

The Juberg-Marsidi Syndrome Maps to the Proximal Long Arm of the X Chromosome (Xq12-q21)

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Summary

Juberg-Marsidi syndrome (McKusick 309590) is a rare X-linked recessive condition characterized by severe mental retardation, growth failure, sensorineural deafness, and microgenitalism. Here we report on the genetic mapping of the Juberg-Marsidi gene to the proximal long arm of the X chromosome (Xq12-q21) by linkage to probe pRX214H1 at the DXS441 locus ($Z = 3.24$ at $\theta = .00$). Multipoint linkage analysis placed the Juberg-Marsidi gene within the interval defined by the DXS159 and the DXYS1X loci in the Xq12-q21 region. These data provide evidence for the genetic distinction between Juberg-Marsidi syndrome and several other X-linked mental retardation syndromes that have hypogonadism and hypogenitalism and that have been localized previously. Finally, the mapping of the Juberg-Marsidi gene is of potential interest for reliable genetic counseling of at-risk women.

Introduction

X-linked mental retardation syndromes represent a genetically heterogeneous group of diseases in which many clinical entities have been identified on the basis of their association with specific malformations. Among them, several syndromes of hypogonadism and/or hypogenitalism have been described, including Borjeson syndrome, Aarskog syndrome, FG syndrome, Simpson-Golabi-Behmel syndrome, Lowe syndrome, and Juberg-Marsidi syndrome (Glass 1991). While most of them have been mapped to specific regions of the X chromosome, no information regarding the genetic mapping of the Juberg-Marsidi syndrome has been available hitherto.

The Juberg-Marsidi syndrome is an X-linked recessive condition characterized by severe mental retardation with growth failure, sensorineural deafness, and microgenitalism (McKusick 309590; Juberg and Mar-

sidi 1980). We have previously reported on a second Juberg-Marsidi family including seven affected males (Mattei et al. 1983), and here we provide evidence for mapping of the disease gene to the proximal long arm of the X chromosome by linkage analysis in the latter family.

Patients and Methods

Patients

For the purpose of the present linkage study, the pedigree reported by Mattei et al. has been extended to a total of seven affected males and seven asymptomatic obligate carriers (fig. 1). Y.L. (IV-1) was born after a 40-wk pregnancy and normal delivery. His parents are healthy, but a maternal uncle (III-3) and four maternal cousins of his mother (III-10, III-12, III-15, and III-18) died at an early age with multiple malformations (fig. 1). He was small for gestational age (birthweight 2,680 g, length 48 cm, and head circumference 33 cm). Dysmorphic features and multiple malformations were noted immediately after birth: flat nasal bridge, upslanting palpebral fissures, preauricular pits, camptodactyly of the second fingers, cryptorchidism, small penis, and hypospadias (Mattei et al. 1983). At 10 years of age, he is bedridden, unable to sit unaided, and has severe mental

