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Craniofacioskeletal Syndrome: An X-Linked Dominant Disorder With Early Lethality in Males

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Abstract

A syndrome with multisystem manifestations has been observed in three generations of a Caucasian family. The findings in seven females provide a composite clinical picture of microcephaly, short stature, small retroverted ears, full tip of the nose overhanging the columella, short philtrum, thin upper lip, soft tissue excrescences at the angle of the mouth, small mandible, small hands and feet with brachydactyly, finger V clinodactyly, flat feet, an excessive number of fingerprint arches, and mild impairment of cognitive function. Two males were more severely affected and died in the initial months of life. They showed intrauterine growth retardation, broad cranium with wide sutures and fontanelles, cardiac defects, small hands and feet with abnormal digital creases and small nails, and genital abnormalities. The affected males had low serum calcium in the neonatal period. Serum calcium, phosphorous, and parathormone levels in the females were normal. Radiographs showed cortical thickening of the long bones, underdevelopment of the frontal sinuses, narrow pelvis and hypoplasia of the middle phalanx of finger five. MRI of the brain showed slightly reduced brain volumes and an extra gyrus of the superior temporal region. X-inactivation studies showed near complete skewing in two affected females, but were not informative in three others. X-linkage as the mode of inheritance is proposed on the basis of different severity in males/females, complete skewing of X-inactivation in informative females, and a lod score (1.5) suggestive of linkage to markers in Xq26-q27.

Keywords

X-linked dominant; microcephaly; cognitive impairment; male lethality; birth defects

INTRODUCTION

Among the X-linked multisystem disorders is a distinctive group that has expression exclusively or predominantly among females. In some cases (e.g., Aicardi syndrome, OMIM 304050; incontinentia pigmenti, OMIM 308310), male lethality, especially during gestation, accounts for the female-limited expression; in other cases (e.g., craniofrontonasal dysplasia,

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OMIM 304110; XLMR-epilepsy, OMIM 300088), male gene carriers have little or no phenotypic effect. Mental retardation is an associated finding in most of these disorders.

An additional X-linked multisystem disorder with female expression and early postnatal lethality in males has been noted in three generations of a Caucasian family. Affected females have microcephaly, short stature, small ears, short philtrum, overhanging columella, thin upper lip, small mandible, small hands and feet, mild impairment of cognitive function, skeletal changes, and an unusual extra temporal lobe gyrus. Two males died in early infancy, having intrauterine growth impairment and craniofacial, cardiac, skeletal, and genital anomalies.

MATERIALS AND METHODS

Clinical Reports

A partial pedigree of kindred 9139 is given in Figure 1. Seven affected females and two affected males in three generations were available for clinical evaluation and molecular studies. It is likely that the syndrome existed in prior generations. A summary of the clinical findings in the seven affected females is given in Table I. Details of the evaluation of the affected males and three of the affected females are given below. Laboratory testing included normal high-resolution (>650 band) chromosome analysis (IV-4, IV-5, V-1), MLPA subtelomere studies (IV-3, IV-5), FISH for del 22q11 (IV-5), plasma cholesterol and 7-dehydrocholesterol (IV-5), and sequence analysis of Filamin A (IV-5, V-1). X-inactivation studies using the androgen receptor (AR) locus showed marked skewing (>90:10) in females III-2 and V-1. The AR locus was not informative in the other affected females.

A blood sample from IV-5 was analyzed for a deletion/duplication on the X chromosome utilizing the X chromosome specific oligo array (NimbleGen) which has an average density of 1 probe per 110 base pairs. A possible deletion was detected in the region involving the SPANX gene cluster in Xq27.1. However, this finding could not be confirmed by qPCR using STSs spanning the region nor by using an alternative X chromosome specific microarray developed by the Human Genome Laboratory, University Leuven.

III-2 was evaluated at age 49 years. She completed high school and worked as a clerk and home keeper. She had five pregnancies resulting in three affected daughters, one non-affected son, and a prematurely born son who died in the neonatal period.

Examination showed a height of 147 cm, weight of 52.3 kg, and head circumference of 50.5 cm, all below the third centile (Fig. 2 and Table I). She had a slight widow’s peak, horizontal palpebral fissures, overhanging tip of the nose, retroverted ears, short philtrum, and thin upper lip. When smiling, there appeared a small excrescence of soft tissue lateral to the mouth. Her hands appeared normal, the right second toe was elongated, and the feet flat. Dermatoglyphics showed two arches, one low radial loop, four ulnar loops, two whorls, and one uncertain pattern. Deep tendon reflexes were normal. Serum calcium, phosphorus, growth hormone, and parathormone were normal.

