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Manifestations in Four Males With and an Obligate Carrier of the Lenz Microphthalmia Syndrome

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Lenz microphthalmia syndrome is a rare X-linked recessive condition first described by Lenz in 1955 and comprises of anophthalmia, microcephaly, mental retardation, external ear, digital, cardiac, skeletal, and urogenital anomalies. We present three brothers (ages 15 years, 9 years, and 18 months) and a maternal uncle (age 27 years) with congenital anophthalmia, delayed motor development, hypotonia, and moderate to severe mental retardation. They also have abnormally modeled ears, high-arched palate, pectus excavatum, finger and toe syndactyly, clinodactyly, fetal pads, scoliosis, cardiac, and renal abnormalities. An obligate carrier had abnormally modeled ears and syndactyly of the 2nd to 3rd toes bilaterally. Linkage and haplotype analysis in this family indicates that the gene is located in a 17.65-cM region on chromosome region Xq27-Xq28. Am. J. Med. Gen. 98:92–100, 2001. © 2001 Wiley-Liss, Inc.

KEY WORDS: anophthalmia; microphthalmia; multiple congenital anomalies; linkage; chromosome region Xq27-Xq28

INTRODUCTION

Lenz syndrome is a multiple congenital anomaly syndrome with variable expressivity. Lenz first described this syndrome in a boy with microphthalmia, developmental delay, and anomalies of ears, teeth, urogenital system, spine, and heart [Lenz, 1955]. We describe three brothers and a maternal uncle with Lenz syndrome and an obligate carrier. Graham et al. [1991] reported linkage to Xq27-28 in a family with microphthalmia without the other signs of the Lenz microphthalmia syndrome. We now report linkage in Lenz syndrome to a 17.65-cM region in chromosome region Xq27-Xq28.

CLINICAL REPORTS

Patient 1

This 15-year-old boy was born at term to a gravida 4, para 1, SAB 3 (spontaneous abortion), 20-year-old woman by cesarean section because of failure to progress. Birth weight was 3.5 kg (75th centile) and length was 48 cm (25th centile). Bilateral anophthalmia was noted at birth. Neonatally the infant had jaundice and hypotonia. Motor development was delayed. Subsequent medical problems included rectal prolapse at age 6 months, abdominal pain, severe acid reflux, constipation, esophagitis, chronic otitis media resulting in a mild hearing loss, neurogenic bladder, and left duplicated renal system. Surgeries included removal of an ear tag, two Achilles tendon lengthening procedures at age 4 and 10 years, and triple arthrodesis for planovalgus feet at age 10 years. An electrocardiogram was normal. An electroencephalogram (EEG) showed no focal abnormalities or seizure activity. A magnetic resonance imaging at age 8 years demonstrated normal brain anatomy and bilateral anophthalmia with absence of the optic nerve and chiasm. He has mental retardation, self-mutilating behavior, and mood swings. Puberty occurred at age 12 to 13 years. At age 15 years, height was 150 cm (5th centile), weight 38.2 kg (<3rd centile), and OFC 56.8 cm (75th centile). Overgrowth of the lid margins was noted. Outer canthal distance was 7.62 cm (<3rd centile), inner canthal distance 3.81 cm (>97th centile), and palpebral fissure length 1.91 cm (<3rd centile). He had abnormally modeled ears with overfolded upper pinnae. (Fig. 1) There was mild clinodactyly of the fifth fingers, prominent finger joints bilaterally, and fetal pads on all fingers and toes. There was a high arched palate. Narrow proximal feet, pes planus, medial rotation of the medial malleolus, and syndactyly of toes 2-3 was noted. There was scoliosis, pectus excavatum, gena valga, and low muscle tone. Pubertal development was at Tanner stage V.

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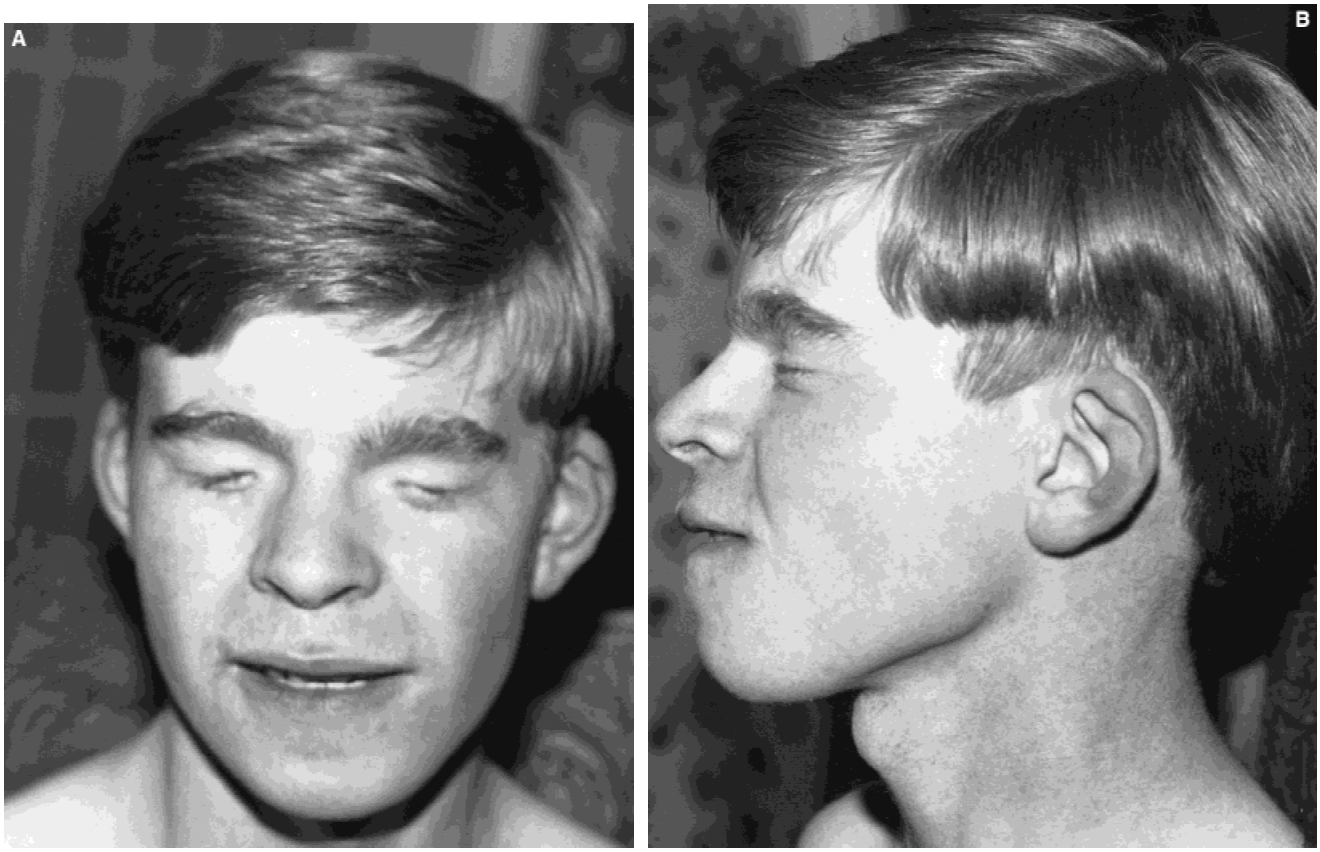

