New autosomal recessive faciodigitogenital syndrome

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SUMMARY Most pedigrees of Aarskog's faciodigitogenital syndrome have suggested X linked inheritance. However, sex influenced autosomal dominant inheritance is also a possibility in some families. We describe an Arab family of normal consanguineous parents with five children (three males and two females) with some features of Aarskog syndrome in addition to some unusual hair changes. The possibility that this family represents a distinct previously unrecognised faciodigitogenital syndrome with short stature and hair abnormalities is suggested and discussed.

In 1970 Aarskog¹ described a syndrome of short stature with facial and genital anomalies in seven males from two generations in a family. Earlier probable cases were reported from the USA in 1966 by Welch and Temtamy² and in 1967 by Hanley *et al.*³ Since then, many reports over two decades have shown that males show full expression and that in females expression, if present, is limited to minor signs only; therefore X linked recessive, X linked semi-dominant, or sex influenced autosomal dominant inheritance have been suggested. Full

male and female expression has been noted recently by Bawle *et al.*⁴ in a mother and her son who have the same balanced X;autosome translocation. Here we report on a family with five affected sibs, males and females, who have a distinct disorder with several features resembling Aarskog's faciodigitogenital syndrome.

Case reports

CASE 1

The proband, a six year old male, was examined in

FIG 1 Family pedigree.

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FIG 2a Front view of case 1.

FIG 2b *Side view of case 1.*

FIG 2c *Hands of case 1.*

FIG 2d *External genitalia of case 1.*

October 1985 because of short stature, unusual facies, and lax hand joints. His parents are second cousin Kuwaiti Bedouins. Both are 38 years old and phenotypically normal with an average height. The proband has five brothers and sisters and four are similarly affected; one of them was born in June 1986. His father is married to a second non-consanguineous wife and has three normal children. Family study showed no other closely related members with similar features (fig 1). The proband's mother had a total thyroidectomy after the birth of

her first child in 1974 with replacement therapy. The proband was born normally at term after an uneventful pregnancy with a birth weight of 2.15 kg and no neonatal problems. At the age of four months he developed severe complicated gastroenteritis and required a long hospital admission during which eczema-like skin changes were noticed, mainly on the extremities, for which he still receives intermittent topical treatment. Developmental milestones were normal.

Examination at the age of six years revealed proportionate short stature with a height of 104 cm (<3rd centile), occipitofrontal head circumference (OFC) of 47 cm (<3rd centile), and weight of 15.5 kg (3rd centile). His craniofacial features (fig 2a, b) included biparietal bossing of the skull with brachycephaly and a triangular face. His hair was coarse, dry, hypopigmented, and slightly sparse with a widow's peak. He had apparent hypertelorism with wide palpebral fissures, a high nasal bridge with short stubby nose and anteverted nares, long, prominent philtrum, high arched, narrow palate, wide mouth with pouty lower lip, relative micrognathia, posteriorly rotated small ears with thickened, downturned helices, and a long neck with sloping shoulders. His hands (fig 2c) were small and broad with mild syndactyly (interdigital webbing), fifth finger clinodactyly, and hyperextensible joints. His feet were small with metatarsus varus and stubby toes. He had a normal penis and testes with a shawl-like scrotum (fig 2d). Examination of other organs revealed no abnormalities. Skeletal radiographs including skull x rays showed a normal bone age and no striking changes. Analysis of prometa-phase chromosomes from peripheral blood using G banding showed a normal 46,XY constitution.

FIG 3a Front view of case 2.

FIG 3b Side view of case 2.

FIG 3c *Hands of case 2.*

FIG 4a *Case 3 and case 4.*

FIG 4b *Hands of case 3.*

CASE 2

Case 2 is a seven year old child, the sister of the proband. Pregnancy and delivery were normal with a birth weight of 3.5 kg. On examination she was short with a height of 100 cm (<3rd centile), OFC 48 cm (<3rd centile), and weight 18.5 kg (3rd centile). Her features (fig 3a-c) were strikingly similar to the proband and are summarised in the table.

FIG 4c External genitalia of case 3.

CASE 3

Case 3 is a five year old child, brother of the previous two cases. Pregnancy and delivery were unremarkable with a birth weight above average (3.75 kg). On examination he was short with a height of 102 cm (10th centile), OFC 47 cm (<3rd centile), and weight 16 kg (10th centile). His features were similar to his brother and sister (fig 4a-c) and are shown in the table.

CASE 4

Case 4 is a four year old female. Pregnancy and delivery were normal with a birth weight of 3.65 kg. On examination she had a height of 95 cm (10th centile), weight 14 kg (10th centile), and OFC 47 cm (10th centile). Her features are shown in figs 4a and 5 and in the table.