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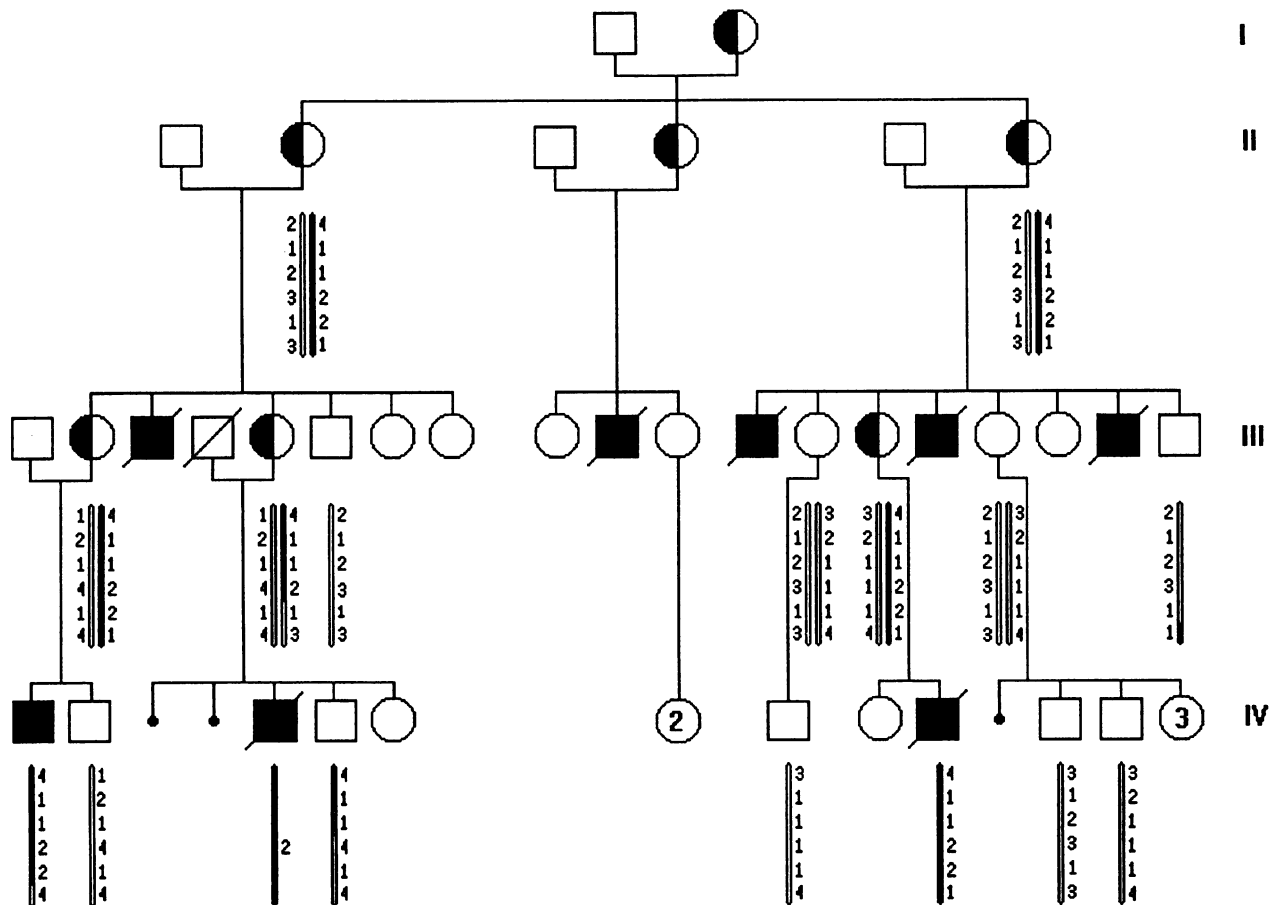


Figure 1 Pedigree of the family affected with Juberg-Marsidi syndrome. Haplotypes at loci AR, DXS159, DXS453, DXS441, DXYS1X, and DXS456 are presented (from top to bottom). The haplotypes are inferred assuming the least number of recombinant events.

retardation, joint retractions, and major truncal hypotonia. Dysmorphic features are still present (fig. 2A). Standard blood karyotyping was normal.

A.B. (IV-3), born after a 38-wk pregnancy, was also small for gestational age (birthweight 2,230 g, length 45 cm, and head circumference 32 cm), and several malformations were noted at birth: upslanted palpebral fissures, prominent epicanthic folds, a marked saddle nose, and hyperfolded ears (Mattei et al. 1983). The external genitalia showed a micropenis (1 cm), a very hypoplastic scrotum, and ectopic testes. Psychomotor development was markedly abnormal, with poor head control, poor spontaneous movements, and absent following with eyes at 5 mo of age. Audiometric-evoked potential showed a hearing defect for high-pitched sounds below 60 decibels (Mattei et al. 1983). Standard blood karyotyping was normal. Age and circumstances of death are unknown.

J.B. (IV-10) was born after a term pregnancy and normal delivery (birthweight 3,030 g and head circumference 33 cm). His length was small for gestational age (47 cm; 10th percentile), and he failed to thrive thereafter. Major dysmorphic features were observed immediately after birth—namely, prominent forehead, hypertelorism, upslanted palpebral fissures, flat nasal bridge, anteverted nares, posteriorly rotated and hyperfolded ears, short neck, and clubbed feet (fig. 2B). Malformations of the external genitalia included micropenis (17 mm) and balanoscrotal hypospadias with the urethra ending at the origin of the penis (fig. 2B). Scrotum, testes, and kidney were normal, and genitography showed unremarkable male genitalia. Standard karyotyping was normal. Laboratory investigations showed low basal levels of plasma testosterone (0.05 ng/ml; normal mean ± 1 SD = 1.09 ± 1.43 ng/ml), with a normal response to the chorionic gonadotropin menopausal hormone

