

Autosomal dominant inheritance of abnormalities of the hands and feet with short palpebral fissures, variable microcephaly with learning disability, and oesophageal/duodenal atresia

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Abstract

We report two families with an autosomal dominant syndrome of abnormalities of the hands and feet, short palpebral fissures, and variable microcephaly with learning disability. Between a third and a quarter of cases are born with oesophageal atresia, duodenal atresia, or both. Individual patients have hypoplastic thumbs or congenital heart disease. The phenotype of the syndrome reported here is similar to that observed in 13q22-qter deletion patients. However, chromosome analysis has not detected any structural abnormality in our patients.

Oesophageal atresia and tracheo-oesophageal fistula occur in approximately 1 in 3000 births.^{1,2} Approximately half of the cases have additional malformations, mostly cardiac malformations, other gastrointestinal atresias, renal abnormalities, or radial ray defects. In some 6% of patients with oesophageal atresia and associated anomalies, an abnormal karyotype can be detected. Recurrence of oesophageal atresia is rare, with empirical risk estimates of 0.43 to 1.7% in sibs²⁻⁴ and 3.6% in children.⁵ In a review of published reports on familial cases of oesophageal atresia, van Staey *et al*⁴ concluded that the data were most compatible with polygenic inheritance. Similarly, large series of cases with oesophageal atresia have shown little evidence for monogenic inheritance.^{2,3,6}

We report on two families with an autosomal dominant syndrome of short palpebral fissures,

microcephaly, mild mental retardation, fifth finger clinodactyly, and syndactyly of the toes. Several affected subjects have shown congenital atresias of the gastrointestinal tract, especially oesophageal atresia and duodenal atresia. Two other families reported may have had the same syndrome.

Case reports

CASE 1 (III.8, FAMILY 1)

This boy was the first child born to non-consanguineous Dutch parents. The pregnancy was complicated by polyhydramnios. Delivery occurred spontaneously at 38 weeks' gestation. Birth weight was 2840 g. Examination showed upward slanting, short palpebral fissures, marked clinodactyly of the fifth fingers, bilateral syndactyly of the fourth and fifth toes, and a large gap between the first and second toes. An oesophageal atresia with tracheo-oesophageal fistula was repaired on the second day of life. Laparotomy showed duodenal obstruction by an annular pancreas. A duodenoduodenostomy was performed. The child died on the fourth day of life. At necropsy, a complex cardiac malformation consisting of tricuspid atresia, VSD, and interrupted aortic arch was found. Chromosome studies showed a normal karyotype, 46,XY.

CASE 2 (III.9, FAMILY 1)

In her second pregnancy, the mother of case 1 again experienced polyhydramnios, confirmed by ultrasound from the 24th week onwards. Delivery occurred at 38 weeks. Birth weight was 3500 g. On the first day of life, an oesophageal atresia with tracheo-oesophageal fistula and duodenal atresia (in combination with annular pancreas) were repaired. Similar phenotypic features to his brother's were noted (figs 1 to 3) with clinobrachydactyly of both little fingers and syndactyly of toes 2/3 and 4/5 bilaterally. In addition he had camptodactyly of the middle finger of the left hand. At the age of 12 months he is doing well.

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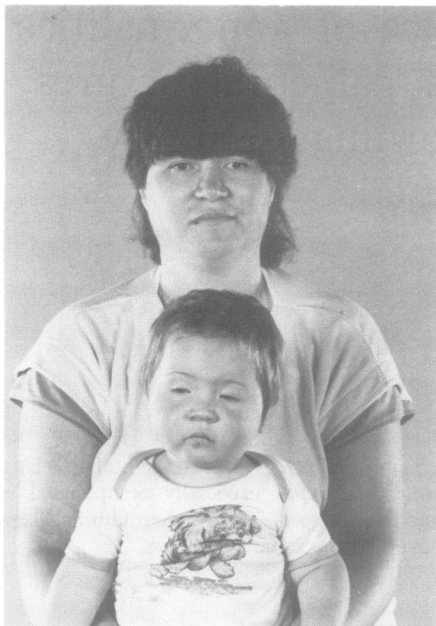


Figure 1 Cases 2 and 3 (III·9 and II·7, family 1). Note short palpebral fissures.