Fig. 1. Patient 1 at age 15 years. Note bilateral anophthalmia and abnormally modeled ears with overfolded helices.

Patient 2

This 9-year-old boy is the brother of patient 1. His mother was 25 years old at the time of his birth. Prenatal ultrasonography at 13 weeks of gestation showed anophthalmia and diaphragmatic hernia. Fetal echocardiogram was normal. Karyotype by amniocentesis was normal. He was delivered by cesarean section at term. Birth weight was 3 kg (25th centile) and length 48 cm (25th centile). Neonatally he had unilateral pulmonary hypoplasia requiring mechanical ventilation, an intraventricular hemorrhage, and hypotonia. At age 1 year he had normal renal ultrasound findings. A magnetic resonance imaging at age 4 years was consistent with anophthalmia with absence of the optic chiasm and optic nerves. Other medical problems included tight Achilles tendon, apparent megacolon with frequent impaction, recurrent otitis media with mild hearing loss, and seizures. An EEG at age 7 years demonstrated significant epileptiform activity in the left occipital and posterior temporal areas. He rolled over at age 6 months, crawled at 9½ months, and walked at 4 years. He was diagnosed with attention deficit disorder with hyperactivity. He demonstrates severe sensory impairment, head banging, aggressiveness towards others, self-mutilation, tactile defensiveness, and autistic behavior. At age 9 years height was 122.6 cm (<3rd centile), weight 25 kg (5th centile), and OFC 51.4 cm (25th centile). He had bilateral anophthalmia, prominent philtrum, high arched palate, crowded teeth, and abnormally modeled ears (Fig. 2). He also has a pectus excavatum and scoliosis. There were broad bases of the fingers, clinodactyly of the right fifth finger, and mild webbing between the fingers. There was syndactyly of the left 2nd and 3rd toes with medial deviation of the toes with overlap of the great toe. There were fetal pads on all fingers and toes, narrow proximal feet, and pes planus.

Patient 3

This 18-month-old brother of patients 1 and 2 was born by cesarean section to his gravida 7, para 2, SAB 4, 33-year-old mother. Prenatal ultrasonography suggested bilateral anophthalmia and a normal heart. Birth weight was 3.25 kg (50th centile) and length 46 cm (5th centile). At birth, the diameter of the right and left cornea was 4.0 and 9.0 mm, respectively. Infancy was complicated by hypotonia, feeding problems necessitating gastrostomy, pyloric stenosis, frequent respiratory problems, and laryngotracheobronchomalacia requiring a tracheotomy. Renal ultrasound findings were normal. He required intermittent hip bracing due to shallow sockets. He has developmental delay. He began crawling at age 16 months. There are no behavior concerns. At the time of examination he could sign approximately 20 words. On examination at age 18 months, his weight was 8.2 kg (<3rd centile) and OFC was 45 cm (25th centile). The right eye was present although it was very small with a rudimentary iris and

