Am J Hum Genet 32:714–722, 1980

A New Form of X-Linked Mental Retardation with Growth Retardation, Deafness, and Microgenitalism

RICHARD C. JUBERG,[1,2] AND IRENE MARSIDI[2]

SUMMARY

The proband and two maternal uncles were similarly affected by a unique constellation of mental retardation and physical abnormalities. There were severe retardation, growth less than the third percentile, and significantly delayed bone age. They manifesfed deafness, a flat nasal bridge, several ocular abnormalities, and a rudimentary scrotum with cryptorchidism, and one had a small penis. The proband also had onychodystrophy of his fingers and toes. Their birth weights and lengths were less than expected. No chromosomal or biochemical abnormality was detected. Both uncles died, but the proband is healthy at 4 years. Their phenotype is distinguished from other forms of X-linked mental retardation and appears to be a new syndrome.

INTRODUCTION

With the increasing availability of prenatal diagnosis, the recognition and documentation of new hereditary syndromes that can be prenatally investigated become ever more important. In the past, describing another entity was mainly taxonomic, although the delineation of new entities was diagnostically beneficial just as the classification of causes of mental retardation contributed to understanding. However, once prenatal diagnosis becomes possible, prevention becomes available as well.

This report describes three male relatives with a seemingly unique combination of mental retardation and physical abnormalities. This constellation would appear to be

Received November 23, 1979; revised January 29, 1980.

This research was partially supported by grant 5D28-PE-15199 from the Department of Health, Education, and Welfare.

[1] Department of Medical Genetics and Birth Defects, Children's Medical Center, One Children's Plaza, Dayton, OH 45404.

[2] Department of Pediatrics, Wright State University School of Medicine, Dayton.

monogenic and transmitted as an X-linked recessive. Further, it can be differentiated from all previously reported forms of X-linked mental retardation and, thus, represents a new syndrome. Its recognition has already affected the marital relationship and reproductive planning of four couples in two generations.

CASE REPORTS

We describe the three similarly affected male relatives in this kindred, the proband and his two maternal uncles, as they came to medical attention, which is also their order of birth.

Case 1

The older of the two uncles (fig. 1, IV-6), was born on August 31, 1961. His mother reported spotting through the first trimester. The pregnancy was at term, but his birth weight was 2,440 g and his length, 46 cm.

By 4 months he weighed 3,990 g, less than the third percentile. It was recorded that he smiled. His bone age was slightly retarded, and a ventriculogram showed left hemicerebral atrophy. He was hospitalized briefly at 3⅔ years following a convulsion of 45 min. He was more thoroughly evaluated at 4½ years. By this time, severe retardation was obvious because he had been walking only since age 3 and was yet unable to feed himself. His only speech was "mama."

Physical examination showed his height, weight, and head circumference to be less than the third percentile. The examiner noted shortness of stature, a high forehead (fig. 2), and a rudimentary scrotum with impalpable testes. Neither cerebellar signs nor localized neurological deficits were evident, although his behavior was considered to be no more than that of a 15- to 18-month-old in gross motor function. An ophthalmological consultant reported that the retina and choroid appeared lightly pigmented without evidence of chorioretinitis. He had a slight exotropia. His ears were said to be dysplastic, "lop" was the term used, and the nasal bridge was flat. Although he appeared to hear, by audiometry he responded only to stimuli above the normal threshold. Psychometrically, he showed a level of 13.4 months.

Studies included urinalysis, hemogram, and urinary phenylpyruvic acid and amino acid analyses, the results of which were normal. Radiographically, his bone age was approximately that of a 1-year-old. An electroencephalogram showed neither significant focal abnormality nor seizure discharge, but it was nevertheless interpreted as grossly abnormal due to generalized slowing of the background activity. His unbanded karyotype was 46,XY. He was eventually placed in a state institution and died at 9 years with respiratory disease, but there was no autopsy.