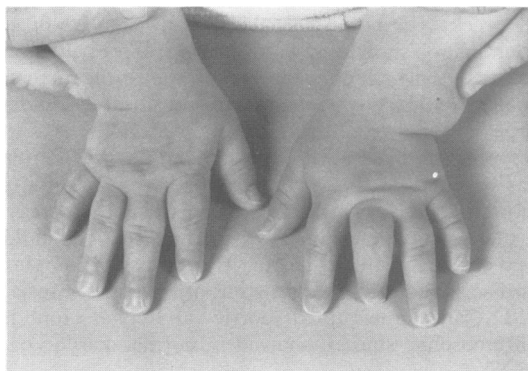


Figure 2 Hands of III·9 (family 1). Note flexion deformity of the left middle finger.

Length and weight are appropriate for his age. The OFC is 46 cm (10th centile). The palpebral fissures are short. ICD is 33 mm, OCD is 78 mm. Ultrasound examination of the heart and kidneys showed no abnormalities. A G banded karyotype was normal, 46,XY.

CASE 3 (II.7, FAMILY 1)

This is the mother of subjects III·8 and III·9. She has a similar phenotype with brachymesophalangy of the

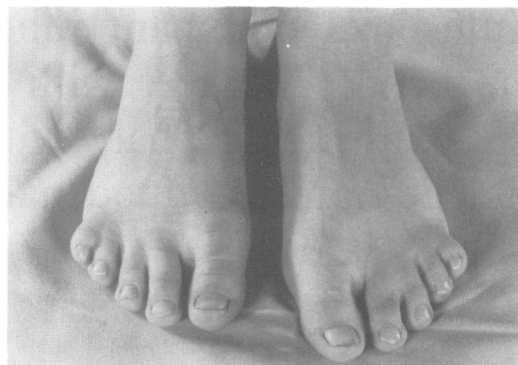


Figure 3 Feet of III·9 (family 1). Note bilateral syndactyly of toes 4/5 and mild syndactyly of toes 2/3.

index and little fingers bilaterally (fig 4). Both feet show 4/5 syndactyly. The OFC is 53 cm (10th centile). Her palpebral fissures are short. She has attended a special school because of learning problems. High resolution chromosome analysis with special attention to chromosome 13 was normal.

Eight other family members have the same abnormalities of the hands and feet. Three have had operations in the neonatal period for oesophageal or duodenal atresia or both (figs 5 to 8, table).

CASE 4 (II.2, FAMILY 2)

This was the second child born to non-consanguineous Indian parents. Delivery occurred spontaneously at 37 weeks. At birth, weight was 1990 g, length was 39 cm, and OFC was 28 cm (all <3rd centile). She has a peculiar face with short palpebral fissures (fig 9). On examination, hypoplastic thumbs (fig 10), clinodactyly of the fifth fingers with a single flexion crease, and a large gap between the first and second toes were found. At 4 days of age she was admitted to the

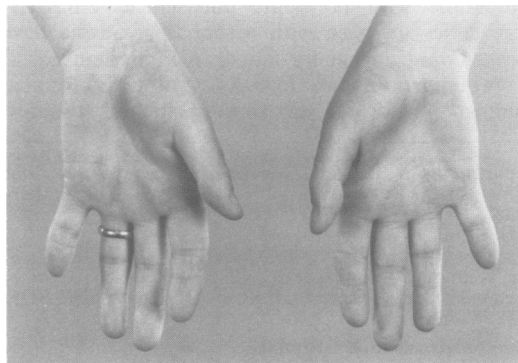


Figure 4 Hands of II·7 (family 1). Note clinodactyly of second and fifth fingers.



Figure 5 Sister of case 3 (II·3, family 1). Note microcephaly (OFC=50.8 cm) with short palpebral fissures (ICD=28 mm, OCD=78 mm).

