

## A new syndrome of cleft palate associated with coloboma, hypospadias, deafness, short stature, and radial synostosis

**SUMMARY** A new syndrome characterized by cleft palate, coloboma, hypospadias, deafness, short stature, and radial synostosis has been described. The family history suggests either an autosomal dominant mode of inheritance with limited expression in females or X-linkage. Other syndromes with similar phenotypes and modes of inheritance are discussed. The need for accurate and complete family histories in cases involving cleft palate and cleft lip/palate is discussed in relation to genetic counselling and recurrent risk estimates.

The frequency of cleft palate, as distinguished from cleft lip/palate, has been estimated to be between 0.4 and 0.5 per 1000 births (Drillen *et al*, 1966). Very little is known about the genetic mechanisms involved in cleft lip/palate. Only about 3% of all cleft palate or cleft lip/palate can be considered as part of a syndrome and even in these 3%, all types of single gene inheritance patterns have been described (Fraser, 1970). The remaining 97% of cases are usually considered to be the result of multiple gene systems.

In genetic counselling situations it is important to recognize cases with specific syndromes, so that accurate recurrent risks can be given. Recognition of specific syndromes is also of benefit in understanding the underlying biochemical mechanism for embryonic closure.

In this paper we describe a new syndrome which combines cleft palate, coloboma, hypospadias, deafness, short stature, and radial synostosis, and we discuss the possible modes of inheritance for this single gene mutation.

### Case reports (see Fig. 1)

#### Case I.1

It is not known if this individual is still alive. He was not known to have coloboma, hypospadias, cleft palate, deafness, or arm problems. His height was said to be about 6 feet.

#### Case I.2

This patient had no history but was examined. She did not have large ears nor did she have a facial configuration similar to her partially affected daughter or fully affected grandsons. Her palate was not high arched and her uvula was single. Examination of the extremities showed no increased distance between the second and third finger nor did it show ulnar deviation of the second digit. Examination of the feet showed a normal toe configuration.

#### Case II.1

He was the product of a pregnancy possibly complicated by poor nutrition. Labour started near the expected date of confinement and was said to be 'prolonged'. His birthweight was 3515 g and there were no problems other than a cephalohaematoma in the immediate neonatal period. However, he did not suck well and there

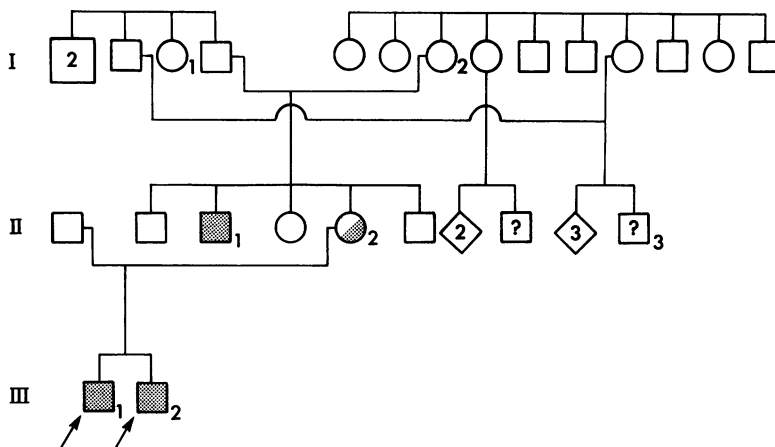


FIG. 1 Pedigree of the family indicating relationships of individuals reported.