CASE 5

Case 5 is a six month old male with a birth weight of 3 kg and similar features to the others (table). Unfortunately no clinical photograph is available.

Discussion

On the basis of a family with seven affected males and no male to male transmission of the trait over two generations, Aarskog¹ suggested X linked recessive inheritance for Aarskog's faciodigitogenital syndrome. Subsequently, other authors supported this view.⁵⁻¹⁷ Further reports of male patients,¹⁸⁻²⁴ more than 110 so far, show complete expression which includes, in addition to the 'shaw scrotum', short stature, a round face, prominent forehead with widow's peak, hypertelorism, broad

FIG 5 Hands of case 4.

TABLE 1 Features of the five sibs.

Features	Case 1 (proband)	Case 2	Case 3	Case 4	Case 5
Age	6 y	7 y	5 y	4 y	6 mth
Sex	M	F	M	F	M
Short stature (at or below 10th centile)	+	+	+	+	-
Hair changes (coarse, dry, and hypopigmented)	+	+	+	+	-
Widow's peak hair anomaly	+	+	-	+	+
Skull bossing	+	-	-	+	+
Brachycephaly	+	-	-	-	+
Triangular or elongated face	+	+	+	+	-
Apparent hypertelorism	+	+	+	+	+
Wide palpebral fissures	+	+	+	-	+
Upward slanting eyes	-	-	-	+	+
High nasal bridge	+	+	-	-	-
Short stubby nose	+	+	+	+	+
Anteverted nares	+	+	+	+	+
Long, deep philtrum	+	+	+	+	+
Wide mouth	+	+	+	+	+
Pouty lower lip	+	+	+	+	+
High and narrow palate	+	+	+	+	+
Dental malocclusion	-	+	+	+	-
Relative micrognathia	+	-	-	-	-
Ear anomalies	+	+	+	-	+
Long neck with sloping shoulders	+	+	+	+	+
Pectus excavatum	-	-	-	+	+
Clinodacty of 5th finger	+	+	+	+	-
Small and broad hands	+	+	+	+	+
Interdigital webbing	+	+	+	+	+
Hyperextensible hand joints	+	+	+	+	-
Hyperelastic skin	-	+	-	-	-
Metatarsus varus	+	-	-	+	+
Bulbous toes	+	+	+	+	-
Shawl scrotum	+	-	+	-	+
IQ or DQ	Normal	Normal	Normal	Normal	Normal
Bone age	Normal	Normal	Normal	Normal	Normal
Karyotype	46.XY	46.XX	46.XY	-	-

nasal bridge, short, stubby nose with hypoplastic maxilla, and small hands with interdigital webbing. In females expression, if present, is partial and limited to minor signs only.^{8 12 25-27} Therefore, X linked semidominant²⁵ or sex influenced autosomal dominant inheritance has been suggested.^{18 21 24 26} However, Berman *et al*⁸ suggested that autosomal dominant inheritance is unlikely based on statistical analysis of four reported affected males who produced seven normal sons. However, a few examples of male to male transmission of Aarskog syndrome have been documented.^{21 26} In a large family reported recently there was one male with short stature, ptosis, antimongoloid eye slant, and thickened ear lobes who transmitted ptosis and antimongoloid slant to one son and antimongoloid slant and thickened ear lobes to another son.²⁴ Recently, complete expression of the syndrome in a mother and her son who have the same balanced X;autosome translocation has been reported.⁴ The authors concluded that Aarskog syndrome is an X linked disorder and that Xq13 is the likely site of its locus.

The males and females in this family have small stature with all body proportions at or below the

10th centile. They also show several features similar to those of Aarskog syndrome. They include normal intelligence, hand and foot anomalies, and some characteristic facial features with apparent hypertelorism, short, stubby nose, anteverted nostrils, and ear anomalies, but without antimongoloid slanting of the eyes or ptosis. The males had penoscrotal skin folds, commonly described as shawl scrotum, which is considered to be one of the diagnostic criteria of Aarskog syndrome. In addition, males and females have hair abnormalities not previously described in Aarskog syndrome.

Affected subjects in this family appear to have a new faciodigitogenital syndrome readily distinguishable from the well characterised Aarskog syndrome. In the absence of any chromosomal abnormality with five affected male and female sibs and parental consanguinity, autosomal recessive inheritance is highly likely.