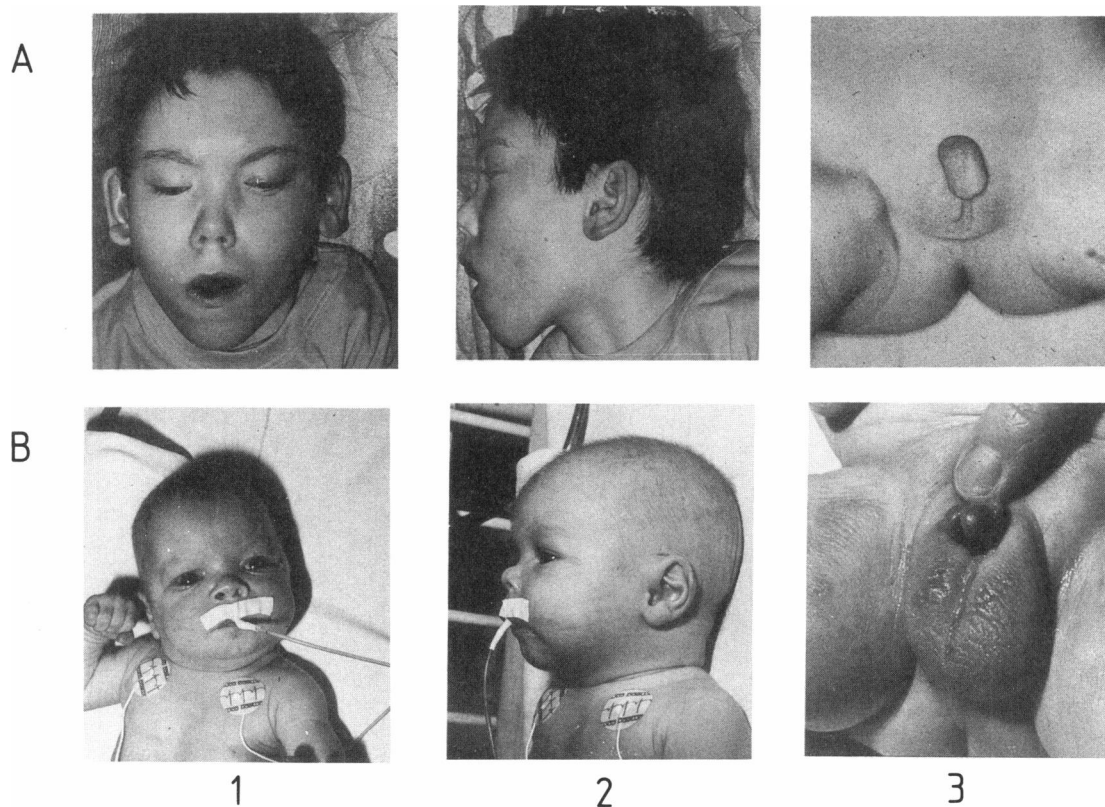


Figure 2 Affected individuals: dysmorphic features (panels 1 and panels 2) and hypogonitalism (panels 3). A, Patient Y.L. (IV-1) age 10 years. B, Patient J.B. (IV-10) age 5 mo.

test but a low response to the luteinizing hormone-releasing hormone (LHRH) test, consistent with pituitary gonadotropin deficiency (not shown; data available on request). He was floppy immediately after birth, and his neurological condition gradually worsened thereafter. At 15 d of life, he had severe truncal hypotonia, poor head control, and weak crying, and he could not follow with eyes. Computed tomography showed bifrontal and bioccipital hypodensities of the white matter (not shown), and electroencephalogram showed slow waves and diffused theta-delta waves. He died of an acute pulmonary infection at 6 mo of age.

Methods

Genomic DNA was prepared from circulating leukocytes. Southern blots and hybridization to radiolabeled DNA probes (table 1) were carried out according to standard procedures. For IV-3, the only material available was nonviable frozen fibroblasts, which were directly used for PCR analysis after denaturation (10 mM NaOH, 200 mM NaCl, 0.05% SDS) and boiling. PCR

amplification of short tandem repeats (STR) was carried out according to a method described elsewhere (Luty et al. 1990; Weber et al. 1990; La Spada et al. 1991; Barker et al. 1992; Ram et al. 1992), and amplification products were electrophoresed on a 6% denaturing polyacrylamide/urea gel, transferred onto a nylon membrane, and then hybridized for 3 h at 42°C either with a [³²P]dCTP-labeled poly-AC probe or with [³²P]dCTP-labeled amplification primers (table 1; Hazan et al. 1992).