IV-5 was age 28 years at the time of evaluation. She graduated from high school after requiring special classes and works in a day care center. She has had four pregnancies, resulting in one affected son, one affected daughter, a 2–3 month miscarriage, and a stillborn male associated with abruptio placenta.

Examination showed a height of 145 cm, weight of 42.7 kg, and head circumference of 50.3 cm, all below the third centile (Fig. 2 and Table I). She had small retroverted ears and small hands and feet. The philtrum was short. She had a (repaired) cleft palate, small chin, and

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small tissue excrescence at the left angle of the mouth. A systolic ejection heart murmur of undetermined significance was present. She had a small left fifth finger, slightly hyperextensible fingers, bulbous tips to the toes, bilateral syndactyly of toes II–III, and flat feet. Dermatoglyphics showed two arches, one low ulnar loop, one low radial loop, four ulnar loops, and two whorls. Serum calcium, phosphorus, growth hormone, and parathormone were normal.

V-5, a male infant, was born at 33 weeks gestation. Labor was induced because of intrauterine growth retardation and delivery was by cesarean because of fetal distress. The birth weight was 698 g, length was 33 cm, and head circumference was 24.3 cm, all well below the third centile for 33 weeks gestational age. The cranium was broad with widened sutures and large fontanelles (Fig. 3). The eyes were prominent, palpebral fissures small and horizontal, inner canthal measurement was 1.5 cm, and outer canthal measurement was 4.1 cm. The ears appeared low and measured 2.1 cm in length, and the nose was small. The craniofacial appearance was triangular with broad cranium and small chin. The chest appeared broad with widely spaced nipples. Hypospadias was present and the testes were undescended. The thumbs appeared proximally placed, the digits short with single flexion creases with tapering of fingers II and V. The feet were suggestive of rocker bottom deformation. His fingernails were narrow and toenails small. Laboratory studies included normal chromosome analysis, FISH for 22q11 deletion, plasma 7-dehydrocholesterol and cholesterol. Calcium was low (8.4 and 8.6 mg/dl) on two occasions.

Infant V-5 died at 12 days having experienced respiratory insufficiency, hyperbilirubinemia, bilateral intracranial hemorrhages, hydrocephaly, anemia, and thrombocytopenia. Autopsy showed cerebellar hypoplasia, patent ductus arteriosus, atrial septal defect, interrupted aortic arch, absent gallbladder, and hydronephrosis.

V-4, a male infant, was born at 35 weeks gestation and required immediate intubation because of poor respiratory effort. His weight was 1,720 g, length 43 cm, and head circumference 30.5 cm, all between the 10th and 25th centiles. A two-vessel umbilical cord was noted. The cranium was broad and the chin small, giving the face a triangular appearance (Fig. 3). Cranial sutures and fontanelles were wide. The palpebral fissures were downslanting, the inner canthal measurement was 2.5 cm and outer canthal measurement was 5.2 cm, both in the upper centiles. The ears were small (2.9 cm), lowest, and posteriorly rotated. The nose was short. The penis was small, the glans penis was partially uncovered, and the testes were descended. Fingers II–V were small with distal hypoplasia and small nails. The toes and nails were small with bilateral syndactyly of the second and third toes.

Infant V-4 lived for 3 months. He was found during this time to have choanal atresia, distal tracheal stenosis, ventricular septal defect, and right hydronephrosis. Chromosome analysis (580 band level) was normal. Serum calcium level was low on multiple occasions. Autopsy was not performed.

V-1 was born at 36 weeks gestation weighing 2.2 kg and with a length of 46 cm. She had capillary hemangiomas over the posterior neck, glabella, eyelids, and nose. The forehead was broad with a large anterior fontanelle. The orbits appeared shallow, the lips thin, and the chin small.

Examination at age 7 3/12 years showed height of 113 cm (5th centile) and head circumference of 47.8 cm (<3rd centile). Interpupillary measurement was 4.9 cm (20th centile). She had a broad midface, narrow alae nasi, retroverted ears, short philtrum, and small mouth and chin (Fig. 2). Her hands measured 12 cm (<3rd centile), feet were small and flat, and toes IV–V were incurved. Dermatoglyphics showed eight arches and two low loop fingertip patterns.