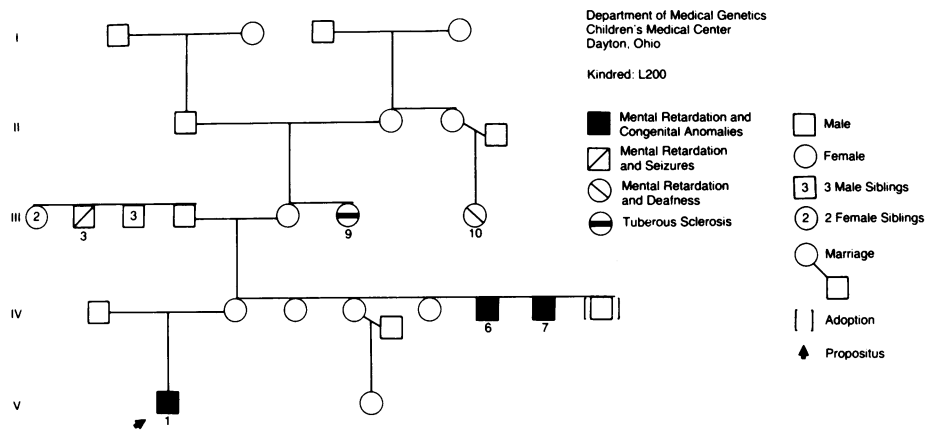

FIG. 1.—Pedigree of the L kindred

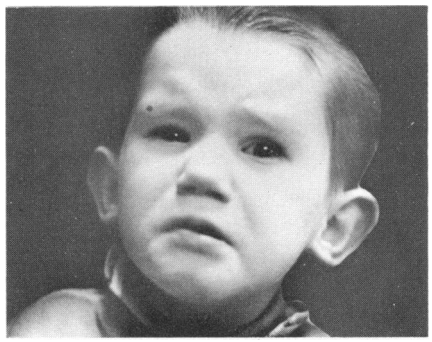

FIG. 2. —IV-6, the older uncle, at 4½ yrs. Note high forehead and prominent ears

Case 2

The second similarly affected male, a younger brother of the patient just described (fig. 1, IV-7), was born on April 21, 1965, and expired 10 months later. The mother recalled spotting during the first trimester. Although the pregnancy was at term, his weight was 2,495 g and his length, 46 cm, essentially the same as his brother.

His only thorough evaluation was at 10 months, by which time his weight, length, and head circumference were less than the third percentile. He was unable to sit and had inadequate head balance (fig. 3). There was a 40° alternating esotropia, and the ophthalmologist found both the choroid and retina pale but without evidence of chorioretinitis. There was an epicanthus bilaterally. The palate was highly arched. The scrotum was rudimentary, and the testes were impalpable.

He would not bear weight on his lower extremities. He had a deep coccygeal dimple and rather prominent dimples on the left side of the knees. The neurological consultant thought that his development had progressed no further than 3 or 4 months. He had no response to sound by audiologic evaluation.

The studies completed before his death were hemogram, urinalysis including phenylpyruvic acid and amino acid analyses, protein-bound iodine, and an electroencephalogram, all results

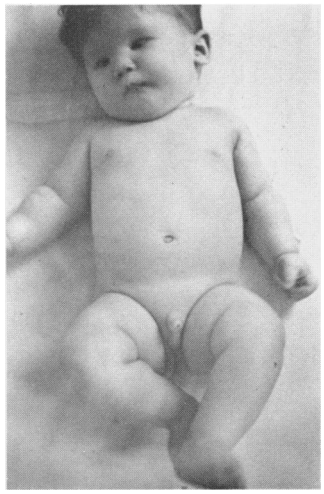

FIG. 3. —IV-7, the younger uncle, at 10 mos. Note esotropia and microgenitalism

being normal. His bone age was less than the 6-month level. His unbanded karyotype was 46,XY. He developed diarrhea and died. An autopsy was not performed.

The medical impression conveyed to the parents was that these two brothers were similarly affected and that the disorder was probably genetically determined. Thus, the parents decided against another pregnancy and adopted a child, a male (fig. 1).

