Discussion

The karyotype-phenotype correlation in patients with trisomy 8 has been controversial. Riccardi[4] proposed the assignment of the clinical features of trisomy 8 to the q2 segment of chromosome 8. However, Rethoré *et al*[5] and Schinzel[6] argued from features found in patients with partial trisomies that extra material from both the long and short arms of chromosome 8 contributed to the clinical features of the trisomy 8 syndrome.

The present patient with only the short arm trisomy had most of the craniofacial features of trisomy 8 syndrome, including microcephaly, asymmetrical skull, hypertelorism, prominent nasal bridge, high arched palate, micrognathia, and low set, malformed ears. Although most of the patients with 8p trisomy did not have the major skeletal features of the trisomy 8 syndrome, the present patient had the cranial, vertebral, and rib anomalies. These findings provide further support for the view of Rethoré *et al*[5] and Schinzel[6] that extra chromosome material from both the short and the long arm segments of chromosome 8 are responsible for the clinical features of trisomy 8 syndrome.

Although clinical features of the 8p trisomy syndrome were thought to be non-specific,[3] the presence of deep skin creases, 'plis capitonnes', on the palms or soles can provide an important clue for the clinical diagnosis, as it did in the present patient.

Nearly all reported trisomy 8 patients have been mosaic, presumably because full trisomy in most instances would disturb embryogenesis sufficiently to cause intrauterine loss. The reported trisomy 8 mosaics generally have mild mental retardation and normal growth. However, the growth retardation and the clinical features in two cases of 8p trisomy, including the present patient and another patient reported by Clark *et al*,[7] were much more severe than those of trisomy 8 patients. This can be explained in part by the presence of extra chromosome material in each cell in the 8p trisomy group as opposed to mosaicism in the trisomy 8 patients. The associated monosomy in the formation of translocations, and the position effect on the expression of genes involved in the translocation, provide further explanation of the clinical severity in some cases of 8p trisomy.

The authors are grateful to Dr Berle Stratton for the description of the necropsy findings, and to Mrs S Lovejoy and Mrs D Chesnut for their technical assistance. This work was supported in part by the Ranken Jordan Trust for The Crippling Diseases of Children.

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Aarskog's syndrome with Hirschsprung's disease, midgut malrotation, and dental anomalies

SUMMARY A 23-year-old man with Aarskog's syndrome had Hirschsprung's disease, midgut malrotation, a renal cyst, a cartilaginous projection of the pinna, geographic tongue, and dental anomalies. The family history, negative for these features, included several malignancies. Any or all of these features could be considered part of Aarskog's syndrome and may represent anomalies of neural crest development.

Case report

The patient, a white male medical student, was ascertained because of his minor anomalies and history of Hirschsprung's disease. The unrelated parents were in good health when the patient was born; his mother was aged 33 and his father 40. The mother's only previous pregnancy resulted in a normal male child. After normal term gestation and breech presentation, birthweight was 3860 g. As a newborn he developed constipation, abdominal distension, and fever. Ultimately, Hirschsprung's disease was diagnosed by barium enema and treated symptomatically until he was 6 years old when he underwent a Swenson pull through operation at which long segment Hirschsprung's disease was noted. Other operations were bilateral inguinal herniorrhaphies and a unilateral orchiopexy (at ages 1 and 3 years), tonsillectomy and adenoidectomy (at 3 years), and an exploratory laparotomy with lysis of adhesions (at 14 years).

The patient's father died in an accident at the age of 47. He was 188 cm in height and weighed 106 kg; he had no known physical abnormalities. His mother, 168 cm tall, had metastatic carcinoma of the breast, glaucoma, and a thyroglossal duct cyst. The patient's brother was 190 cm in height, weighed 97 kg, and had a pilonidal cyst. Hospital records verified colon carcinoma in one of three maternal aunts, ovarian carcinoma in one paternal aunt, and hypernephroma in the other. By report, a maternal aunt had acute intermittent porphyria and her son had bilateral duplication of the kidneys and collecting system. There was no family history of colour blindness.