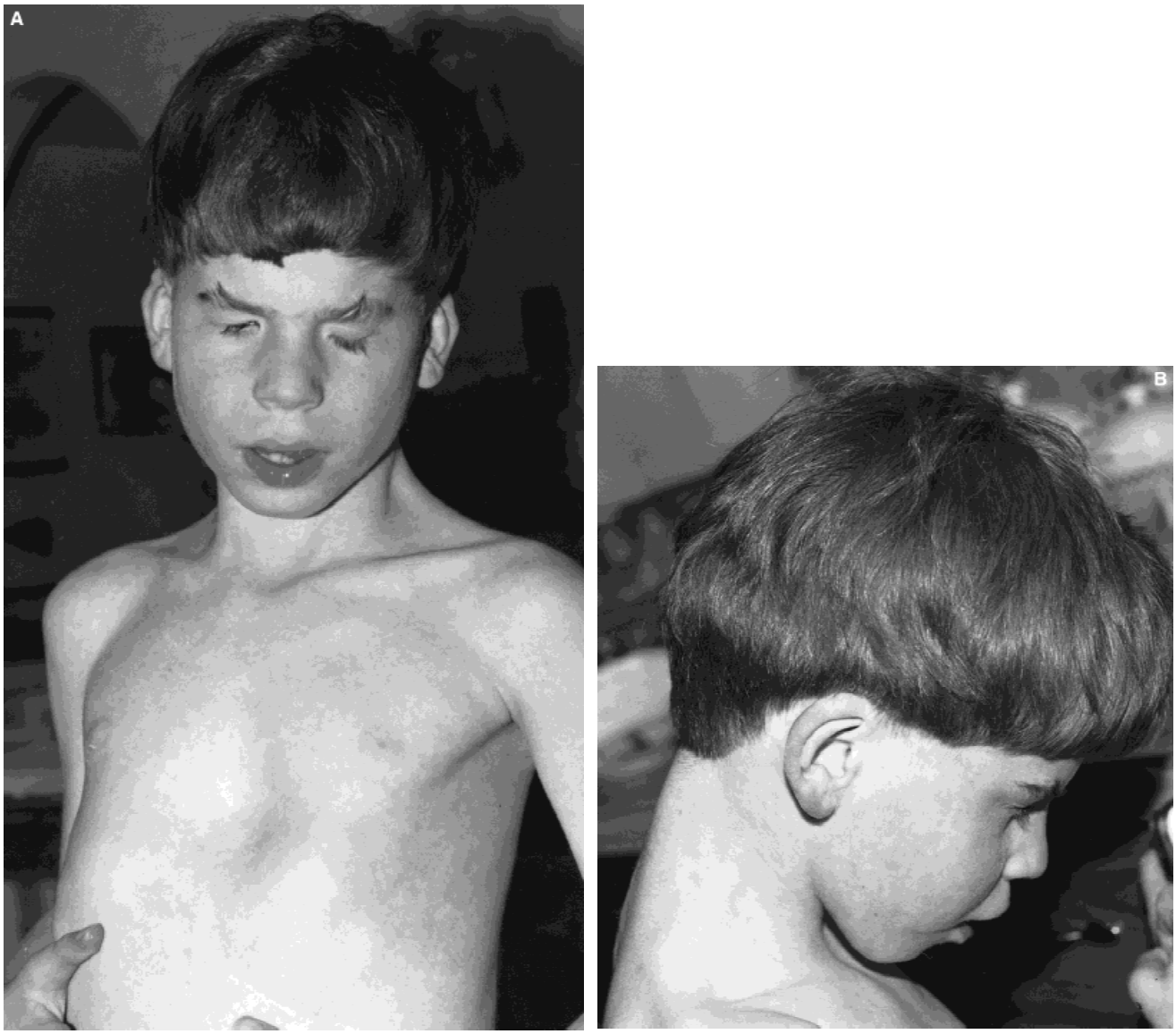

Fig. 2. Patient 2 at age 9 years. Note bilateral anophthalmia, prominent philtrum, abnormally modeled ears, and pectus excavatum.

absent pupil. The left eye was small with corneal sclerosis. Abnormally modeled, slightly low placed ears with a residual skin tag on the right were noted (Fig. 3). Bilateral 2-4 syndactyly of the toes was noted. There was bilateral 3-4 finger syndactyly and 5th finger clinodactyly. Talipes equinovalgus, a high arched foot, and fetal pads on the toes were noted, as well as a high arched palate, accessory nipple on the left, pectus excavatum, and substantial generalized hypotonia.

The mother of the three brothers we describe had low-set, abnormally modeled ears, mild bitemporal narrowness, a high arched palate, a short fifth finger, fifth finger clinodactyly, bilateral 2-3 toe syndactyly, and OFC of 57 cm (90th centile). She has had four spontaneous abortions. Her mother, also an obligate carrier, had had three spontaneous abortions. Her sister, later found to be a possible carrier by linkage analysis, has short stature and 2-3 toe syndactyly by report.

Patient 4

This 27-year-old man is the maternal uncle of patients 1, 2, and 3. Limited history is available on him. He was born prematurely to a gravida 8, para 4, SAB 3, 31-year-old woman. Birth weight was 1.4 kg (<5th centile). Bilateral anophthalmia was noted at birth. Medical complications include cerebral palsy, right ventricular hypertrophy, megacolon, and constipation. He is severely mentally retarded with an IQ below 20. A Vineland Adaptive Behavior Scales at age 21 years demonstrated an age equivalency of 3 years. He also has self-injurious behavior. On examination, his height was 150 cm (<3rd centile), weight 35 kg (<3rd centile), and OFC 54.4 cm (25th centile). He also had dolichocephaly, brachycephaly, bitemporal narrowness, and bilateral anophthalmia. Inner canthal distance was 3.1 cm (60th centile), palpebral fissure length was 1.6 cm (<3rd centile). Teeth were peg-like (Fig. 4). Ear length