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Skeletal Findings

Radiographs of the skeleton were made on all females over age 6 years (Fig. 4). Cranial ossification appeared normal, but the frontal sinuses were underdeveloped or absent (three cases) or asymmetrically developed with one side being absent or nearly so (one case). The vertebral bodies appeared foreshortened and of normal to increased height. The iliac wings were tall and appeared narrow in relation to the sacrum. All long bones appeared to have cortical thickening with the marrow cavity reduced to one-third or less of the bone diameter. The hand bones appeared normal except for cortical thickening of the metacarpals and shortening of the middle phalanx of the fifth digits. Radiographs were not available on the two male infants (V-4 and V-5).

Cognitive Testing

The Stanford-Binet Intelligence Scale, 4th edition [Thorndike et al., 1986] was used to ascertain cognitive abilities of the females above age 6 years. Normal abilities in all areas range from 85 to 115 (±1 SD). Verbal reasoning included vocabulary abilities as measured by picture recognition (receptive vocabulary) and definitions (expressive vocabulary) and comprehension (utilizing learned data). Abstract/visual reasoning was a non-verbal measure involving reproduction and analysis of patterns. Quantitative reasoning assessed arithmetic and numeric abilities. Short-term memory assessed immediate recall of beads, and sentences. Results are given in Table II. The data indicated that these patients had greater difficulty with verbal reasoning and short-term memory.

Individual V-8 was tested at age 1 9/12 years using the mental scale of the Bayley Scales of Infant Development, 2nd edition. Testing indicated moderate developmental delay (Mental Developmental Index of 54) and significant language delay.

Brain Morphology (Figs. 5a–c and 6)

MRI acquisition—All MRI scans used in this study were obtained with whole body GE Signa scanners (GE Medical Systems, Milwaukee, WI) at Stanford University School of Medicine. Coronal brain images were acquired from a 3D volumetric radio frequency spoiled gradient echo pulse sequence using the following scan parameters: TR = 35 msec, TE = 6 msec, flip angle = 45°, NEX = 1, matrix size = 256 × 256, field of view = 24 cm, slice thickness = 1.5 mm, 124 contiguous slices. Subjects V-1, IV-5, and III-2 were scanned as part of the multi-disciplinary evaluation of this family.

MRI analysis—MRI scans were imported into *BrainImage 5.x* (cibr.stanford.edu) for semiautomated whole brain segmentation and quantification in the coronal plane. Data processing steps included removal of non-brain tissues from the images, correction of equipment related image artifacts including bias field inhomogeneity, separation (segmentation) of tissue into gray matter, white matter, and cerebrospinal fluid (CSF) components, normalization of image position, and parcellation of the cerebral cortex into lobe and subcortical regions based on a stereotaxic atlas template [Talairach and Tournoux, 1988]. This procedure, as described and validated in previous reports [Reiss et al., 1998; Kates et al., 1999], results in reliable measurements for global and regional brain volumes of interest. Inter-rater reliability obtained by interclass correlation exceeded 0.90 for all variables reported in this study.

Volumetric measurements from affected family members were compared to a group of 16 age-matched healthy females (mean age = 34.1 ± 20; range = 7.0–60.8). All results are shown in Figure 5.

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Study females showed slightly reduced brain volumes compared to controls. This primarily involved white matter and the decrease in tissue volume was relatively consistent across all cerebral lobes. Cerebral CSF volumes were comparable to controls. Cerebellar volume was similar to controls for III-2 and IV-5 but was markedly reduced for V-1. Cerebellar size reduction in V-1 appeared to exclusively involve white matter. Despite ventricular CSF volumes that were comparable to controls, all three studied females demonstrated reduced subcortical gray matter volume. V-1 and IV-5 showed lower corpus callosum areas for their age groups. V-1 and IV-5 also demonstrated relatively lower hippocampal volumes. An incidental CSF cyst was observed in IV-7 in the area of the inferior lenticular nucleus.

One of the most prominent and consistent findings among the study females involved unusual morphology of the superior temporal region. Specifically, all study females demonstrated an extraneous gyrus that extended from or merged with Heschl's gyrus (Fig. 6).