were some flu-like symptoms. At 7 weeks he developed a strangulated hernia and was admitted to hospital for repair of the hernia. He had a difficult postoperative course, with little weight gain. By 15 months he was starting to walk. At this time he had more infections and his walking was set back and started again at age 2 years. At about 4½ years he was noted to have a cardiac murmur and had extensive cardiac examinations which showed an atrial septal defect for which there was an attempted closure at age 9 years. The immediate post-operative catheterization study still showed some shunt but a later catheterization study showed correction of the shunt. He had left cryptorchidism and an attempted orchiopexy was performed, which was unsuccessful. There was also a history of a 'polio-like' illness, without residua, when he was about 15 years of age. The patient developed neurosensorial hearing loss at age 20 which is now corrected by hearing aids. This has been a progressive defect and is now severe. There is limited rotation of the right forearm probably the result of a childhood break but there was no identified occurrence of such an accident. Height 5 feet (in contrast to 5' 8" heights of two brothers). The patient looked an abnormal, very short individual, older than his stated age of 34 years. Head circumference was 53.5 cm with normal hair line. He had a flat facies with large, soft ears. The eyes showed a small corneal diameter of 10 mm bilaterally. There was no evidence of retinal or corneal defect. The mouth showed a high arched palate and a bifid uvula, and teeth were irregular. The chest showed bilateral thoracotomy scars with hypodevelopment of the left lower scapular area. Cardiac examination showed no murmur. Genitalia showed a tender left testes at the external inguinal canal and a grade I hypospadias. Examination of extremities showed that both hands had wide spacing between the second and third fingers and ulnar deviation of the second digit. His hands were short for his body size. The right arm was severely limited in supination compatible with radial synostosis. His feet were small, with a size 5 shoe, but did not show other abnormalities.

#### Case II.2

This patient looks very similar to her sons, with large ears and flat malar configuration (Fig. 2a). Her eyes did not have colobomas. Her palate was high, with unusual rugosities (Fig. 2b). Her uvula was broad but not bifid. Her hands showed wide spacing between the second and third digits and the second digit showed slight ulnar deviation (Fig. 3a). There was webbing of the second and third toes and she had had foot operations which caused a fibular deviation of the hallux, but the total foot configuration had been changed by the orthopaedic surgery that she had as a child.

#### Case II.3

This young man was said to look like Case II.1 and his nephews, with lop ears and a similar facial configuration. He had a mild degree of hypospadias which was not surgically corrected until his mid-20s. Apparently he did not have other defects. He was not available for examination.

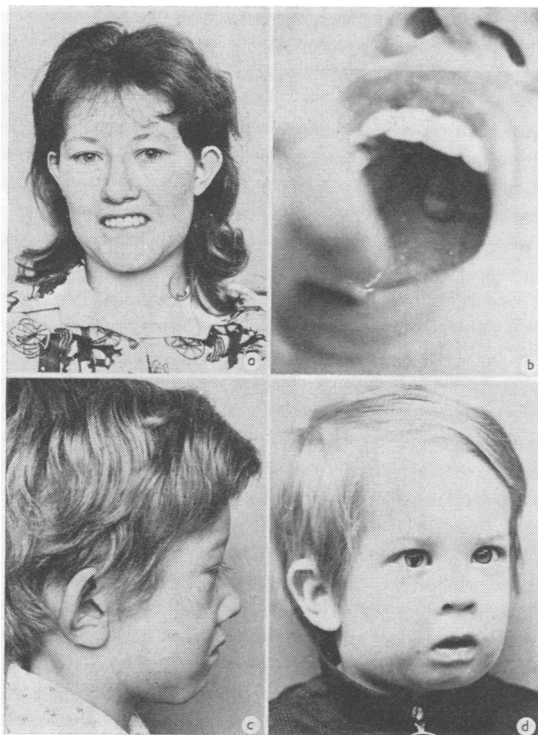


FIG. 2 Facial features of patients: (a) frontal view of II.2; (b) palate of II.2; (c) lateral view of III.1; (d) frontal view of III.2.

#### Case III.1

This boy was the product of an uncomplicated pregnancy and delivery, and was immediately noted to have multiple birth defects which included coloboma, cleft palate, and a chordee with coronal hypospadias, and penile torsion. He had had multiple surgical procedures to correct these defects and a left eye muscle resection and recession for esotropia. Physical examination showed a pleasant co-operative boy who was much below the 3rd centile for height and weight. His facial appearance was abnormal because of slightly flat facies (Fig. 2c), especially in the malar area, and a short dimpled chin. His head circumference was 50.7 cm and the ears were large and protruded slightly. His eyes had slight epicanthic folds. Examination of his eyes showed near vision in the right eye of J1 and in the left eye of 'count fingers' at two feet. Extraocular movements were full. He had slight left esotropia. He was noted to have a coloboma of the left iris; and there was a retinal coloboma at 6 o'clock inferior to the disc in the left eye. The disc and macula were uninvolved. His soft palate had been repaired but was still short. His mouth movements were slightly asymmetrical, with less movement on the right than on the left and his right eye was slightly higher than the left eye. There was no cardiomegaly or murmur. Renal abnormalities were not palpated and his hypospadias was repaired. There was wide spacing