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References

- ¹ Aarskog D. A familial syndrome of short stature associated with facial dysplasia and genital anomalies. *J Pediatr* 1970;**77**: 856–61.
- ² Welch JP, Temtamy S. Hereditary contractures of the fingers (camptodactyly). *J Med Genet* 1966;**3**:104–13.
- ³ Hanley WB, McKusick VA, Barranco FT. Osteochondritis dissecans with associated malformations in two brothers. *J Bone Joint Surg (Am)* 1967;**49**:925–37.
- ⁴ Bawle E, Tyrkus M, Lipman S, Bozimowski D. Aarskog syndrome: full male and female expression associated with X-autosome translocation. *Am J Med Genet* 1984;**17**:595–602.
- ⁵ Scott CI. Unusual facies, joint hypermobility, genital anomaly and short stature: a new dysmorphic syndrome. In: Bergsma D, ed. *The endocrine systems*. Part X. New York: March of Dimes, 1971:240–6.
- ⁶ Kunze J, Spranger J. Aarskog syndrome. *Klin Paediatr* 1973; **185**:490–4.
- ⁷ Berman P, Desjardins C, Fraser FC. Inheritance of the Aarskog syndromes: In: Bergsma D, ed. *Malformation syndromes*. Miami: National Foundation–March of Dimes, 1974:151–9.
- ⁸ Berman P, Desjardins C, Fraser FC. The inheritance of the Aarskog facial-digital-genital syndrome. *J Pediatr* 1975;**86**: 885–91.
- ⁹ Kirkham TH, Milot J, Berman P. Ophthalmic manifestations of Aarskog (facial-digital-genital) syndrome. *Am J Ophthalmol* 1975;**79**:441–5.
- ¹⁰ Duncan P, Klein RM, Wilmont PL, Shapiro LR. Additional features of the Aarskog syndrome. *J Pediatr* 1977;**86**:885–91.
- ¹¹ Escobar Y, Weaver DD. Aarskog syndrome. *JAMA* 1978;**240**: 2638–41.
- ¹² Fryns JP, Macken J, Vinken L, Igodt-Ameye L, van den Bergh H. The Aarskog syndrome. *Hum Genet* 1978;**42**:129–35.
- ¹³ Ricotti GC, Giovannucci-Uzielli ML, Pepi M, Prosperi P, Torricelli F. La sindrome di Aarskog. *Acta Med Auxol* 1978;**10**:135–50.
- ¹⁴ Andrassy RJ, Murthy S, Woolley MM. Aarskog syndrome: significance for the surgeon. *J Pediatr Surg* 1979;**15**:462–4.
- ¹⁵ Berry C, Cree J, Mann T. Aarskog's syndrome. *Arch Dis Child* 1980;**55**:706–10.
- ¹⁶ Hassinger DD, Mulvihill JJ, Chandler JB. Aarskog's syndrome with Hirschsprung's disease, midgut malrotation and dental anomalies. *J Med Genet* 1980;**17**:235–8.
- ¹⁷ Kodama M, Fujimoto S, Namikawa T, Matesuda I. Aarskog syndrome with isolated growth hormone deficiency. *Eur J Pediatr* 1981;**135**:273–6.
- ¹⁸ Saggese G, Bertelloni S, Baroncelli GI, Calisti L. Aarskog's syndrome. Description of a case and endocrinological study. *Pediatr Med Chir* 1983;**5**:613–8.
- ¹⁹ de Saxe M, Kromberg JG, Jenkins T. The Aarskog (facio-digital-genital) syndrome in South Africa. A report of three families. *S Afr Med J* 1984;**65**:299–303.
- ²⁰ van den Bergh P, Fryns JP, Wilms G, Piot R, Dralands G, van den Bergh R. Anomalous cerebral venous drainage in Aarskog syndrome. *Clin Genet* 1984;**25**:288–94.
- ²¹ Grier RE, Farrington FH, Kendig R, Mamunes P. Autosomal dominant inheritance of the Aarskog syndrome. *Am J Med Genet* 1983;**15**:39–46.
- ²² Hurst DL. Metatarsus adductus in two brothers with Aarskog syndrome. *J Med Genet* 1983;**20**:477.
- ²³ Shinkawa T, Yamauchi Y, Osada Y, Ishisawa N. Aarskog syndrome. *Urology* 1983;**22**:624–6.
- ²⁴ van de Vooren MJ, Niermeijer MF, Hoogebdon AJ. The Aarskog syndrome in a large family, suggestive of autosomal dominant inheritance. *Clin Genet* 1983;**24**:439–45.
- ²⁵ Furukawa CT, Hall BD, Smith DW. The Aarskog syndrome. *J Pediatr* 1972;**81**:1117–22.
- ²⁶ Sugarman GI, Rimoin DL, Lachman RS. The facial digital-genital (Aarskog) syndrome. *Am J Dis Child* 1973;**126**:248–52.
- ²⁷ Oberiter V, Lovrencic MK, Schmutzer L, Kraus O. The Aarskog syndrome. *Acta Paediatr Scand* 1980;**69**:567–70.

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