Molecular Findings

Linkage analysis was performed using 25 markers distributed on the X chromosome. A suggestion of linkage as found with markers in Xq26-q27 (lod score of 1.51 with $\theta = 0$ for markers HPRT and DXS984, data not shown). X-inactivation was studied using polymorphism in the AR locus. Two females were informative and showed marked skewing (>90:10) of X-inactivation.

DISCUSSION

Consideration that a gene on the X chromosome is responsible for the syndrome described here rests with the differing phenotypic severity in males and females, the near complete skewing of X-inactivation in female gene carriers, and suggestive linkage results.

This entity may be considered to be X-linked dominant in that females are affected, but less severely than males. Alternatively, one might consider it to fit among a group of remarkable X-linked syndromes which occur predominantly among females (Table III). The paucity of affected males in these syndromes has been attributed in most cases to male lethality, usually in the form of early pregnancy loss. Impairment of cognitive function occurs in over half of the X-linked conditions with predominant expression in females (Table III). Most of these X-linked conditions can be easily excluded on the basis of the clinical and radiological findings, location of the disease loci, or molecular studies. Although CODAS (cerebral, ocular, dental, auricular, skeletal anomalies) syndrome, a possibly X-linked entity, has findings involving the same systems as the craniofacioskeletal syndrome reported here, the findings are of quite a different nature [Shebib et al., 1991].

Other XLMR syndromes that must be considered because of the manifestations in the males includes Brooks, Schimke, and Hamel cerebropalatocardiac syndromes. The last can be excluded on the basis of normal *PQBP1* analysis. While the genes responsible for Brooks and Schimke syndromes are not known, cognitive defect in female gene carriers has not been described in either syndrome.

The skeletal changes in the females and the hypocalcemia in the affected male infants suggest the possibility that calcium–phosphorus metabolism may be disturbed in this condition. An X chromosomal locus for hypoparathyroidism is present in Xq27 [Nesbit et al., 2004]. The gene for hypoparathyroidism at this locus has not been identified. Our linkage analysis shows only suggestive linkage (lod score 1.5) to this region and we could not demonstrate an abnormality in serum calcium, phosphorus or parathormone levels in the females. Further, the families with hypoparathyroidism linked to Xq27 do not have female

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manifestations, mental retardation, or the constellation of birth defects present in the two male infants [Peden, 1960; Whyte and Weldon, 1981; Whyte et al., 1986]. The skeletal changes are also suggestive of Kenny-Caffey syndrome. There appears to be several forms of Kenny-Caffey syndrome: one autosomal recessive, one autosomal dominant, and one associated with deletion 22q11.2 [Kenny and Linarelli, 1966; Fanconi et al., 1986; Tahseen et al., 1997; Sabry et al., 1998; Spranger et al., 2002]. Some individuals with Kenny-Caffey syndrome have microcephaly and mental impairment, but an X-linked form has not been described.

In terms of brain morphology, the study females demonstrated decreased brain volume compared to age-matched controls, particularly in terms of white matter. Certain regional volumes, including hippocampus, corpus callosum and cerebellum were additionally reduced in V-1 and IV-5 but not III-2. Volume reductions in regional areas appeared to be particularly marked for V-1, the youngest subject. Cerebral and ventricular CSF volumes were comparable to those of controls for all study females. When examining CSF, one might expect to see a reciprocal *increase* in CSF in the study females if brain tissue was reduced secondary to atrophy. This is typically referred to as ventriculomegaly ex vacuo and is seen in dementia and other progressive neurological disorders, for example. However, this was not the case in the study females, suggesting that reduced brain volumes are likely secondary to an early neurodevelopmental process such as reduced cellular proliferation. In addition to the well-known association between reduced brain volume and various mental retardation syndromes, lower brain volume has been associated with lower cognitive function as well as lower cognitive reserve, or the capacity to adapt to neurological damage or disease [Reiss et al., 1996; Kesler et al., 2003].

Additionally, all study females demonstrated an extra convolution bilaterally in the Heschl's gyrus region of the superior temporal lobe. There are no data as to the frequency for this morphology and, therefore, it may be syndrome specific. The functional consequence, if any, of this altered morphology is unknown. However, as Hechl's gyrus is the usual location for the primary auditory cortex in humans [Hall et al., 2003], abnormalities in this area may negatively impact sound processing and receptive language.