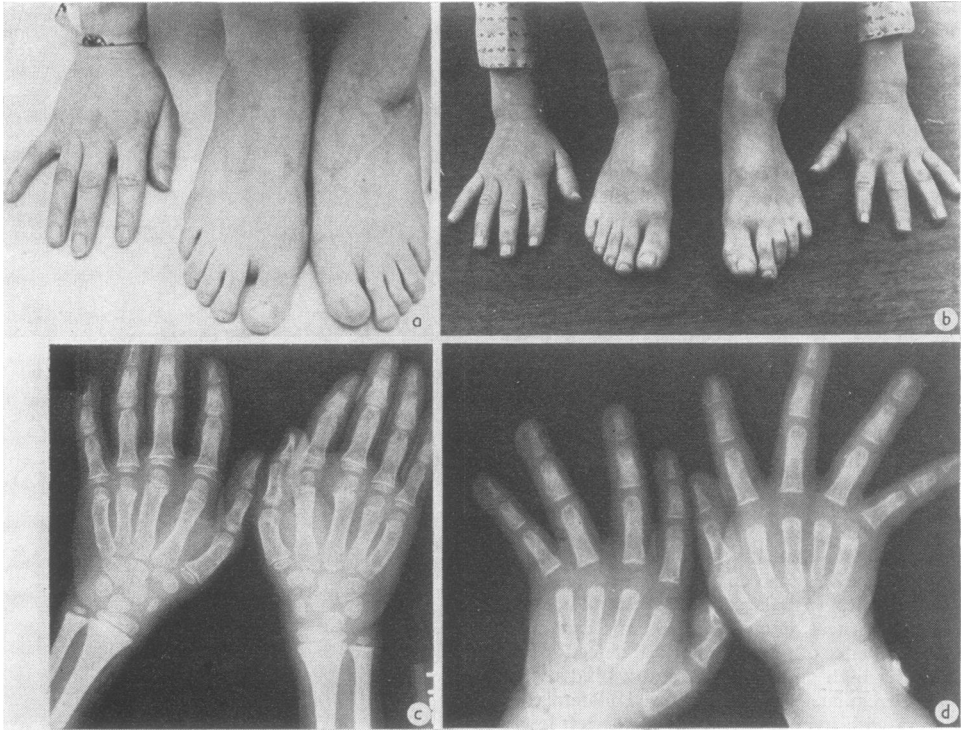


FIG. 3 Extremity features of patients: (a) right hand and feet of II.2; (b) hands and feet of III.1; (c) x-rays of hands of case III.1 at 7 years of age; (d) hands of III.2 at age 10 months.

between the second and third digits and ulnar deviation of the second digit (Fig. 3b). Additional studies included a bone survey which showed no osseous abnormalities but confirmed the side spacing between the second and third digits of the hands (Fig. 3c). An electrocardiogram was normal. Audiometry showed a 10 to 20 decibel neurosensorial impairment and a 15 to 40 decibel conductive hearing impairment compatible with numerous episodes of otitis media and tympanic membrane tube placements, all secondary to the palate situation. A karyotype showed a normal 46,XY configuration. Giemsa banding studies showed no deficiencies or additions to bands in any of the 44 autosomes or the X and Y chromosomes.

