Interstitial Deletion 4q32-34 With Ulnar Deficiency: 4q33 May Be the Critical Region in 4q Terminal Deletion Syndrome

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We report on an infant with Robin sequence; mild developmental delay; a left ulnar ray defect with absent ulna and associated metacarpals, carpals and phalanges; and a right ulnar nerve hypoplasia. He had a de novo interstitial deletion of 4q32→q34. The critical region involved in the 4q terminal deletion syndrome may be 4q33. This conclusion was suggested by showing that del(4)(q31qter), del(4)(q32qter), and del(4)(q33qter) result in a similarly severe phenotype. In addition, we propose that genes for distal arm development, in particular for development of the left ulnar ray, central nervous system development, and cleft lip and palate, may be located at 4q33.

INTRODUCTION

The patient was born of the first pregnancy of healthy non-consanguineous Caucasian parents. His mother was 19 years old and his father 21 at the time of his birth. He had an uneventful antenatal course and delivery. At full-term birth, he weighed 2,800 g (10th centile), and was 51 cm long (50th centile). He had a head circumference of 37 cm (90th centile). His Apgar scores were eight at one minute and ten at five minutes. His left arm was hypoplastic, with a shortened humerus, absent ulna, and absent third, fourth, and fifth digits of his left hand (Fig. 1). He was noted to have a complete cleft of the secondary palate, with micrognathia. He had anteverted nares, a smooth philtrum, and a mild left facial hemihypertrophy. He had mild plagiocephaly and epicanthic folds. His left elbow was held in flexion by a pterygium. He held the fourth digit of his right hand in flexion, although it could be passively extended with ease (Fig. 2). He had clinodactyly of the fifth digit on his right hand. By the age of 12 months he had not been seen to flex the third or fifth digits of his right hand, but instead used only the thumb and index finger to grasp objects. He could passively flex those fingers.

Radiography showed that his left ulna and left ulnar ray metacarpals and phalanges were absent. (Fig. 3). His right arm and feet appeared normal on radiography. Echocardiography revealed a 1-mm patent foramen ovale, and renal ultrasound demonstrated normal kidney morphology. Responses evoked from the sedated auditory brainstem were normal. Examination at the age of 13 months showed that his growth parameters were at the 90th centile, and that his overall developmental age was eight months.

G-banded chromosomal analysis showed a reduction in length of the long arm of one chromosome 4 homologue, with an anomalous banding pattern at the distal end of the chromosome arm (Fig. 4). This was interpreted as an interstitial deletion with breakpoints at 4q32 and 4q34. Whole chromosome painting showed that no other chromosome was involved in the rearrangement, and comparative genomic hybridization demonstrated that there was an overall loss of chromosomal material of 4q32→q34 (data not shown). A 4q sub-telomeric probe confirmed the interstitial nature of the deletion (data not shown). Parental karyotypes were normal.

Fig. 1. The proband at 12 months of age. The features of note are the rounded face, epicanthic folds, small nose with anteverted nares, micrognathia, and an ulnar ray defect of the left arm resulting in absence of the third, fourth and fifth digits of the left hand, with a rudimentary left thumb and index finger. There is pterygium of the left elbow that prevents extension of the elbow.