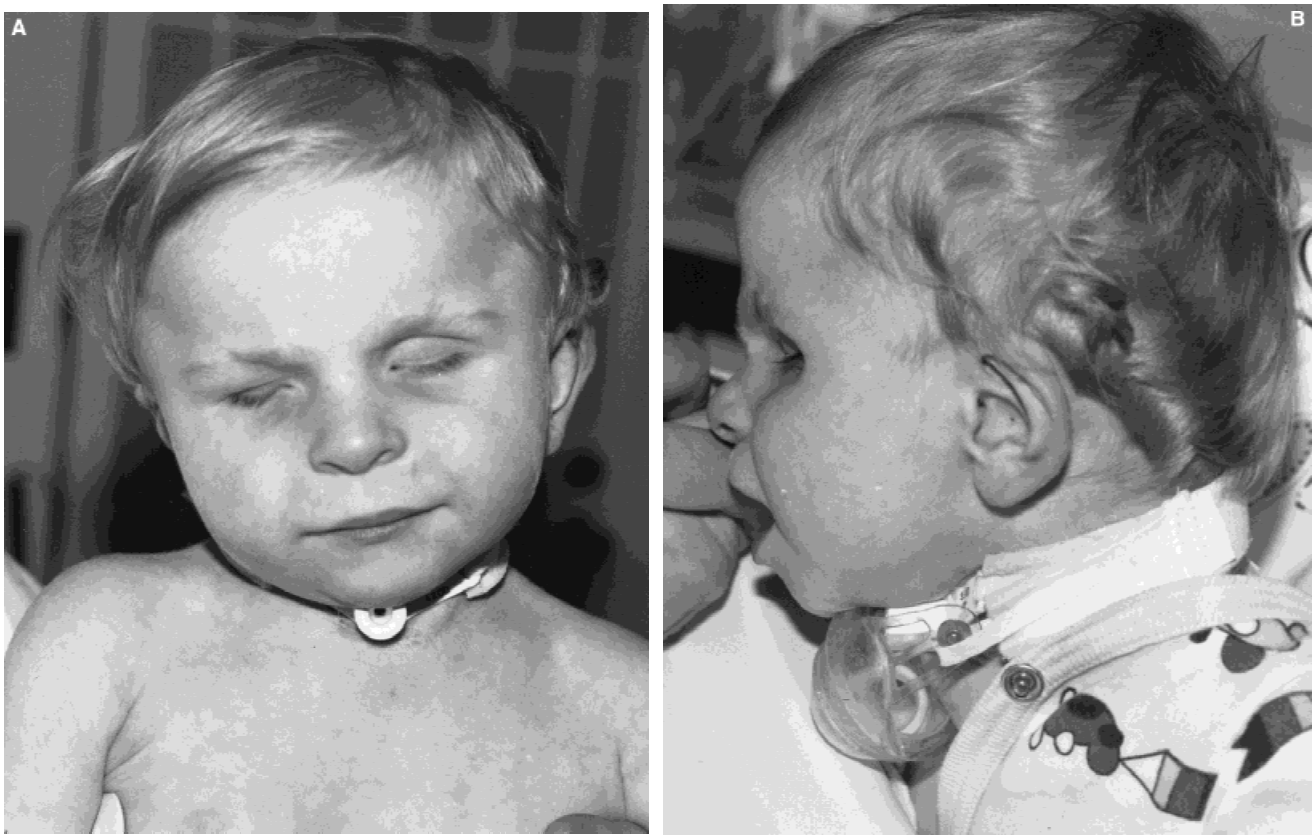

Fig. 3. Patient 3 at age 18 months. Note bilateral microphthalmia, overfolded helices, and tracheostomy.

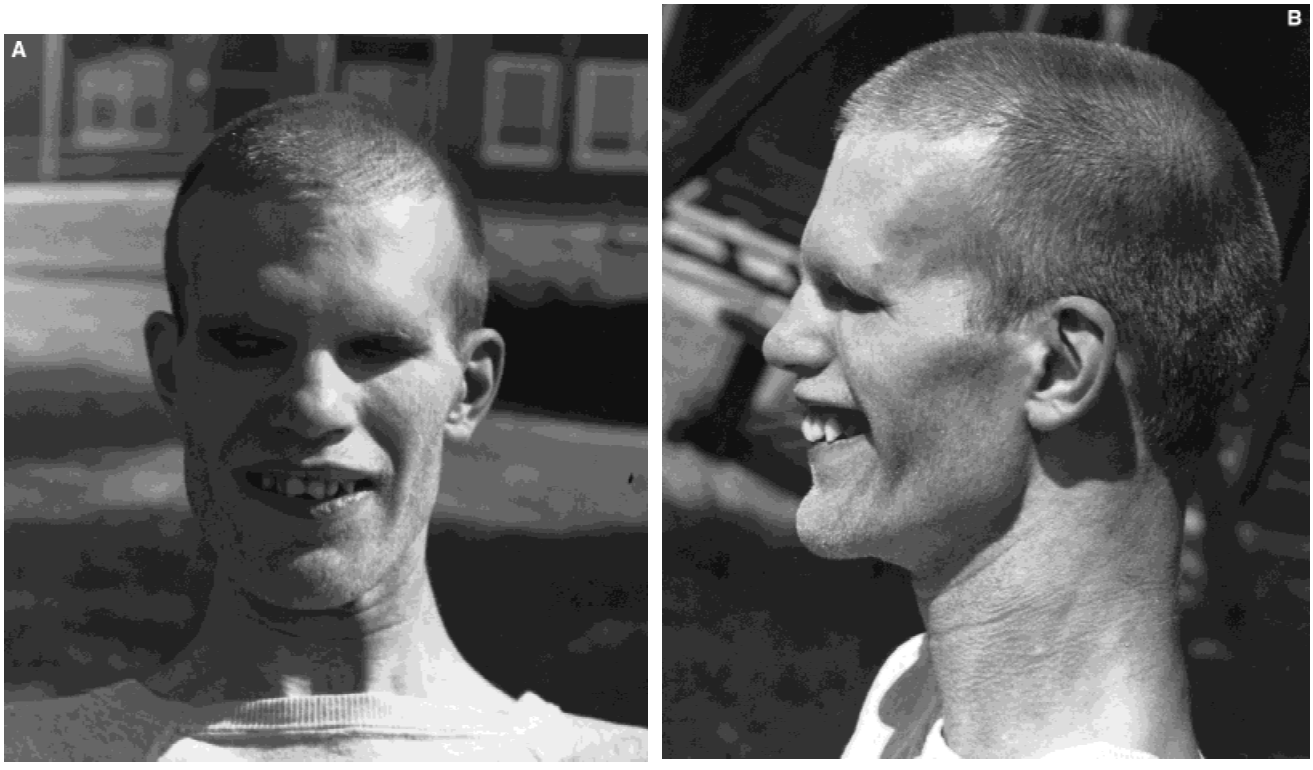

Fig. 4. Patient 4 at age 27 years. Note anophthalmia, dolichocephaly, and peg-like teeth.

and configuration was normal. There was partial syndactyly of the 3rd and 4th fingers, a short fifth finger, and prominent knuckles (Fig. 5). The right foot had a Y-shaped syndactyly of the 2nd and 3rd toes, and the left foot had 1st and 2nd toe syndactyly and minimal syndactyly between the other toes. Fetal pads were noted on all the fingers and toes. There was scoliosis, a mild pectus excavatum, and hypotonia.