#### Case III.2

He was the product of an uncomplicated pregnancy and delivery which followed a 2-month spontaneous miscarriage to Case II.2. He was noted at birth to show multiple defects including Pierre Robin anomaly of the small mandible and cleft palate as well as coloboma of the right eye and hypospadias. Physical examination showed a pleasant co-operative boy who is less than 3rd centile for height and weight. His face was less unusual than that of his brother but also showed a flat malar bone. His head circumference was 47 cm. He had slight epican-

thic folds with a coloboma of the right eye (Fig. 2d). Vision in his right eye without correction was good and central; in his left eye it was good, central, and maintained. He objected to covering his left eye. He had slight right esotropia. Extraocular movements were full. The fundus examination showed that the coloboma involved the iris and retina at 6 o'clock and not the disc or macula. His ears were large and protruding. His palate was repaired and the defect seemed to have been less extensive than the brother's but it was also currently short. He had no abnormalities of the alveolar ridges, excessive frenulae, or lip pits. His heart had no murmur. The abdomen did not show hepatosplenomegaly, and renal enlargement was not palpated. He had a slight chordee of his penis and hypospadias had been repaired. Wide spacing between the second and third digits of the hands (Fig. 3d) was less obvious than his brother while he showed distinct cutaneous syndactyly between the second and third toes, the left foot more severely involved than the right. There was limited external rotation of the right arm and x-ray films showed radial synostosis. Further studies included a bone survey which did not show further osseous abnormalities other than somewhat wide spacing between the second and third metacarpals (Fig. 3d) while an IVP disclosed horseshoe kidney. Electrocardiogram was normal.



the syndrome presented here because of the association of hypospadias and cleft palate and because of the variable expression in obligate female carriers. It should be noted, however, that cleft palate does not occur in all cases of the hypertelorism-hypospadias syndrome and coloboma is not mentioned as an associated characteristic while our patients showed no hypertelorism.

The variety of syndromes associated with cleft palate and the many varied modes of inheritance make it increasingly important in genetic counselling to treat each family with these defects individually and to base the counselling as much as possible on the individual family history instead of some 'melting pot' empirical risk. Further studies on the underlying biochemical defects are needed before the precise genetic systems involved in cleft palate or cleft lip/palate will be understood.

We wish to thank Drs Bryan Hall, James O'Donnell, and Wes Dempsey for their help in studying this family.

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#### Announcements

##### **The Harold Cummins Memorial Dermatoglyphics Symposium and Dermatoglyphics Workshop**

To honour the late Dr Harold Cummins of Tulane University, New Orleans, these meetings will be held 28-31 March 1977 in the Convention Center at the Gulf State Park Resort, Gulf Shores, Alabama. The meetings being jointly sponsored by the American Dermatoglyphics Association and the Department of Medical Genetics, University of South Alabama, Mobile, are designed both to introduce newcomers to dermatoglyphic techniques and to review the present status of the science in some detail.

For information write to Dr W. Wertzlecki, Department of Medical Genetics, University of South Alabama, 2451 Fillingim Street, Mobile, Alabama 36617, USA.

##### **Conference on Clinical Delineation of Birth Defects**

The University of Tennessee Center For The Health Sciences, Memphis, Tennessee, and The National Foundation—March of Dimes will sponsor the 1977 Conference on the Clinical Delineation of Birth Defects, 8 to 10 June 1977, in Memphis. For information write Robert L. Summitt, M.D., Department of Pediatrics, University of Tennessee Center for The Health Sciences, Memphis, Tennessee 38163, USA.

##### **Fourth International Workshop on Human Gene Mapping**

The Fourth International Workshop on Human Gene Mapping will be held in Winnipeg, Canada from Sunday 14 August to Thursday 18 August 1977. Attendance at this meeting will be limited to 125 participants. Those wishing to attend should apply, indicating the contribution they propose to make to the Workshop, to the Chairman of the Organizing Committee: John L. Hamerton, D.Sc., F.C.C.M.G., Department of Genetics, Children's Centre, 685 Bannatyne Avenue, Winnipeg, Manitoba, R3E 0W1 Canada.

Closing date for applications is 1 April 1977.

##### **Fourteenth International Congress on Genetics**

The Fourteenth International Congress of Genetics will be held in Moscow, USSR, 21-30 August, 1978. The Congress will be concerned with Genetics and Human Welfare. The main subjects of contemporary genetics will be included in the programme of the plenary and other sessions and symposia.

For further information write to: National Organizing Committee for the XIV ICG, 11 Fersman Street, Pouch 4, 117312 Moscow, USSR.