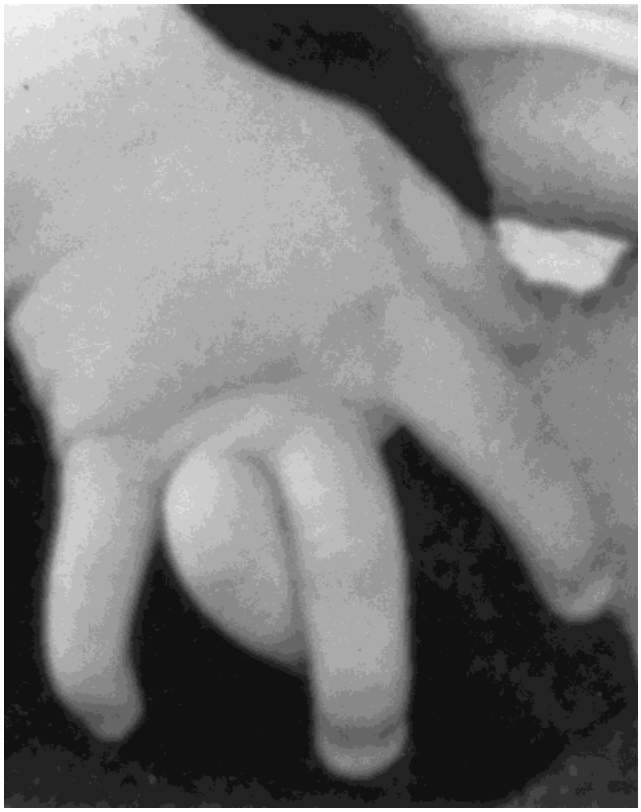

Fig. 2. A close-up view of the right hand showing its usual posture with the fourth digit flexed.

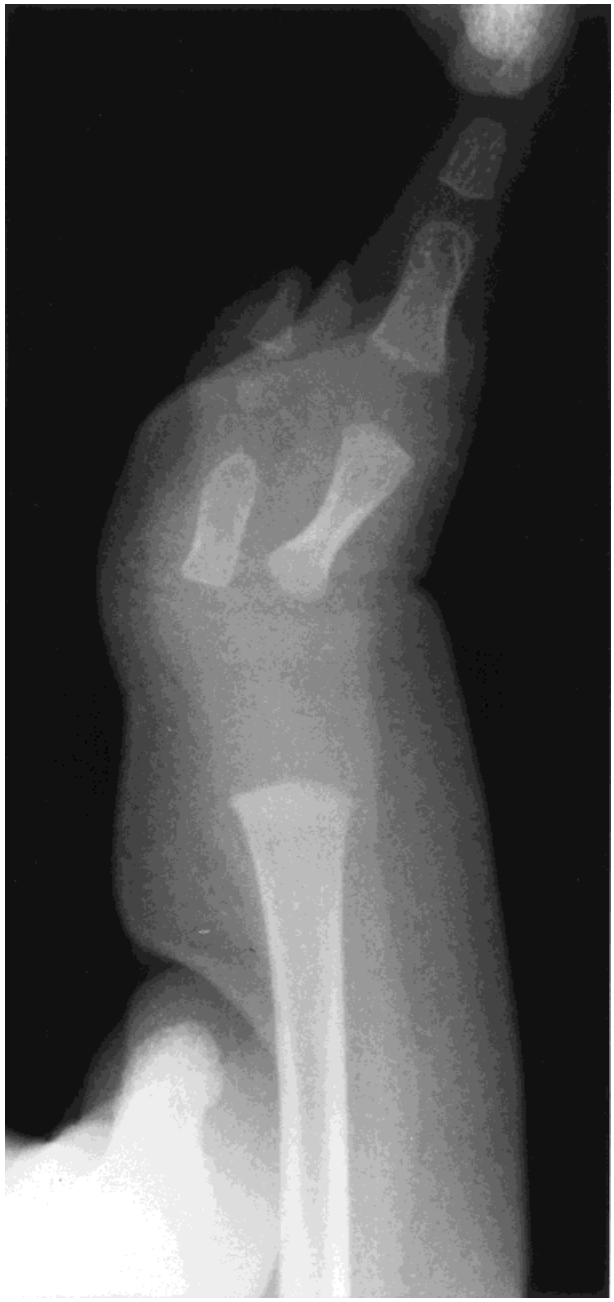

Fig. 3. Radiograph of the patient's left arm, showing the absence of the ulna and the third, fourth, and fifth ulnar rays.