MATERIALS AND METHODS

DNA Marker and Linkage Analysis

Genomic DNA for polymerase chain reaction analysis was extracted from blood obtained by venipuncture. In the case where blood could not be obtained buccal scrapings were collected. DNA was extracted from blood by means of the Pure Gene DNA Isolation Kit (Gentra Systems, Minneapolis, MN) and from buccal scrapings by standard methods. Amplification was performed with forward primers tagged with fluorescent dyes (Research Genetics, Inc., Huntsville, AL). Primers not provided in tagged form were labeled with fluorescein isothiocyanate using a 5′-oligolabelling kit (Amersham-Pharmacia Biotech, Uppsala) according to manufacturer's instructions. The polymerase chain reactions were performed using an initial denaturing step of 5 min at 95°C, after which amplification was done for 35 cycles (1 min/95°C; 1 min/55°C; 1 min/72°C) followed by a final extension at 72°C for 7 min. Amplification products prepared in a denaturing formamide loading solution were analyzed on a 6% denaturing polyacrylamide gel by electrophoresis for 1 to 3 hr. The results were visualized with an FMBIO-100 fluorescent image-scanning unit (Hitachi, South San Francisco, CA). A PowerPlex allelic ladder (Promega, Madison, WI) was loaded onto each gel to permit sizing of individual alleles. Alleles were scored and the genotype data were entered into the pedigree file of the LINKAGE computer package. For linkage analysis a standard LOD-score approach using LINKAGE was used, MLINK for the two-point, and LINKMAP for the multipoint.

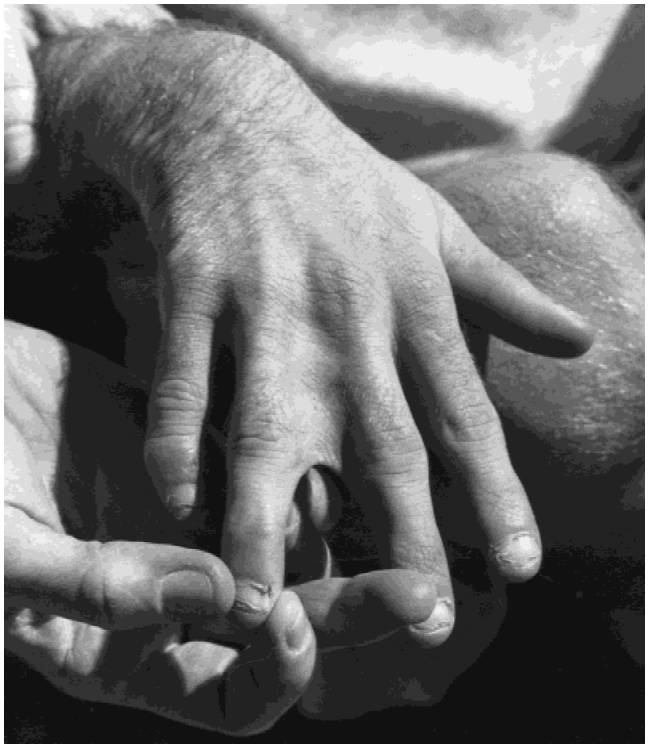

Fig. 5. The hands of patient 4 shows syndactyly of 3rd-4th fingers bilaterally.

RESULTS

Genetic Linkage and Haplotype Analysis

Genotyping was performed with a series of low-density microsatellite markers spanning the entire length of chromosome X. Linkage to chromosome Xpter-Xq24 was excluded based on genetic recombination events with markers proximal to and including GATA172D05 in individual V-11 (data not shown). A previous report of X-linked anophthalmos mapping to chromosome region Xq27-q28 prompted linkage analysis with microsatellite in this region [Graham et al., 1991]. Table I presents the LOD scores obtained from the two-point linkage analysis. A maximum LOD score of 1.21 at recombination fraction of 0.00 was obtained with marker DXS1205. Multipoint linkage analysis gave a maximum LOD score of 1.83 positioned within the interval flanked by markers DXS1205 and DXS1227 (Fig. 6). Although the size of the study group was not sufficient to generate a LOD score ≥ 3, a disease haplotype could be constructed, assigning the most likely linkage phase by minimizing the number of recombinants within a pedigree (Fig. 7). The haplotype of individual V-4, an affected male, was used as the reference for the disease haplotype. The minimal segment of chromosome X that cosegregated with the disease was defined by two informative recombinations. In patient 3 and his mother (V-11), a recombination event occurred between markers DXS1192 and DXS1232 that excluded the region centromeric to DXS1232. The second informative recombinant, V-12, is a male with unexplained mild mental retardation and corneal opacities, however, without the severe microphthalmia and syndactyly associated with Lenz microphthalmia syndrome and seen in the other four patients. This male shares the disease haplotype with individual V-4 for markers DXS8043, DXS8028, DXS8091, DXS1193, DXS8011, and DXS15. If this individual is unaffected, recombinations indicate that the critical region for Lenz Syndrome is in a 17.65-cM region on chromosome Xq27.1-Xq28 between markers DXS1232 and DXS8043. It is possible however that the mild phenotype in V-12 may represent a form-fruste of Lenz microphthalmia syndrome. This would result in gene localization to an approximate 32-cM region on chromosome Xq26-qter. Individual V-6 has not been examined however may be a carrier female, since she is reported to have toe syndactyly and has the entire disease haplotype. Her daughter, VI-4, shares part of the disease allele. However, she does not have the findings of the other carriers in the family. Figure 8 summarizes the conclusions derived from haplotype analysis.

TABLE I. Two Point LOD Score Analysis Between Lenz Syndrome and Chromosome X Markers

Marker	Chromosome location	Recombination fraction Θ										
		0.00	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
DXS9896	Xp22.1–q23	–	−2.16	−1.34	−0.90	−0.61	−0.41	−0.27	−0.16	−0.08	−0.03	0.00
DXS6810	Xp11.4–11.3	0.69	0.62	0.54	0.46	0.38	0.30	0.23	0.15	0.09	0.04	0.00
DXS6789	Xq21.3–q22	–	−1.70	−1.11	−0.78	−0.56	−0.39	−0.27	−0.17	−0.10	−0.04	0.00
GATA172D05	Xq22–q23	–	−0.45	−0.22	−0.11	−0.05	−0.02	0.00	0.01	0.01	0.01	0.00
DXS1192	Xq26	–	0.43	0.63	0.68	0.67	0.62	0.54	0.43	0.31	0.16	0.00
DXS1232	Xq27	0.90	0.85	0.79	0.72	0.65	0.56	0.47	0.37	0.26	0.14	0.00
DXS1205	Xq27	1.21	1.11	1.00	0.89	0.77	0.65	0.53	0.40	0.27	0.14	0.00
DXS1227	Xq27	0.93	0.84	0.75	0.66	0.56	0.47	0.38	0.29	0.19	0.10	0.00
DXS8043	Xq27.3–q28	0.85	0.85	0.80	0.72	0.63	0.52	0.41	0.31	0.20	0.11	0.00
DXS8028	Xq28	0.64	0.61	0.58	0.54	0.49	0.43	0.36	0.29	0.20	0.11	0.00
DXS8091	Xq28	−0.18	−0.15	−0.12	−0.10	−0.08	−0.06	−0.05	−0.03	−0.02	−0.01	0.00
DXS1193	Xq28	0.15	0.15	0.13	0.10	0.07	0.04	0.01	−0.01	−0.02	−0.02	0.00
DXS8011	Xq28	0.55	0.57	0.55	0.50	0.43	0.35	0.27	0.20	0.13	0.06	0.00
DXS15	Xq28	0.90	0.88	0.82	0.74	0.65	0.54	0.43	0.32	0.21	0.11	0.00