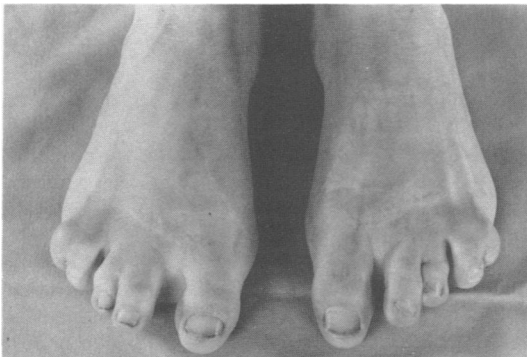


Figure 6 Feet of II·3. Note bilateral syndactyly of toes 2/3 and 4/5.

surgical department because of persistent, not bile stained vomiting and a double bubble appearance on abdominal radiographs. Laparotomy at 4 days of age showed a duodenal obstruction owing to a wind sock type of membrane at the junction of the first and second parts of the duodenum. A duodenoduodenostomy was performed. The child recovered uneventfully. At 2 years of age she shows apparently normal development. On examination, the mother and brother of case 4 were found to have the same syndrome (figs 11 to 13, table).

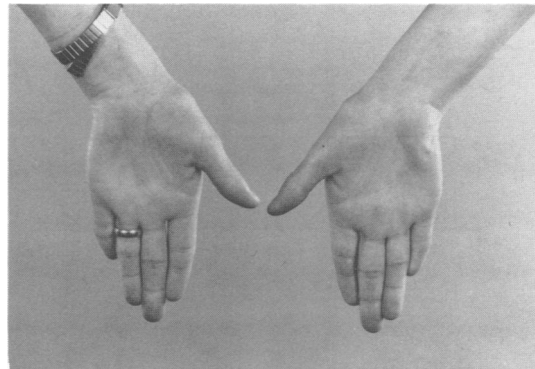


Figure 7 Hands of II·3. Note clinodactyly of fifth fingers.

Family study

Eleven subjects in family 1 and three subjects in family 2 are known to be affected. Two subjects in family 1 were unavailable for examination. II·2 died at the age of 15 months. Information about this girl was collected from her medical records and from her mother. II·6 could not be personally examined because she is living abroad. Information about this woman was obtained from the family and by examination of photographs.

Details of the two families are given below and are summarised in the table, together with data from two reports by Feingold^{7,8} that describe the same syndrome.

HAND AND FOOT ABNORMALITIES

These are remarkably constant and occur with full penetrance. All affected subjects have brachymesophalangy of the fifth finger bilaterally. Marked syndactyly of the fourth and fifth toes was found in 12/13 cases. Syndactyly of the second and third toes was usually less prominent and occurred in about 70% (8/11).

The proband in family 2 (II·2) has very small thumbs, but in all other persons thumb hypoplasia has been either mild or absent. Two subjects have clinodactyly of the index finger. In family 1, subject III·9 has camptodactyly of the middle finger which has improved substantially over time. One person in family 1 and two in family 2 have a wide interdigital space between toes 1 and 2.

CRANIOFACIAL

Affected subjects have short palpebral fissures with normal ICD and decreased OCD. In family 1, affected persons tend to have lower OFCs than their unaffected sibs. However, only half of those for whom

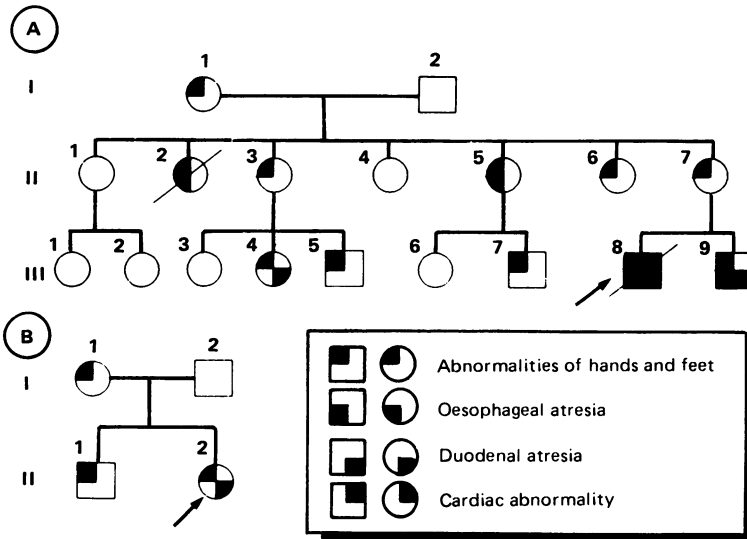


Figure 8 Pedigrees. Probands are indicated by an arrow.