Clinical examination and detection of marked skewing of X-inactivation in females offers the best approach to diagnosis at present. Further testing of candidate genes in the area of suggestive linkage or elsewhere will be necessary to identify the causative gene and provide more specific molecular diagnostic confirmation.

Acknowledgments

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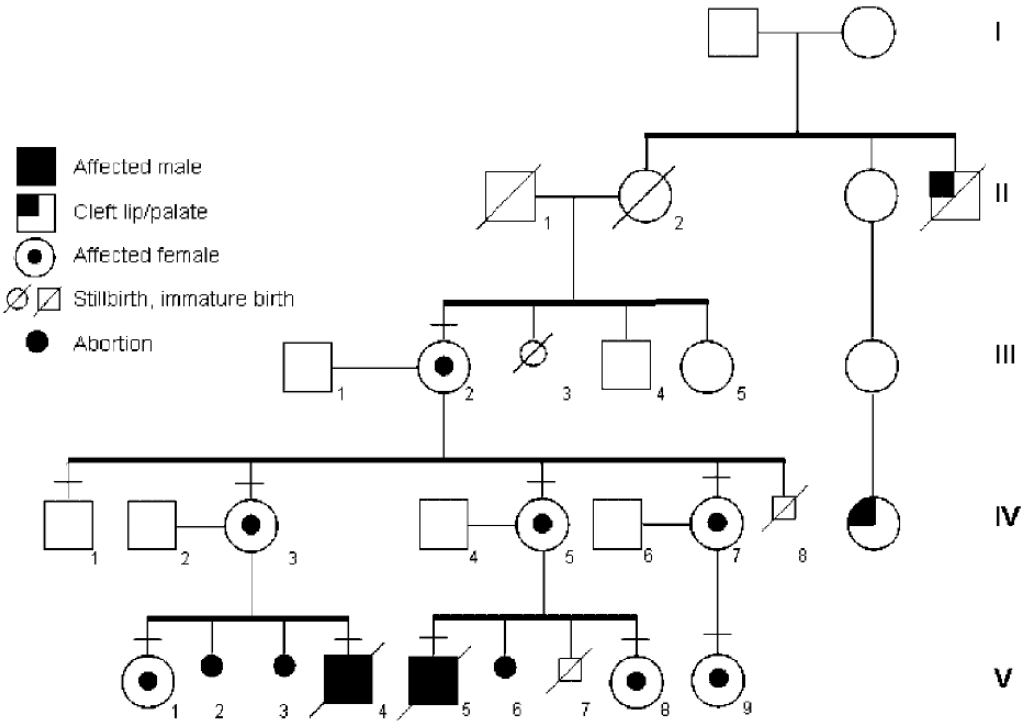

Fig. 1.
Partial pedigree of kindred 9139.

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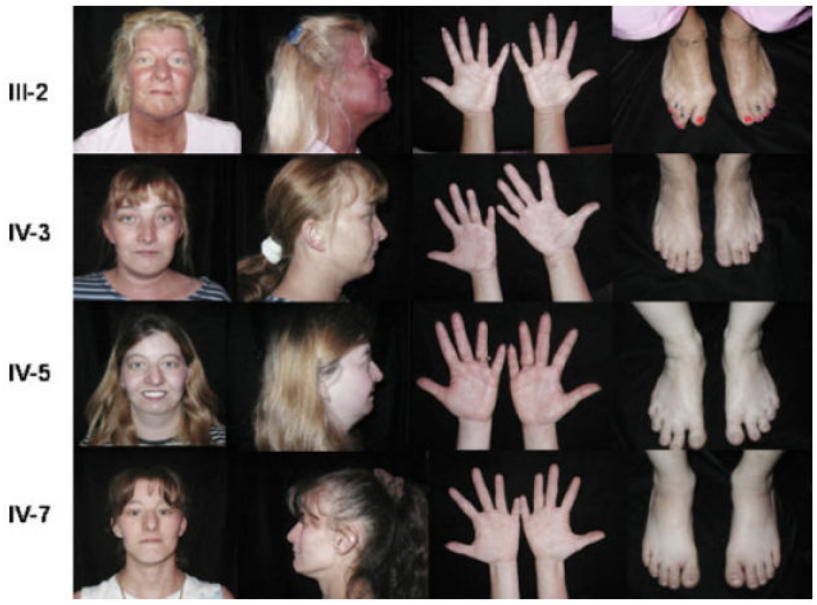

Fig. 2.