DISCUSSION

Fourteen previously reported cases were reviewed and combined with our four cases to determine the frequency of the congenital anomalies of Lenz syndrome (Table II). Developmental delay or mental retardation was present in all individuals. Ninety-three percent had growth retardation, 69% had microcephaly, 88% had ear anomalies, 76% had dental anomalies, 65% had a palatal deformity, 12% had a congenital heart defect, 50% had a urogenital anomaly, 47% had a spinal deformity, and 69% had anomalies of the fingers or toes. Karyotypes were done in 7 of the 18 and all were reported as normal. The aforementioned characteristics were also present in the four males we describe here. Novel findings in our patients include fetal pads. Pectus excavatum was reported previously by Antoniades et al. [1993]. Behavior problems in three of the four males include aggression, self-injurious behavior, tactile defensiveness, and autism.

Other reports of obligate carriers include recurrent spontaneous abortions [Lenz, 1955; Hoefnagel et al., 1963; Baraitser et al., 1982; Herrmann and Opitz, 1969; Antoniades et al., 1993], short stature [Lenz, 1955; Herrmann and Opitz, 1969], and syndactyly of 2nd and 3rd toes [Herrmann and Opitz, 1969; Antoniades et al., 1993]. These reports suggest that the pres-

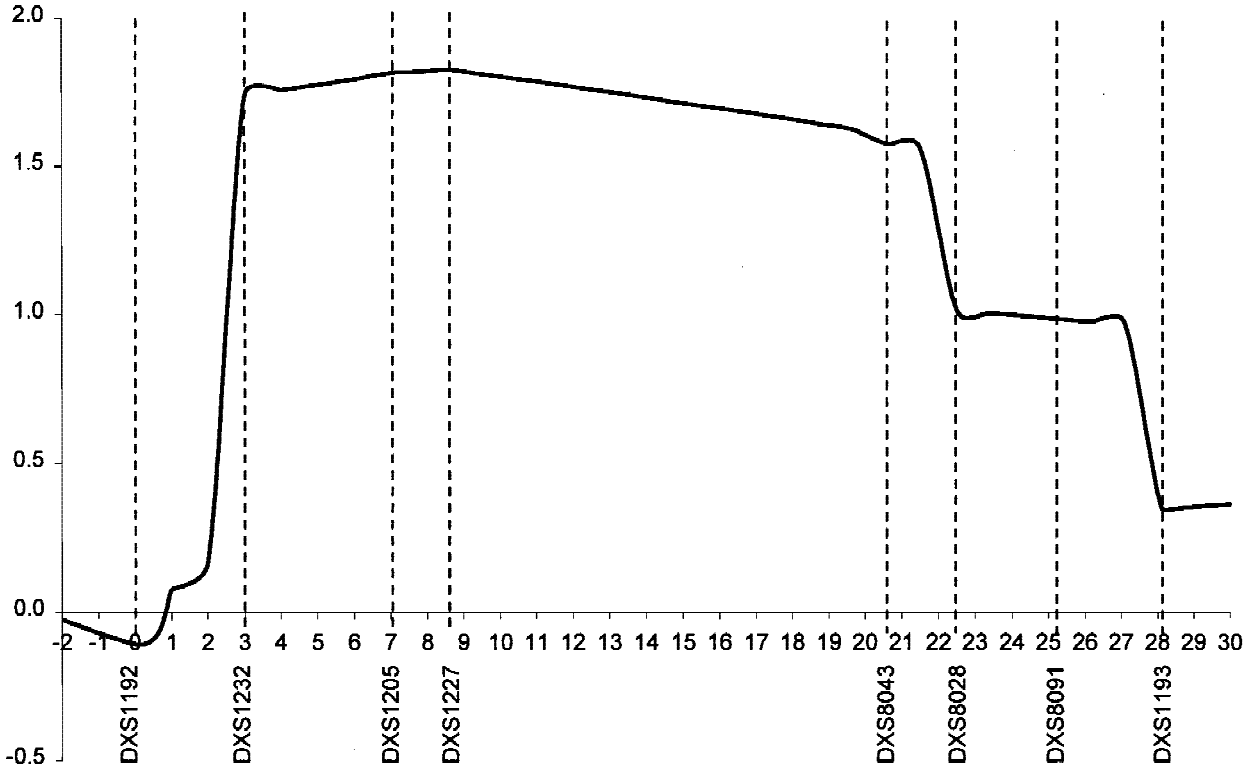

Fig. 6. Multipoint graph of markers mapped to the chromosome Xq. The relative positions of markers are indicated with dashed lines. The *x* axis represents the approximate distance between markers in cM.