DISCUSSION

There is a consensus in the literature concerning the phenotype of a syndrome involving deletion of the terminal third of the long arm of chromosome 4, known as the 4q terminal deletion syndrome. The gestalt of Robin sequence, comprising small nose with anteverted nares, epicanthic folds, cardiac anomalies, limb deficiencies, and developmental delay, is well described [Townes et al., 1979; Mitchell et al., 1981; Yu et al., 1981; Lin et al., 1988].

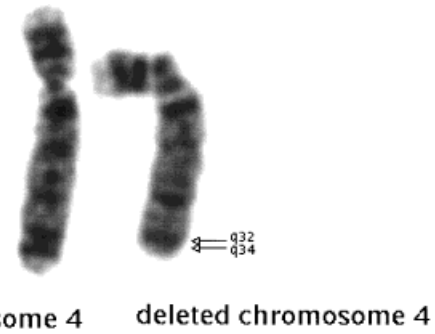

Fig. 4. G-banded karyotype of chromosome 4 for the proband. The arrows indicate the sites of del(4)(q33.4q34.4).

Chromosomal deletion syndromes with slightly differing breakpoints and different phenotypes contribute to the localization of genes with specific functions, by subtraction comparison. A review of the features reported in patients with del(4)(q32qter), del(4)(q33qter) and del(4)(q34qter) (Tables I and II) showed that there was a clear difference in the frequency and severity of anomalies in children with a deletion from either 4q32, or 4q33, to 4qter and del(4)(q34qter).

Of particular interest was the range of limb anomalies in 4q terminal deletion syndrome (Table II). The limb defects were usually reduction deformities. The defects were more notable in the left arm and hand than in the right, and involved ulnar ray defects. The abnormalities, often clinodactyly, or hypoplastic nails, were also seen in the post-axial rays of the hands and feet. Toe malposition was frequently seen. The only hypermorphic, or duplication, phenotypes seen were a partially duplicated fingernail of the left hand [Tsai et al., 1999], partially duplicated fingernail of the right hand [Lin et al., 1988] and a supernumerary digit of the left hand [Sandig et al., 1982].

We propose that the critical region for the 4q terminal deletion syndrome is 4q33. The region from 4q31 to 4q33 is suggested by the clear differentiation of the phenotype, resulting in deletions from 4q31, 4q32, and 4q33 to 4qter compared with the phenotype resulting in deletion from 4q34 to 4qter (Tables I and II).

The literature has not addressed the preponderance of cases in which 4q terminal deletion results predominantly in left hand deformities and arm reduction. Most reports of major hypoplastic arm abnormalities in the 4q terminal deletion syndrome involve the left arm and the left ulnar ray [this report; Tegada et al., 1990; Menko et al., 1992; Tomkins et al., 1982; Lin et al., 1988]. There are two children reported with facial and limb phenotypes almost identical to the current case. One child, reported by Tomkins et al. [1982], had the appearance of left facial hemihypertrophy, a left ulnar ray defect, anteverted nostrils, and micrognathia similar to the patient in the current report. The second child, reported by Menko et al. [1992], had a left ulnar ray reduction deformity almost identical to our findings.

Most reported cases of terminal 4q deletions arose de novo. There are only two reports of familial 4q terminal deletion syndromes, and these are affected mothers with affected sons [Descartes et al., 1996; Curtis et al., 1989].

In summary, we propose that the critical region for the 4q terminal deletion syndrome is 4q33, and that the features of this syndrome are the Robin sequence (micrognathia and cleft palate), small nose with anteverted nares, smooth philtrum, epicanthic folds, and up-slanting palpebral fissures. The facies also often appear full-cheeked and the mouth is held open. There are developmental delay, limb abnormalities, and variable cardiac defects. The major limb anomalies are uni- or bilateral ulnar ray defects with an overwhelming preponderance of left- side defects. The minor limb defects include fifth-digit clinodactyly of hands and feet, hypoplastic nails, and overlapping toes. Occasional defects are cryptorchidism, duplication of the nails of the fifth fingers, and talipes equinovarus.