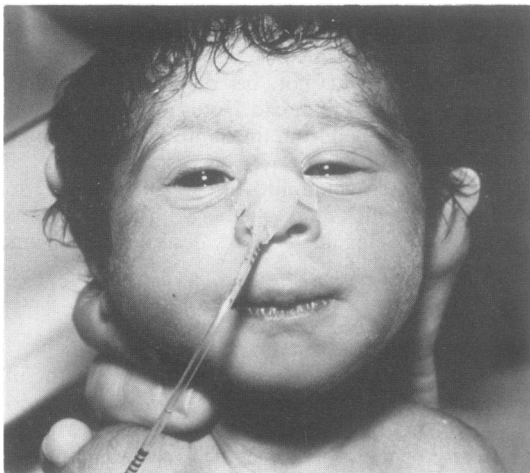


Figure 9 Case 4 (II·2, family 2). Note short palpebral fissures and nasopharyngeal tube.



Figure 10 Left hand of II·2 (family 2). Note hypoplastic thumb.

measurements are available (4/8) have an OFC below the 3rd centile. One subject has an OFC on the 25th centile. In family 2, all three affected subjects are microcephalic.

INTELLIGENCE

Although none of the affected persons in family 1 is considered mentally retarded, five out of seven have attended special schools for children with learning disabilities. In contrast, all nine unaffected family members show normal cognitive development. In



Figure 11 Mother and brother of case 4 (I·1 and II·1, family 2). Note short palpebral fissures.

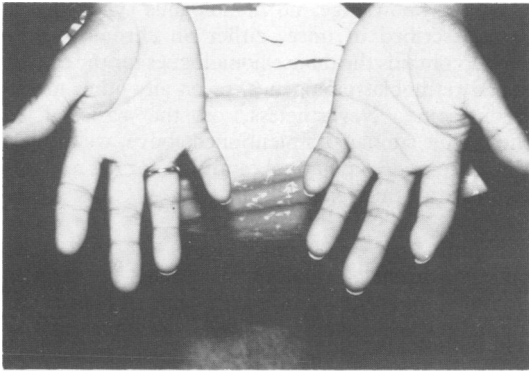


Figure 12 Mother of case 4 (I·1, family 2). Note clinodactyly of the second and fifth fingers with single flexion crease on fifth finger.

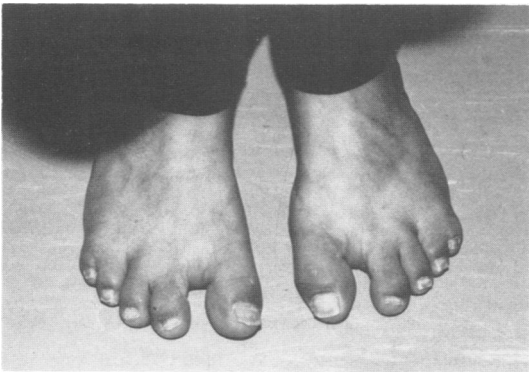


Figure 13 Feet of I·1. Note bilateral syndactyly 2/3 and 4/5 with wide space between toes 1 and 2.

family 2, intelligence appeared normal, but was not formally assessed.

INTESTINAL ABNORMALITIES

Four subjects in family 1 were born with oesophageal atresia. In two (III·8 and III·9) this was accompanied

by a duodenal stenosis secondary to annular pancreas. III·4 was operated upon on the third day of life for duodenal atresia. The proband in family 2 (II·2) also had congenital duodenal atresia.

OTHER ABNORMALITIES

One subject (III·5, family 1) has a unilateral total sensorineural deafness. Another (II·5, family 1) has a missing upper lateral incisor tooth. The index case in family 1 (III·8) was born with tricuspid atresia, a VSD, and an interrupted aortic arch.