Pairwise and multipoint linkage analysis was performed using version 5.1 of the LINKAGE package (Lathrop and Lalouel 1984; Lathrop et al. 1984). Genetic distances between polymorphic probes were as follows (recombination fractions in parentheses): cen-AR-(.034) - DXS159 - (.034) - DXS453 - (.01) - DXS441 - (.07) - DXYS1X - (.146) - DXS456 - Col4A5 - tel (Fain et al. 1991; Huang et al. 1992; J. L. Mandel, personal communication).

The Juberg-Marsidi gene was arbitrarily given the frequency of 10^{-5} , with no new mutations, a full penetrance

Table 1**List of Polymorphic Probes Used**

Locus	Probe	Map Location
DXS278	CRI-S232	Xp22.32
DXS41	p99-6	Xp22.1
DXS84	L754	Xp21.1
OTC	pOTC	Xp21.1
DXS7	L1.28	Xp11.4-p11.3
DXS255	M27 β	Xp11.22
AR	AR	Xq11.2-q12
DXS159	cpX289	Xq12
DXS453	Mfd66	Xp11.23-q21.1
DXS441	pRX214H1	Xq13.3
DXYS1X	pDP34	Xq21.31
DXS17	S21	Xq22
DXS456	XG-30B	Xq21-q22
COL4A5	2B6	Xq22
DXS424	XL5A	Xq24-q26
DXS52	St14	Xq28

SOURCES.—Davies et al. (1991) and Barker et al. (1992).

in hemizygous males, and a null penetrance in heterozygote carriers.

Results

Positive pairwise lod scores (Z) were obtained with probes AR and pDP34 at the androgen receptor and DXYS1X loci, respectively ($Z = 1.50$ and $Z = 1.15$, respectively, at recombination fraction $[\theta] = .10$; table 2). These results prompted us to further investigate the Xq12-q21 region by using two STRs mapping within the AR-DXYS1X interval. Pairwise lod scores between the disease locus and probes Mfd66 and pRX214H1 at loci DXS453 and DXS441, respectively, gave maximum lod scores of 1.66 and 3.24, respectively, at $\theta = .00$. Two other STRs, mapping distal to DXYS1X at loci DXS456 and COL4A5, respectively, gave negative lod scores, suggesting that the disease gene maps proximal to DXYS1X, most probably within the AR-DXYS1X interval (15 cM; table 2).

Indeed, two recombination events occurred between DXYS1X and DXS456 (in III-19 and IV-1), the disease locus segregating with the former marker (fig. 1). In a third recombination event (in III-5), a crossover occurring between DXS441 and DXYS1X placed the disease locus proximal to DXYS1X. Finally, a fourth recombination event (in IV-4) occurred between DXS159 and DXS441, with the disease locus segregating with the latter marker. Multipoint linkage analysis placed the

Juberg-Marsidi gene consistently within the AR-DXYS1X interval (location score 3.33).

It is worth noting that negative lod-score values were obtained with polymorphic probes mapping to the other two regions that are known to contain mental retardation genes—namely, the Xp22 and the Xq28 regions (table 2). Finally, a series of nonpolymorphic probes mapping close to an X-linked deafness gene (DFN3) at loci DXS26, DXS121, DXS169, DXS232, and DXS233 showed normal patterns of hybridization in affected individuals (not shown).

Discussion

We report here on the genetic mapping of the Juberg-Marsidi syndrome—an X-linked mental retardation syndrome associated with multiple malformations—to the proximal long arm of the X chromosome (Xq12-q21) by linkage to probe pRX214H1 at the DXS441 locus ($Z = 3.24$ at $\theta = .00$) in the pedigree originally reported by Mattei et al. (1983). All affected males fulfilled the clinical criteria for Juberg-Marsidi syndrome—namely, intrauterine growth retardation, severe psychomotor retardation, facial dysmorphism, hypogonadism with rudimentary scrotum and small penis, hearing defect, and poor survival (Juberg and Marsidi 1980).

Table 2**Two-Point Lod Scores between X Chromosome Markers and the Juberg-Marsidi Locus**

Locus	Z AT $\theta =$			θ_{\max}
	.00 ^a	.10	Z_{\max}	
DXS278	$-\infty$	-.93	.05	.40
DXS41	NI			
DXS84	NI			
OTC	$-\infty$.09	.39	.30
DXS7	NI			
DXS255	$-\infty$.23	.33	.20
AR	$-\infty$	1.50	1.50	.10
DXS159	$-\infty$	-.08	.15	.30
DXS453	1.66	1.34	1.66	.00
DXS441	3.24	2.96	3.24	.00
DXYS1X	$-\infty$	1.15	1.15	.10
DXS17	$-\infty$.49	.49	.10
DXS456	$-\infty$	-.43	.21	.30
COL4A5	$-\infty$	-.44	.18	.30
DXS424	$-\infty$	-1.04	.10	.40
DXS52	$-\infty$	-2.38	.00	.50

^a NI = not informative.

