors were felt to be at least partially attributable to the poor tongue control exhibited by the testable subjects. Whether the differences found in auditory reception and manual expression in Family D are

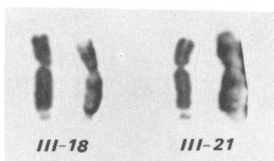

FIG. 5.—Appearance of the marker X with regular staining *(left)*, and GTG-banding *(right)* from Family D.

significant or not can only be determined by studying other families with the marker X.

This report involved a small number of affected males, and the verbal studies employed showed little promise as tools for differentiating X-linked verbal disability. However, such studies of a large number of affected males might be more informative as well as making it possible to compare marker X vs. non-marker X families.

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Detailed data on the verbal evaluations can be obtained by writing the senior author.

Note added in proof: A recent publication [17] suggested the possibility of using the presence of macro-orchidism in males after puberty to ascertain families having X-linked mental retardation with a marker X chromosome. Staff physicians checked the following individuals in Family D for macro-orchidism: III-18 was negative, III-19 was positive, and III-24 exhibited slight enlargement. The inconsistency present in our family may be relevant, since the positive data from Turner et al. [17] included only the family probands. Was macro-orchidism present in all mature affected males in these families?

Three other available males, Family A, IV-18, Family B, II-6, and Family C, III-9, were checked for macro-orchidism. All were negative.

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