Discussion

Feingold^{7, 8} briefly reported two families with autosomal dominant inheritance of microcephaly with normal intelligence and hand and foot abnormalities. In the first family described by this author,⁷ a boy, his father, and his paternal grandmother all had microcephaly and clinodactyly of the little fingers. Narrow palpebral fissures and syndactyly of toes 2/3 were noted in the proband. In the initial report no mention is made of abnormalities of the feet in the other affected subjects, but a second report on this family⁸ mentions identical toe anomalies in both the father and the grandmother. The proband in the first family described by Feingold had a type C tracheo-oesophageal fistula with concomitant duodenal atresia. Whether the internal manifestations were part of the syndrome was considered uncertain. The second family reported by Feingold consisted of a girl about whom no data are given, except for microcephaly and the presence of 'similar abnormalities' of the hands and feet. This constellation was also found in the mother. A maternal uncle and the maternal grandfather are reported as having exactly the same syndrome, all of them being of normal intelligence.⁸ No further details were provided. On the basis of the two families described here, the syndrome can now be more completely delineated. This syndrome shows apparently full penetrance and variable expressivity. Data are available on 21 subjects (nine males, 12 females) from four families. Transmission through

Clinical details of present families and those reported by Feingold.^{7, 8}

	This report		Feingold ^{7, 8}		Total (n=21, 9M; 12F)
	Family 1 (n=11, 4M; 7F)	Family 2 (n=3, 1M; 2F)	Family 1 (n=3, 2M; 1F)	Family 2 (n=4, 2M; 2F)	
Microcephaly	4/8	3/3	3/3	2/2	12/16
Short palpebral fissures	7/8	2/3	1/1	?	10/12
Clinodactyly 5 of hands	11/11	3/3	3/3	2/2	19/19
Syndactyly of toes	11/11	2/3	3/3	?	16/17
Intestinal atresia:	5/11	1/3	1/3	0/4	7/21
Oesophageal atresia/TOF	4/11	0/3	1/3	0/4	5/21
Duodenal atresia/stenosis	3/11	1/3	1/3	0/4	5/21
Congenital heart defect	1/11	0/3	0/1	?	1/15

three generations in three families and male to male inheritance in the families described by Feingold^{7,8} suggest autosomal dominant inheritance.

The hallmark of the syndrome is the combination of clinodactyly of the fifth fingers bilaterally and syndactyly of the toes (usually 4/5). Head circumference is decreased compared to the normal sibs and about two-thirds of cases are microcephalic. In contrast to the reports by Feingold,^{7,8} we consider learning problems to be a frequent component of this syndrome. The most serious problem is the occurrence of oesophageal or duodenal atresia or both. Since three out of four families were ascertained through a proband with intestinal atresia, our estimate of its frequency (33%) may be too high. However, after eliminating all probands, the frequency of intestinal atresias is still 4/17 (24%). Case 1 had a severe congenital heart abnormality, which may be a low frequency feature of this syndrome.

Differential diagnosis includes disorders with syndactyly of the fourth and fifth toes, such as auralcephalosyndactyly⁹ and 13q- syndrome, various forms of autosomal dominant microcephaly,¹⁰ and, finally, familial duodenal atresia¹¹ and familial oesophageal atresia.⁴ However, the overall pattern of anomalies in the syndrome described here in combination with a normal chromosome analysis should allow easy recognition of this condition.

It is striking, that all features observed in the families reported here can also be found in patients with deletions of chromosome 13 distal to band 13q14. In patients with such deletions, hypoplastic thumbs, syndactyly of toes 4/5, clinodactyly of the little fingers, and microcephaly with short palpebral fissures are all regularly observed. Oesophageal atresia and other intestinal atresias occur more rarely.¹² However, G banded chromosomes were normal in cases 1, 2, and 4, while high resolution chromosome analysis in case 3 also failed to show any abnormality of chromosome 13.

To our knowledge, no homologous syndrome has been described in mice, either on chromosome 14 (which contains the mouse homologues for the esterase D and retinoblastoma genes) or on any other murine chromosome. Nevertheless, on the basis of the phenotypic similarities mentioned above, we consider chromosome 13 a potential candidate for the mutation described in this report.

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Note added in proof

Another mother and son with this syndrome have recently been described by König *et al* (*Dysmorphol Clin Genet* 1990;4:81-2).

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