Case 3

Our proband (fig. 2, V-1), the maternal nephew of the foregoing brothers, was born on August 25, 1975, the result of his parents' first pregnancy. It was complicated by renal infection, vaginal warts, and hemorrhoids. The mother received ampicillin in the first trimester and also Bendectin (Merrell-National Laboratories, Cincinnati, Ohio) for nausea. Although duration of the pregnancy was 39 weeks, his weight was 1,730 g and length 41 cm at birth. He was hospitalized for 3 weeks and by the time of discharge was thought to be "a floppy infant with clubbed feet and a pilonidal cyst." The feet were subsequently treated by casting, and there was no abnormality of the back.

His growth had been significantly below normal. At 5 months, his weight and height were less than the third percentile. At 21 months and again at 32 months, his weight, height, and head circumference were less than the third percentile.

His development has been severely retarded. At the time of his first hospitalization at 5 months, he was unable to hold his head up but did occasionally roll over. He grasped objects and seemed to respond to stimuli. At 21 months he was able to hold his head up but could not sit unaided. He did not crawl but was able to pick up and transfer. By 32 months, he was able to hold his bottle as well as pull to the standing position, crawl, and get about.

Physical abnormalities resembled those of his uncles. There was cranial asymmetry with slight flattening of the left frontotemporal region (fig. 4). There were small palpebral fissures. His inner canthal distance was at the twenty-fifth percentile, and his outer canthal distance was just at the third percentile. His interpupillary distance was between the third and twenty-fifth percentiles. There was an epicanthus bilaterally. His nose appeared broad with a flattened bridge. His mouth was fish-shaped at times, and the palate was moderately high. By the age of 32 months he had 18 teeth. The right ear was slightly lower than the left. His toenails were dysplastic, and the great toenails were also ingrown. There were dimples over the knees. The penis was small, both in diameter and length; the scrotum was small, and testes were not palpable (fig. 5).

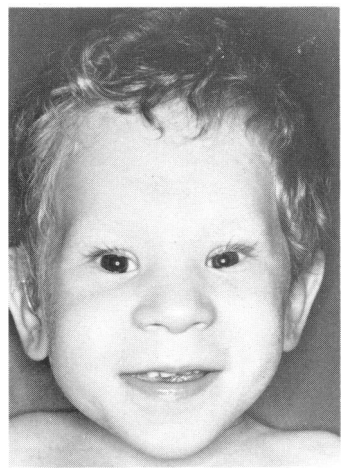

FIG. 4.—V-1, the nephew, at 2⅔ yrs. Note high forehead, small palpebral fissures, and flat nasal bridge.

His hearing was severely deficient. The ophthalmological opinion was that his eyes were normal in size but with phimosis of the lid apertures. He had an "essentially normal EEG" when awake.

Roentgenograms at 21 months showed some maturity markers less than that of a newborn with the maximal development at the newborn level as shown by the distal femoral epiphyseal centers. The fingers showed tuftal hypoplasia. By 32 months his bone age had not progressed.

Results of complete blood count and urinalysis were normal. Results of the following chemical studies were normal: sweat Cl; serum Cl, CO_2 content, Na, K, pH, BUN, PCO_2, P, alkaline phosphatase, Ca, and total protein. Stool analysis was normal. Studies of T_3 and T_4 uptakes were normal. Fasting glucose was normal. Analyses of urinary amino acids and one test for mucopolysaccharide excretion were normal. His chromosomes by G-banding were 46,XY.

To look for the fragile site at Xq27, the marker chromosome reported in some patients with X-linked mental retardation, we established leukocyte cultures in medium 199 with 5% fetal bovine serum (FBS) with and without increased pH, in medium 199 with 20% FBS, as well as in the common media for our laboratory: RPMI 1640 (Gibco, Grand Island, N.Y.) with 20% FBS [1]. Frequency of chromosomal gaps, chromosomal breaks, and chromatid breaks was 4/61 (number of cells with disruption/number of cells examined) in medium 199 with 5% FBS cultures, including one at Xq27 or 28 and 0/8 in medium 199 with 20% FBS culture. There were 5/31 gaps and breaks in the RPMI culture. The frequency of chromosomal disruption was most unusual for our laboratory, which we attributed to the possibility of an effect from the respiratory disease for which he was hospitalized, presumably viral.