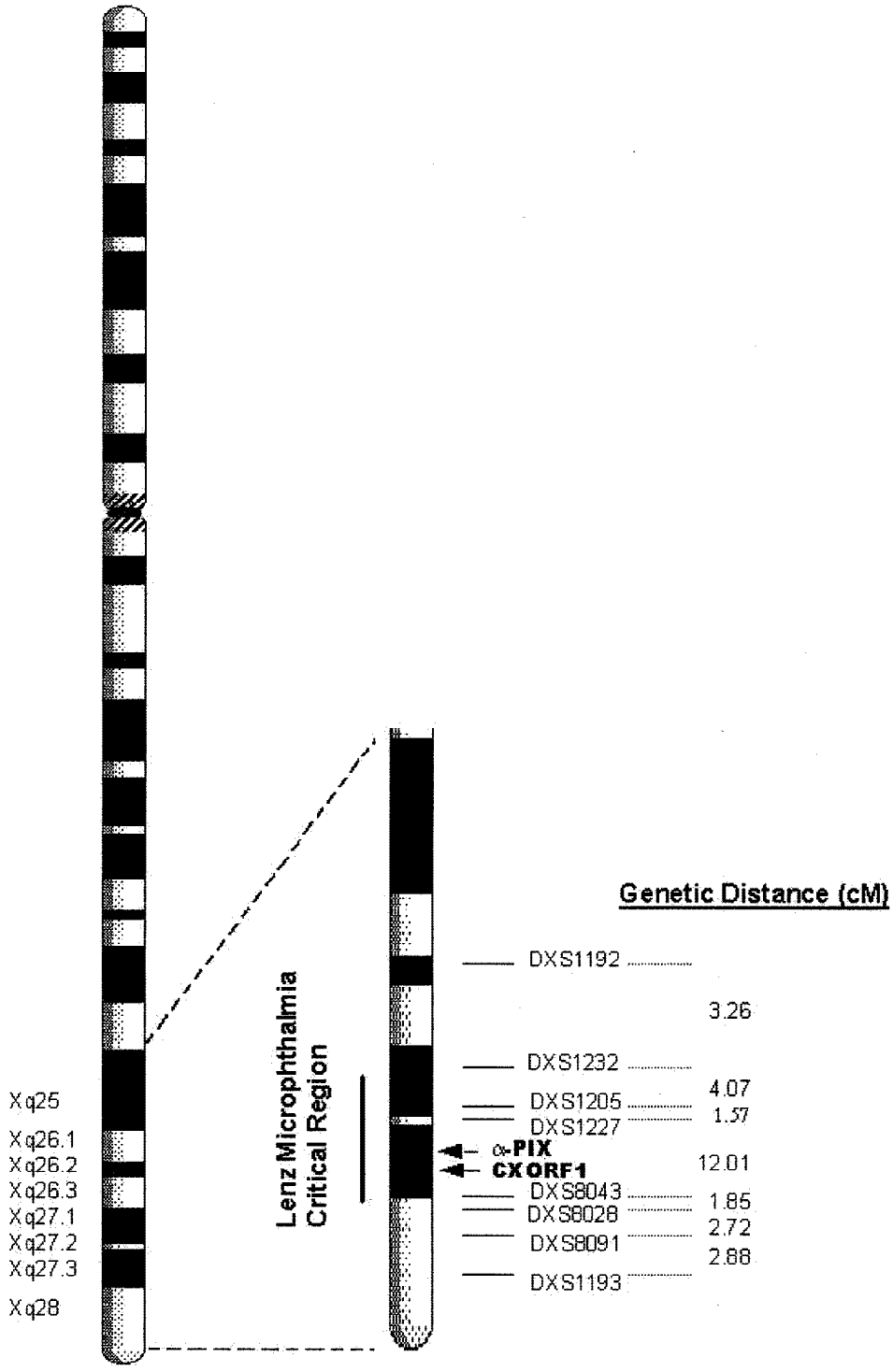

Fig. 7. Chromosome X showing marker order and intermarker distances (cM) based on the Marshfield female genetic map. The critical region associated with Lenz microphthalmia is indicated by a vertical black bar. Arrows show the relative position of candidate genes mapped to the disease.

ence of recurrent spontaneous abortions with short stature and toe syndactyly may be helpful in diagnosing carriers.

We have established linkage for Lenz microphthalmia to a 17.65-cM region of Xq27.1-q28 flanked by microsatellite markers DXS1232 and DXS8043. This region overlaps the anophthalmos locus ANOP1 [Graham et al., 1991], but excludes the OCRL locus for Lowe oculocerebrorenal syndrome, another X-linked recessive disorder causing mental retardation, cataracts, and renal tubular dysfunction. Genes that map to this critical interval include *CXORF1* and *KIAA0006*. *CXORF1* represents a promising candidate gene for Lenz microphthalmia because of its chromo-