Table 3**Rare X-linked Mental Retardation Syndromes with Hypogonadism**

Syndrome Name	McKusick Number	Description	Map Location	Reference
Sutherland (MRXS3)	309470	Small testes, microcephaly, short stature, spastic paraplegia	Xp11-q21.3	Sutherland et al. 1988
Simpson-Golabi-Behmel	312870	Cryptorchidism, macrosomia, coarse facies, polydactyly, extra nipples, heart defect	Xq13.1-q22.3	Hughes-Benzie et al. 1992
Renpenning	309500	Microorchidism, microcephaly, short stature	Xq21	Stevenson et al. 1991
Miles-Carpenter		Hypogonadism, microcephaly, asymmetric face, exotropia, joint laxity	Xq21.3	Miles and Carpenter 1991
Borjeson	301900	Microgenitalia, gynecomastia, hypogonadotrophic hypogonadism, obesity, round face, narrow palpebral fissures, skeletal anomalies, microcephaly	Xq26-q27	Turner et al. 1989
Myhre-Ruvalcaba	304350	Hypogonadism, small penis, small testes, deafness, postnatal growth retardation, thickened calvarium, immature behavior		Myhre et al. 1982
FG	305450	Hypospadias, cryptorchidism, macrocephaly, agenesis of corpus callosum, deafness, gastrointestinal anomalies		Thompson and Baraitser 1987
Rud	308200	Hypo- and hypertrophic hypogonadism, ichthyosis, deafness, retinitis pigmentosa		Marxmiller et al. 1985
Chudley	309490	Cryptorchidism, microorchidism, short stature, obesity, microcephaly		Chudley et al. 1988
Juberg-Marsidi	309590	Rudimentary scrotum, small penis, intrauterine growth retardation, hearing defect	Xq12-q21	Present study

Hitherto, hypogonadism has been reported in several forms of X-linked mental retardation syndromes (table 3). Most of them are clinically distinct from the Juberg-Marsidi syndrome and have been assigned to other regions of the X chromosome (e.g., Aarskog syndrome, Lowe syndrome, and Norrie syndrome). On the other hand, the X-linked mental retardation syndromes that have been assigned to the Xq21-q22 region are markedly different in clinical course and severity (e.g., Simpson-Golabi-Behmel syndrome, Miles-Carpenter syndrome, and Sutherland syndrome; table 3) and could not be misdiagnosed as the Juberg-Marsidi syndrome. We believe therefore that the disease gene mapping to the proximal long arm of the X chromosome in the present pedigree indeed accounts for the Juberg-Marsidi syndrome and not for another hitherto reported X-linked mental retardation syndrome. In support of this, it is interesting to bear in mind that duplication of the q13.1-q21.1 region of the X chromosome—46, dup (X) (q13.1-q21.1) Y—has been associated with a syndrome of mental retardation, intrauterine growth retardation, cryptorchidism, and facial dysmorphism closely resembling the Juberg-Marsidi syndrome, in three boys belonging to the same family (Thode et al. 1988).

Because the Juberg-Marsidi syndrome includes hypogonadism and deafness, at least two genes mapping to the Xq21 region could be regarded as candidate genes in this syndrome—namely, a gene for X-linked deafness (DFN3; McKusick 304400) and the gene encoding the androgen receptor (AR), which is responsible for Kennedy disease (La Spada et al. 1991). In fact, one recombinant event (in IV-4) between the AR locus and the disease locus (i.e., crossover between DXS159 and DXS441) ruled out this gene as the disease-causing gene in the present pedigree. Similarly, the DFN3 gene, which has been assigned to a small segment of Xq21.1 by careful investigations of patients with Gusher-associated X-linked mixed deafness (DFN3; Bach et al. 1992), was not found to be deleted or rearranged in our probands.

It is hoped that current genetic studies devoted to the ultimate goal of identifying the genetic basis of X-linked mental retardation syndromes will help elucidate the molecular mechanism of this rare condition. At the present time, however, the mapping of the Juberg-Marsidi gene, together with the availability of closely flanking polymorphic markers, will enable reliable genetic counseling to be offered to at-risk women, provided

that the study of additional families with Juberg-Marsidi syndrome confirms this localization.

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