On physical examination, the patient was hirsute, 174 cm tall (<3rd centile for parental stature), and 76 kg in weight. The only skin lesion was a haemangiomatous macule, 2 cm in diameter, on the left anterior chest. Occipitofrontal circumference was 58·5 cm (98th centile for 18 years). The occiput was flat, the forehead was broad, and the facies round. Eyelashes were long and there was a slight antimongoloid slant of the palpebral fissures. Distances between inner canthi, pupils, and outer canthi were 33, 60, and 87 mm, respectively (all between the 60th and 70th centile for 14 years). Ophthalmological examination showed mild myopia and deuteranomalopia. Pinnae were 59 and 60 mm long (50th centile for 14 years) and low-set; the right pinna was posteriorly rotated. A 3 mm pointed cartilaginous excrescence projected from the left upper outer helix (figure). The nares were anteverted, the philtrum long and wide, and the lips thin. Maxillary canine teeth were small and the maxillary premolars showed torsiversion bilaterally. The tongue had geographic markings. The neck was short and broad but not webbed. There were abdominal surgical scars compatible with the patient's history. The escutcheon, testes, and penis were normal; scrotal folds encircled the base of the penis (saddle scrotum). The fingers were short with hyperextensible proximal interphalangeal joints and one palm showed a simian crease. Dermatoglyphs were unremarkable. The first and second toes were widely spaced.

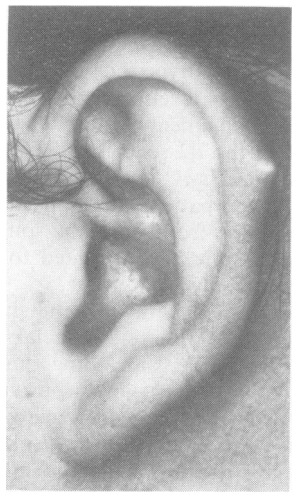

FIGURE *Left ear with cartilaginous pinnal projection.*

Skull *x*-rays were normal. An upper gastrointestinal and small bowel series showed midgut malrotation with an undescended caecum. An intravenous pyelogram showed compression of the left renal pelvis by a (probably cystic) mass. Giemsa banded chromosomes from peripheral blood lymphocytes showed a normal karyotype.

Discussion

Despite regular medical and surgical care, Aarskog's (facial-digital-genital) syndrome was not recognised in our patient until the age of 23 years. Compared with 50 published cases,[1–4] whose mean age at diagnosis was 9 years, he had most of the common features and several additional ones that may be coincidental or extend the spectrum of the syndrome (table).

Hypertelorism, found in 86% of the cases, was not present in our patient. However, primary telecanthus (increased inner canthal distance with normal interpupillary distance) was probably present, since the Mustardé index (ratio of inner

TABLE *Frequencies of selected features of Aarskog's syndrome*

		*Published reports**	*Present case*
Craniofacial anomalies	Macrocephaly	10%	+
	Round facies	34	+
	Broad forehead	24	+
	Occipital flattening	8	+
Nose	Broad nasal bridge	54	+
	Anteverted nares	88	+
Mouth	Hypoplastic maxilla	34	−
	Marked philtrum	50	+
Eyes	Hypertelorism	86	−
	Telecanthus	14	+/-
	Antimongoloid slant	30	+/-
	Ptosis	44	−
Ears	Abnormal helices	50	+
	Low-set ears	30	+
	Malrotated ears	10	+
Skeletal anomalies			
Stature	Short stature	82	+
Neck	Short broad neck	24	+
Trunk	Pectus excavatum	34	−
	Vertebral anomalies	28	−
Hands	Brachydactyly	30	+/-
	Clinodactyly	34	−
	Hyperextensible PIP joints	24	+
	Syndactyly	34	−
	Simian crease	28	+
Feet	Short feet and toes	26	−
	Gap between first and second toes	12	+
Genitalia	Saddle scrotum	78	+
	Inguinal hernia	46	+
	Cryptorchidism	62	+

*Based on 50 of 57 reported cases.

canthal to interpupillary distances[5]) was 0·55, a value at the upper limit of normal. Telecanthus was reported in only 14% of published cases, but in 100% of patients in whom it was specifically sought. Infrequent features of this syndrome, also not seen in our patient, include craniosynostosis, mental retardation, seizures, various cranial nerve deficits, cleft lip and palate, enamel dysplasia, interstitial pulmonary disease, atrial septal defect, hypospadias, club feet, osteochrondritis dissecans, and macrocytic anaemia with haemochromatosis. One reported case,[5] like ours, had blue-green colour blindness, which is inherited as an X linked recessive trait.

Features found in our patient but not previously reported in Aarskog's syndrome were: cartilaginous excrescence of the left helix, dental anomalies, geographic tongue, midgut malrotation, Hirschsprung's disease, renal cyst, and a family history of malignancy. Our patient's pinnal projection differs only in its location on the pinna from the Darwinian tubercle.

Torsiversion, an uncommon dental anomaly consisting of rotation of a tooth on its long axis, is thought to arise for both environmental and genetic reasons.[6] Midgut malrotation, sometimes associated with other congenital anomalies of the gastrointestinal tract, has not been reported to occur with Hirschsprung's disease.