III-2 with widow's peak, overhanging tip of nose, retroverted ears, short philtrum, thin upper lip, soft tissue excrescences at bottom of nasolabial creases, short but otherwise normal hands, lateral deviation of toes of right foot. IV-3 showing overhanging tip of nose, small chin, thin upper lip, a bulge of soft tissue at bottom of nasolabial crease, short hands with single flexion crease on fifth finger and decreased distal crease on third and fourth fingers, short fourth toes and syndactyly of the left second and third toes. IV-5 showing overhanging tip of nose, retroverted ears, short philtrum (repaired cleft lip), small jaw, normal but short hands, wide forefoot with spacing of toes, and bulbous distal toes. IV-7 showing hypotelorism, narrow alae nasi, retroverted ears, thin lips, short fifth fingers, and normal feet. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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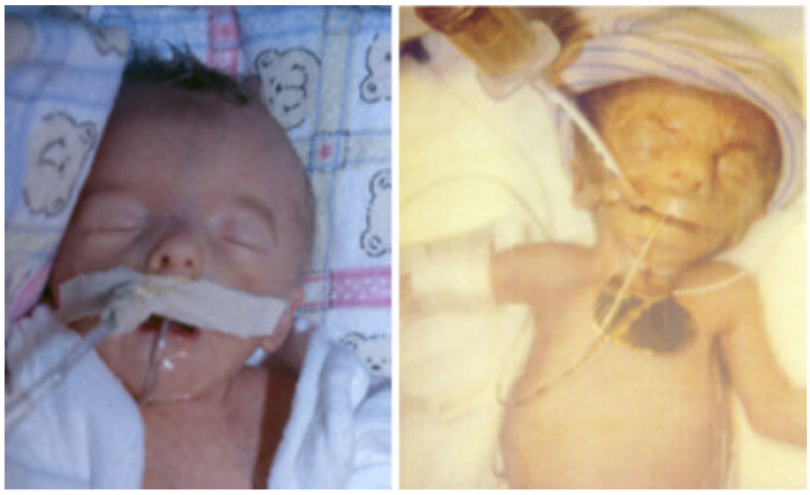

Fig. 3.

Infants V-4 (**left**) and V-5 (**right**) in intensive care during neonatal period. V-4 has broad cranium, downslanting palpebral fissures, small nose and small chin. V-5 has wide cranium, arched eyebrows, small nose and small chin. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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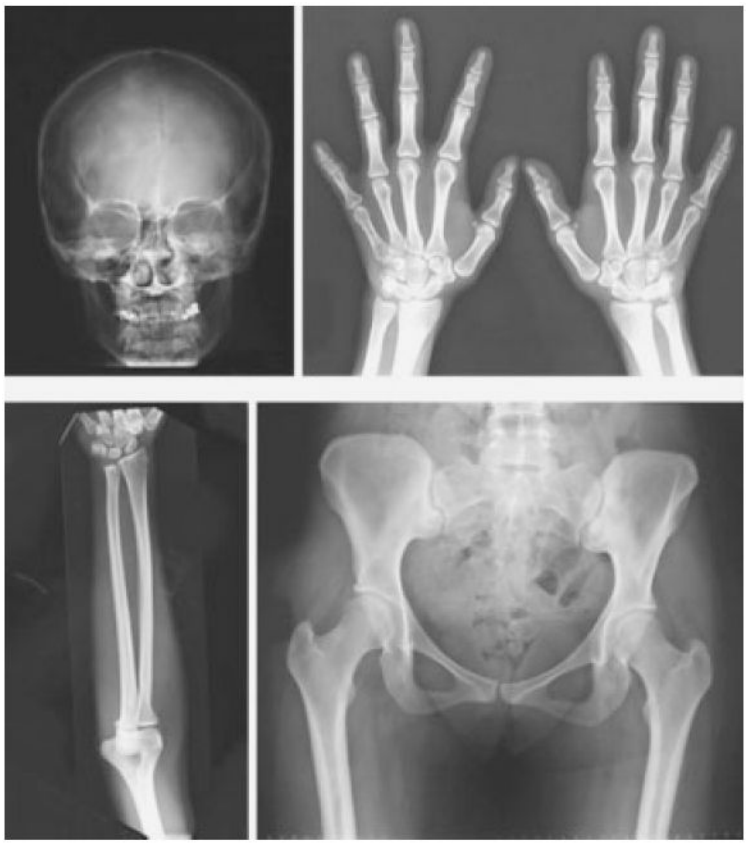

Fig. 4.