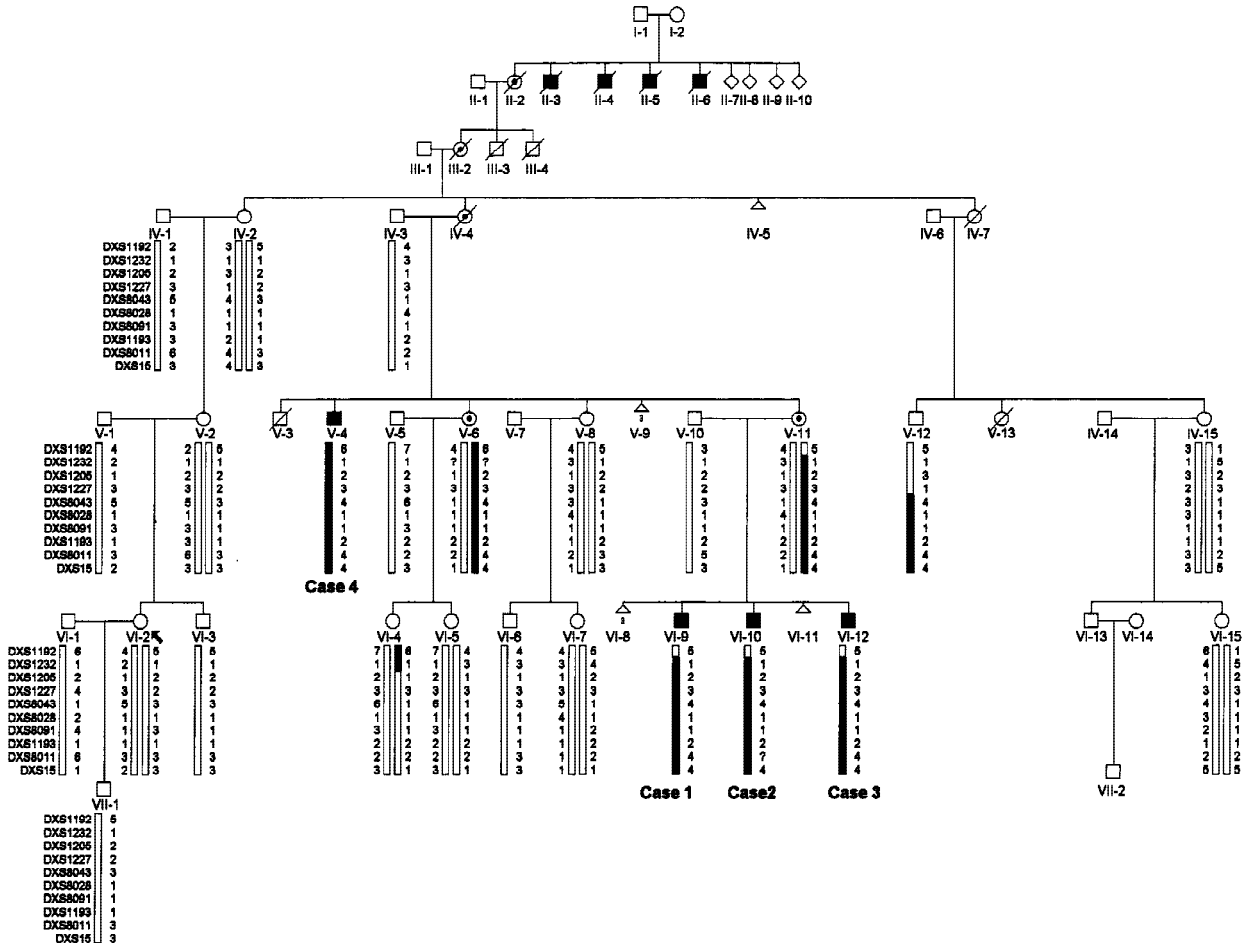

Fig. 8. Pedigree of family affected with Lenz microphthalmia showing haplotype analysis. Markers are listed top to bottom from telomere to centromere. The boldface bars represent the disease haplotype. Circles denote females, squares denote males, slashed symbol denotes deceased individuals, blackened symbol denotes affected individuals, triangles denote spontaneous abortions. An arrow indicates the proband.

TABLE II. Review of Anomalies Seen in Lenz Microphthalmia Syndrome

	Microcephaly	Ear	Teeth	Palate	Urogenital	Spine	Digital
Lenz, 1955	NA	NA	NA	High arched	Hypospadias	NA	NA
Herrmann and Opitz, 1969	+	Single, anteverted tags,	Agenesis of upper incisors	High arched	Hypospadias, cryptorchidism	Lordosis	Syndactyly, clinodactyly, camptodactyly
Hoefnagel et al., 1963 (propositus)	+	Large, anteverted	—	—	—	—	—
Glanz et al., 1983	+	Simple, anteverted, tags	Widely spaced, peg like	Cleft palate	Hypospadias, cryptorchidism	—	Syndactyly
Baraitser et al., 1982	+	Simple, protruding	Crowded	High arched	—	—	Syndactyly, pseudoclubbing
Traboulsi et al., 1988 (case 1)	+	Low set, rotated	Widely spaced	—	—	—	Hypoplastic thumb, clinodactyly
Traboulsi et al., 1988 (case 2)	–	Cup shaped, tag	—	—	Hypospadias	—	Syndactyly, dup thumb, clinodactyly
Ozkinay et al., 1997	–	Simple, anteverted tags	Widely spaced, hypoplastic	High arched	Hypospadias	—	—
Goldberg and McKusick, 1971 (IV-3)	+	Simple, anteverted	—	—	—	—	—
Goldberg and McKusick, 1971 (III-4)	+	—	Diastema	—	—	Kyphosis	—
Goldberg and McKusick, 1971 (III-18)	+	Simple, anteverted	Widely spaced	—	—	—	—
Antoniades et al., 1993	+	Simple, low set, rotated	Delayed dentition	High arched	—	Lordosis	Syndactyly
Pallota, 1983	+	Low set, anteverted	Agenesis of incisors	High arched	Cryptorchidism	Schisis	Broad thumb, clinodactyly
Present case 1	–	Tag, overfolded helices	—	High arched	Left duplicated renal system	Scoliosis	Fetal pads, clinodactyly
Present case 2	–	—	Crowded	High arched	—	Scoliosis	Fetal pads, syndactyly, clinodactyly
Present case 3	–	Low set, overfolded	—	High arched	—	—	Fetal pads, syndactyly, clinodactyly
Present case 4	–	—	Peg like	High arched	NA	Scoliosis	Fetal pads, syndactyly
Incidence	11/16	15/17	13/17	11/17	8/16	8/17	11/16
Percentage with anomaly	69%	88%	76%	65%	50%	47%	69%

NA, Information not available.

somal location and expression pattern. RNA transcripts of *CXORF1* have been detected in sections of human hippocampus, in particular, in the granular-cell layer of the dentate gyrus and in the CA2-CA3 subfields of Ammon's horn [Redolfi, 1998]. These studies suggest that *CXORF1* may have an important function in the brain and consequently mental development. The *KIAA0006* gene encodes for p21-activated kinase (PAK)-interacting exchange factor α (α-PIX). The PAK is a common effector protein of the small GTPases Cdc42 and Rac, which are implicated in cytoskeletal rearrangements and subsequent morphological changes [Van Aelst and D'Souza-Schorey, 1997]. In particular, they have been shown to play important roles in neurite outgrowth and neuronal development [Luo et al., 1997]. Functional studies indicate that α-PIX is activated by phosphatidylinositol 3-kinase and is involved in the receptor mediated signaling leading to the activation of the kinase activity of PAK [Yoshii et al., 1999].

In summary, we present clinical and genetic data on a family with Lenz microphthalmia syndrome, adding to the knowledge of this rare X-linked disorder. Linkage studies in additional families are clearly a priority for the identification of the gene, thus permitting accurate genetic counseling and understanding of the pathogenesis in X-linked microphthalmia.

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