The dermatoglyphic patterns of the nephew and the two uncles appeared neither to be unusual nor more similar to each other than might be expected.

Table 1 presents a summary of the eight phenotypic characteristics of the nephew and his two uncles. Note that although born at term, both uncles had lower birth weight than expected, as did the nephew, born after 39 weeks of gestation.

DISCUSSION

Etiologically, a similar environmental cause for the rather remarkable similarity of the nephew and his two maternal uncles appears to be unlikely. We have no suspicion of a common infectious agent or teratogenic exposure either from our history or from their resemblance to an environmentally determined syndrome.

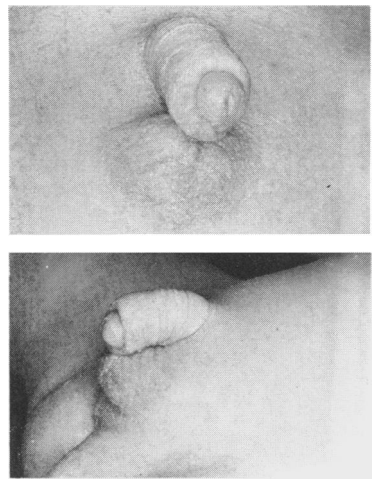

FIG. 5. —V-1, the nephew, at 2⅔ yrs. showing small penis and small, empty scrotum

TABLE 1

CHARACTERISTICS OF THE NEPHEW AND TWO UNCLES

CHARACTERISTIC	PATIENT		
	V-1	IV-6	IV-7
Birth weight (g)	1,730	2,440	2,495
Birth length (cm)	41	46	46
Growth (percentile)	< 3rd	< 3rd	< 3rd
Bone age	Retarded	Retarded	Retarded
Hearing impairment	Severe	Mild	Severe
Eyes	Small fissures	Small fissures; exotropia; light retinal pigmentation	Epicanthus bilaterally; esotropia; light retinal pigmentation
Nose	Flat bridge	Flat bridge	Flat bridge
Genitalia:			
Cryptorchidism	+	+	+
Rudimentary scrotum	+	+	+
Penile size	Small	Small	Small
Mental retardation	Severe	Severe	Severe

Thus, a genetic etiology seemed as likely when we studied the nephew as it did to other physicians in 1965 when they evaluated the two uncles. A single gene cause seemed likely. The father of the proband was not related to his wife. This argued against an autosomal recessive gene. Neither the mother of the proband nor her mother, who was the mother of the two uncles, was phenotypically abnormal. Thus, we postulated an X-linked gene producing this constellation of abnormalities, the most significant being the severe mental retardation.

Table 2 shows features of X-linked mental retardation in a selection of prior reports. Although there were earlier studies suggesting an X-linked basis for mental retardation, the report from Saskatchewan by Renpenning et al. [2] in 1962 is sometimes considered as the first carefully studied family. Their evidence for a single gene lay mainly in the large number of similarly affected males, all related through females, rather than by any physical distinction. In the family reported by some of the same authors [3] from British Columbia and Saskatchewan, the few physical abnormalities did not produce a characteristic phenotype in a majority of the affected males. Evidence for a single gene etiology rested on the large number of similarly mentally retarded males who were related through females, this 1963 report being similar to the prior report.

The next study listed concerns a 7-generation pedigree from Mississippi with 19 affected males, some of whom had similar physical characteristics [4]. Three additional families from Mississippi showed no physical characteristics [5]. Neither was the phenotype distinctive in the kindred reported from Scotland [6].

More recently, under the title "X-Linked Nonspecific Mental Retardation," two large kindreds were studied in Belgium [7, 8], involving 35 affected males. There were no physical abnormalities, but impaired speech was noted.