Top left: Skull radiograph of IV-3 with small right frontal sinus and absent left frontal sinus. Skull is otherwise normal. **Top right**: Hands of IV-3 showing small middle phalanx of fifth fingers and narrow medullary canals of the metacarpals. **Bottom left**: Radius and ulna of IV-3 showing cortical thickening and narrow medullary canals. **Bottom right**: Pelvis of IV-5 showing narrow ilia.

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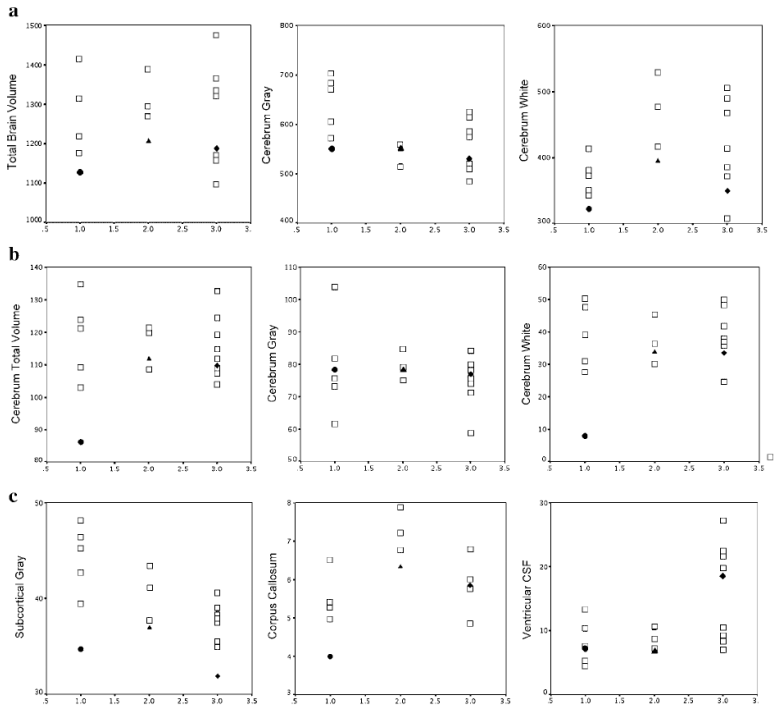

Fig. 5.

a: Total brain volumes including tissue specific (gray, white) demonstrating reduced volumes, particularly in white matter, for study females compared to typically developing age-matched controls. **b**: Cerebellum volumes including both gray and white matter showing reduced cerebellum white matter in V-1 compared to age-matched controls. **c**: Despite comparable ventricular CSF volumes, study females demonstrate reduced subcortical gray matter volumes. Additionally, V-1 and IV-5 show reduced corpus callosum volumes compared to age-matched controls.

All volumes shown in cubic centimeters (cc); typically developing age-matched controls (N=16) are shown as clear squares - □; ● = individual V-1; ▲ = individual IV-5; ◆ = individual III-3

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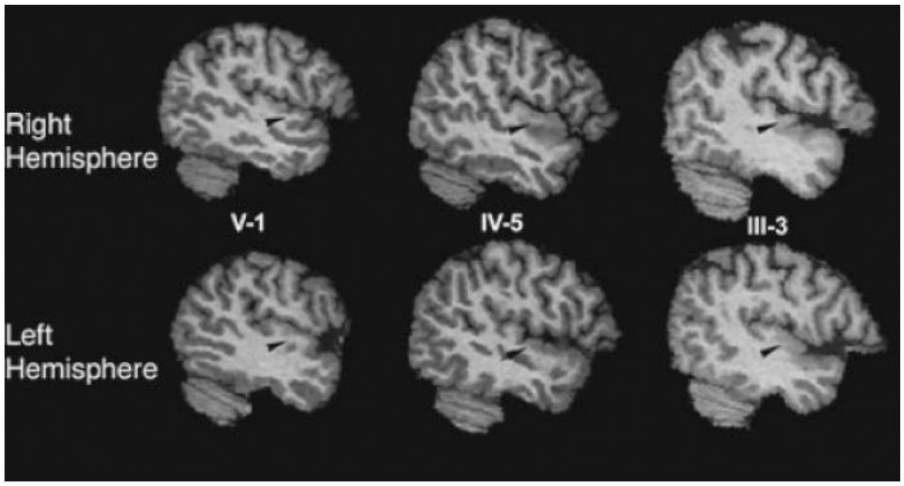

Fig. 6.
Examples in both hemispheres (black arrows) of the extra gyrus in the superior temporal region found in all three study females.