Congenital anomalies occur in some 5 to 20% of patients with Hirschsprung's disease.[7] The patient with Hirschsprung's disease and congenital ptosis reported by Gordon *et al*[8] may represent an undiagnosed case of Aarskog's syndrome. Hirschsprung's disease is thought to originate embryologically by maldevelopment of the neural crest.[9] Brachydactyly, seen in Aarskog's syndrome, is a minor limb reduction defect, which can be produced experimentally by neural crest injury.[10] Waardenburg's syndrome, also postulated to be a neurocristopathy,[11] shares several features with Aarskog's syndrome. The occurrence in our patient of Aarskog's syndrome and Hirschsprung's disease may represent associated anomalies of neural crest development.

The likely mode of inheritance of Aarskog's syndrome is X linked recessive.[1] In this regard, breast carcinoma in the mother and other neoplastic, genetic, and congenital diseases in her relatives are of interest. The association of blue-green colour blindness, usually transmitted in an X linked fashion, suggests close linkage between the two traits. Hirschsprung's disease is inherited in a sex modified multifactorial manner,[7] and pinnal projection and geographic tongue are often autosomal dominant traits.[12] The different patterns of inheritance of these conditions suggest that they are only fortuitously associated with Aarskog's syndrome in our patient. Alternatively, Hirschsprung's disease may have various genetic determinants, including X linked modifiers. If this were the case here, Hirschsprung's disease could be considered an extension of Aarskog's syndrome. Since both disorders may be neurocristopathies, it is intriguing to speculate that an X linked gene contributes to the regulation of neural crest development. Several X linked dysmorphic traits have neurocutaneous defects that could be considered neural crest anomalies, like albinism, incontinentia pigmenti, and ichthyosis.

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A digitopalatal syndrome with associated anomalies of the heart, face, and skeleton

SUMMARY A syndrome of multiple anomalies associated with growth failure and delayed development is described. The facies appear distinctive with globular head, prominence of the eyes, hypertelorism, cleft palate, micrognathia, and abnormal pinnae. Other features include vertebral and costal anomalies, cardiac defects, and a peculiar malformation of the hands. At least five other cases of this condition, all occurring in males, may be found in medical reports. The finding of incomplete expression in three maternal relatives of our patient provides evidence for a genetic cause.

A syndrome of uncertain aetiology but unified by anomalies of the craniofacial structures, hands, heart, and vertebrae has been reported in five cases during the past 12 years.[1–4] Although usually reported as the Pierre Robin syndrome, these patients have distinctive features in addition to the mandibulomaxillary dysplasia. Of particular note is the peculiar hand formation with an accessory bone proximal to the first phalanx of the index fingers. This complex of anomalies results from disturbance during the first eight weeks of embryonic development. In contrast to the defects seen in the Pierre Robin syndrome, the components of this syndrome cannot be easily envisaged as anomalous derivatives of a single primary defect.

We describe here the sixth case, a male, having all of the features previously reported. Features of the syndrome were found in three maternal relatives, providing evidence for a genetic cause.

Case report

The proband (IV.4) was born after a term gestation to a 19-year-old unmarried mother and a 22-year-old father. The mother, a sufferer of chronic emotional problems, took amitriptyline (Elavil) and trifluoperazine (Stelazine) regularly during the first 2½ months of pregnancy. At 3½ months she took an overdose of amitriptyline (1050 mg) requiring admission to hospital. Her initial findings were

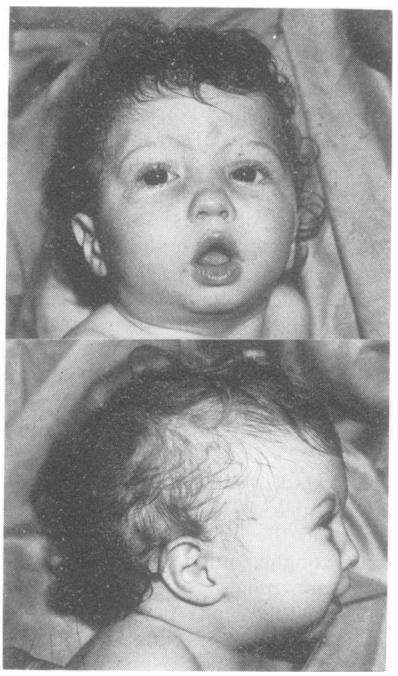

FIG 1 *Frontal and lateral facial appearance of proband at age 15 months. Note the globular head, micrognathia, and low-set retroverted pinnae.*