All of the foregoing reports may concern a similar X-linked gene producing nonspecific mental retardation. Indeed, Deroover et al. [8] provided a table referencing additional reports of the nonspecific type. Table 2 shows that in X-linked mental

TABLE 2

X-LINKED MENTAL RETARDATION

Geographic location	No. affected	Mentality	Physical characteristics
Saskatchewan [2]	20	IQ = 13–70	Prominent ears; head circumference < 2nd percentile
British Columbia and Saskatchewan [3]	20	"Imbecile" and more severely retarded	Prominent mandible (10/20); large ears (10/12); malocclusion (5/20); dolichocephalus (4/20); scoliosis or kyphoscoliosis (3/20)
Mississippi [4, 5]	19	IQ = 30–70	Seizures (3/19); speech disorder; hyperactivity
Mississippi [5]	9	IQ = 55–67	None
Mississippi [5]	11	IQ = 43–76	None
Mississippi [5]	5	IQ = 21–53	None
Scotland [6]	5	IQ = 20–50	None
Belgium [7, 8]	35	...	Speech disorder
Australia [9]	7	Moderately-severely retarded	Macroorchidism (2× normal)
Indiana [10]	4	Moderately retarded	Short stature; 6th nerve palsy; ridged metopic suture; several skeletal anomalies
Sweden [11]	3	IQ = 20–30	Seizures (2/3); short stature (3/3); obesity (3/3); grotesque fatty facies; large ears; narrow palpebral fissures; hypogonadism
Ohio [12]	5	...	Hypogonadism (5/5); micropenis (5/5); short stature (5/5); gynecomastia; obesity; small head (4/5); skeletal defects
Maine [13]	13	Moderately-severely retarded	Nystagmus; strabismus; scoliosis; spastic paraplegia

retardation there appear to be one group of kindreds with affected males without any physical characteristics and another group comprising several kindreds, each with its own characteristic physical abnormalities. Etiologically, such a division implies that many, maybe all, of the nonspecific cases may be due to the same gene, whereas the various cases with their peculiar physical characteristics may be attributed to unique genes.

The next listings in table 2 report particular kindreds in which physical abnormalities were seemingly characteristic. For example, the report from Australia in 1975 [9] concerned two families in whom the affected males had bilateral testicular enlargement.

The boys reported from Indiana in 1977 by Christian et al. [10] had several skeletal anomalies, were moderately retarded, had abducens palsies, and evidence of glucose intolerance. They were clearly different from the three patients we have observed.

The patients reported from Sweden in 1962 [11] had phenotypic characteristics clearly different from those of our patients; specifically: convulsive disorder, marked obesity, swelling of subcutaneous facial tissue, and extremely large, although not deformed, ears. Abnormalities similar to ours included hypogonadism, dwarfism, and very narrow palpebral fissures, although the pictures of their patients certainly do not resemble ours.

Vasquez et al. [12], also reporting from Ohio, presented five male members in four generations with hypogonadism, micropenis, mental retardation, and short stature. The adults had gynecomastia, obesity, and normal-sized hands and feet. The pictures of their patients and the adult phenotype unequivocally looked nothing like that of our patients. Our complete family history and pedigree did not ascertain these people, and so we assume their independence from our kindred in southwestern Ohio.

The last report is from Maine, published in 1966 [13], under the title "Sex-Linked Spastic Paraplegia." Given that our patients did not have spastic paraplegia, and that their patients had no other phenotypic abnormalities, we find no similarity.

In conclusion, we have described a nephew and his two maternal uncles who were similarly affected with severe mental retardation, significant growth retardation, deafness, and microgenitalism. Monogenic inheritance seems likely. As the phenotype of our patients does not resemble that of others reported to date, we suggest that it may represent a new form of X-linked mental retardation syndrome.

Providing the special in vitro conditions for the demonstration of a fragile site [1, 14], we did not see the appearance at Xq27 as reported. The fragile site at Xq27 has been associated with the form of X-linked mental retardation accompanied by macroorchidism [15, 16], although this may not be an exclusive relationship [5, 17–19].

Finally, by way of illustrating the importance today of the recognition of such a genetically determined disorder, in this kindred we have witnessed its impact upon the marital relationship and reproductive planning of four couples in two generations. The first couple were the parents of the two brothers, and they elected to adopt rather than risk another affected male from the conviction that the two boys were clinically similar. The parents of our proband have deferred another pregnancy pending our study of their child and analysis of the kindred. At one time, they inquired about the possibility of an in vitro fertilization employing the father's sperm with an egg to be obtained from a female donor and implantation of the zygote into the mother. Two sisters of the mother of the proband, one with her husband and one normal daughter and the other with a fiancé, have conditioned their reproductive planning by the occurrence of the three affected boys. In our present state of understanding, the most that prenatal diagnosis can offer is determination of the fetal sex with an appropriate probability statement of the likelihood of an affected male.