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TABLE I

Clinical Findings in Females with Craniofacioskeletal Syndrome*

	III-2	IV-3	IV-5	IV-7	V-1	V-8	V-9
Age at exam, years	49	30	28	26	7	1.5	5
School completed, years	12	9[a]	12	11	1	0	0
Birth weight, kg	—	—	—	—	2.2	0.7	1.7
Birth length, cm	—	—	—	—	46	33	—
Height, cm (centile)	147 (<3)	154 (10)	145 (<3)	149 (<3)	113 (5)	72 (<3)	94 (<3)
Weight, kg (centile)	52.3 (10)	52.3 (30)	42.7 (<3)	38.6 (<3)	—	6.4 ()	9.5 ()
Head circumference, cm (centile)	50.5 (<3)	50.4 (<3)	50.3 (<3)	49.5 (<3)	47.8 (<3)	41.6 (<3)	45 (<3)
Inner canthal, cm	2.8	3.2	2.6	2.6	2.8	—	2.5
Interpupillary, cm (centile)	5.7 (5)	5.8 (10)	5.3 (<3)	4.9 (<3)	4.9 (20)	—	4.5 (10)
Hand length, cm (centile)	15.8 (<3)	16.1 (<3)	15.7 (<3)	15.1 (<3)	12.0 (<3)	8.4 (<3)	9.9 (<5)
Shoe size (length, cm)	5.5–6	6–6.5	5	5.5	—	(10.3)	(13.6)
Palpebral fissures	Horizontal	Horizontal	Horizontal	Horizontal	Horizontal	NR	Upslant
Ptosis	0	0	±	0	+	+	0
Narrow alae nasi	0	0	0	+	+	+	NR
Nasal tip overhanging	+	+	+	+	+	NR	0
Ear length, cm (centile)	6.0 (55)	5.8 (30)	5.3 (3)	5.5 (10)	5.3 (20)	4.3 (3)	4.6 (<3)
Ears retroverted	+	+	+	+	+	+	0
Short philtrum	+	+	+	0	+	NR	0
Thin upper lip	+	+	+	0	0	NR	0
Cleft palate	0	0	+	0	0	0	0
Small chin	0	+	+	0	+	+	+
Excrescence beside mouth	+	+	+	+	+	0	0
Heart murmur/defect	0	0	+	0	0	0	0
Number arch fingerprints	2	8	2	6	8	NR	3
Short finger V	0	+	+	+	0	0	0
Clinodactyly toes IV–V	0	+	0	+	+	0	0
Flat feet	+	+	+	+	+	0	+

*Two affected males are described in the text.

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[a] Obtained GED, enrolled in Community College.

NR—not recorded.

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TABLE II

Cognitive Testing Results in Females with the Craniofacioskeletal Syndrome

Patient	Verbal reasoning	Abstract/visual reasoning	Quantitative reasoning	Short-term memory	Test composite
III-2	78	98	86	65	79
IV-3	70	82	78	70	72
IV-5	63	94	62	63	66
IV-7	66	80	68	66	66
V-1	71	110	90	84	87

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TABLE III

X-Linked Syndromes Expressed Predominantly in Females*

Syndromes with cognitive impairment	Syndromes without mental retardation
Aicardi	CHILD
CODAS[a]	Congenital contracts with microcornea/microphthalmia
Craniofacioskeletal (present report)	Conradi-Hunermann chondrodysplasia punctata
Goltz	Kobberling-Dunnigan lipodystrophy
Incontinentia pigmenti	Serpentine fibula–polycystic kidney
MIDAS	Wildervanck
Oral-facial-digital I	
Periventricular nodular heterotopias	
Rett	
XLMR-epilepsy	

*Adapted from Reference Stevenson et al. [2000].

[a]X-linkage not certain [Shebib et al., 1991].