ACKNOWLEDGMENT

Karen K. Kessler carried out detailed chromosomal study of the proband.

REFERENCES

1. SUTHERLAND GR: Heritable fragile sites on human chromosomes. I. Factors affecting expression in lymphocyte culture. *Am J Hum Genet* 31:125–135, 1979
2. RENPENNING H, GERRARD JW, ZALESKI WA, TABATA T: Familial sex-linked mental retardation. *Can Med Assoc J* 87:954–956, 1962
3. DUNN HG, RENPENNING H, GERRARD JW, MILLER JR, TABATA T, FEDEROFF S: Mental retardation as a sex-linked defect. *Am J Ment Defic* 67:827–848, 1963
4. YARBROUGH KM, HOWARD-PEEBLES PN: X-linked nonspecific mental retardation: report of a large kindred. *Clin Genet* 9:125–130, 1976

5. HOWARD-PEEBLES PN, STODDARD GR, MIMS MG: Familial X-linked mental retardation, verbal disability, and marker X chromosomes. *Am J Hum Genet* 31:214–222, 1979
6. FRIED K: X-linked mental retardation and/or hydrocephalus. *Clin Genet* 3:258–263, 1972
7. VAN DEN BERGHE H, DEROOVER J, PARLOIR C, FRYNS JP: X-linked non-specific mental retardation. *Clin Genet* 13:106, 1978
8. DEROOVER J, FRYNS JP, PARLOIR C, VAN DEN BERGHE H: X-linked recessively inherited non-specific mental retardation: report of a large family. *Ann Genet* 20:263–268, 1977
9. TURNER G, EASTMAN C, CASEY J, MCLEAY A, PROCOPIS P, TURNER B: X-linked mental retardation associated with macro-orchidism. *J Med Genet* 12:367–371, 1975
10. CHRISTIAN JC, DEMYER W, FRANKEN EA, HUFF JS, KHAIRI S, REED T: X-linked skeletal dysplasia with mental retardation. *Clin Genet* 11:128–136, 1977
11. BÖRJESON M, FORSSMAN H, LEHMANN O: An X-linked, recessively inherited syndrome characterized by grave mental deficiency, epilepsy, and endocrine disorder. *Acta Med Scand* 171:13–21, 1962
12. VASQUEZ SB, HURST DL, SOTOS JF: X-linked hypogonadism, gynecomastia, mental retardation, short stature and obesity —a new syndrome. *J Pediatr* 94:56–60, 1979
13. BAAR HS, GABRIEL AM: Sex-linked spastic paraplegia. *Am J Ment Defic* 71:13–18, 1966
14. SUTHERLAND GR: Heritable fragile sites on human chromosomes. II. Distribution, phenotypic effects, and cytogenetics. *Am J Hum Genet* 31:136–148, 1979
15. SUTHERLAND GR, TURNER G, GILL R, DANIEL A: Carrier detection in X-linked mental retardation. *Med J Aust* 2:624, 1978
16. HARVEY J, JUDGE C, WIENER S: Familial X-linked mental retardation with an X chromosome abnormality. *J Med Genet* 14:46–50, 1977
17. TURNER G, TILL R, DANIEL A: Marker X chromosomes, mental retardation and macro-orchidism. *N Engl J Med* 299:1472, 1978
18. JACOBS PA, MAYER M, RUDAK E, ET AL.: More on marker X chromosomes, mental retardation and macro-orchidism. *N Engl J Med* 300:737–738, 1979
19. JENNINGS MT, CANFIELD JE, BRYANT EM, HALL JG, HOEHN H: Specificity of marker chromosomes in Renpenning syndrome —quantitative rather than qualitative? *Am J Hum Genet* 31:91A, 1979