TABLE I. Facial Features, Developmental Delay Congenital Heart Defects and Other Features in Patients With Deletions of 4q32-4qter

Anomaly	4q32-qter[a]	4q33-qter[b]	4q34-qter[c]
Cleft lip and/or palate	3/4	3/14	1/6
Micrognathia	4/4	6/14	0/6
Epicanthic folds	3/4	8/14	1/6
Small nose with anteverted nares	2/4	9/14	3/6
Upslanting palpebral fissures	2/4	4/14	2/6
Developmental delay	4/4	7/14	5/6
Congenital heart defect	1/4	4/14	1/6
Other features	Hypospadias,cryptorchidism [Stanberg et al., 1982] Cryptorchidism, mild bilateral conduction deafness[Calabrese et al., 1997] Horizontal nystagmus in mother and son[Descartes et al., 1996] Single umbilical artery, congenital cataract [Evers et al., 1993]		

[a]4q32-qter-4 patients , [this report, del 4q33–4q35; Mitchell et al., 1981; Tuchman et al., 1983; Lin et al., 1988, patient 2].
[b]4q33-4qter-14 patients [Menko et al., 1992; Jefferson et al., 1986; Fagan and Morris, 1989; Curtis et al., 1989 del 4q33q35. 1, mother and 2 sons; Stanberg et al., 1982; Tomkins et al., 1982, 2 patients; Calabrese et al., 1997, patient 1, 4q33–q35; Mitchell et al., 1981, patient 5; Grammatico et al., 1997; Ho and Ng, 1993; Evers et al., 1993].
[c]4q34-qter-6 patients [Lin et al., 1988, patient 4; Tsai et al., 1999; Caliebe et al., 1997; Descartes et al., 1996, mother and 2 sons].

TABLE II. Limb Abnormalities in Patients With del 4q32-4qter

Anomaly	4q32-qter[a]	4q33-qter[b]	4q34-qter[c]
Symmetrical minor anomalies of limbs	3/4 Toe malposition [Mitchell et al., 1981] Short fingers [Tuchman et al., 1983; Lin et al., 1988]	8/14 Clinodactyly of fifth digit of left foot, hypoplastic fifth digit of right hand [Menko et al., 1992] Valgus deformity of toes and overlapping toes, single palmar creases [Jefferson et al., 1986] Clinodactyly of fifth finger bilaterally, equinovarus of both feet, syndactyly of the 2nd and 3rd toes [Stanberg et al., 1982] Overlapping toes [Tomkins et al., 1982] patient 1 Syndactyly of the 2nd 3rd fingers bilaterally [Tomkins et al., 1982] patient 2 Stiff, bilateral 5th finger with "pointed" nail [Calabrese et al., 1997] Malpositioned toes [Mitchell et al., 1981] Clinodactyly of fifth fingers [Grammatico et al., 1997]	1/6 Bilateral partial syndactyly of toes 2 and 3 [Lin et al., 1988]
Asymmetrical or major limb anomalies	2/4 Bilateral ulnar ray defects with severe reduction deformity of the left arm [this report] Ectrodactyly of left hand, stiff, extended fifth digit of right hand with a duplicated fifth fingernail [Lin et al., 1988 patient 2]	4/14 Left-sided unilateral ulnar ray defect with severe reduction deformity [Menko et al., 1992] Decreased flexion and absence of flexure creases of the left fifth finger [Stanberg et al., 1982] Absent distal lateral tip of the left fifth digit [Tomkins et al., 1982 patient 1] Hypoplastic tip and nail of the right 5th and left 2nd and 5th digits, cleft left hand between 4th and 5th fingers, camptodactyly of the right 5th finger [Tomkins et al., 1982, patient2]	1/6 partially duplicated left fifth finger [Tsai et al., 1999]

[a]4q32-qter-4 patients, [this report del 4q33–4q35; Mitchell et al., 1981; Tuchman et al., 1983; Lin et al., 1988, patient 2].
[b]4q33-4qter-14 patients [Menko et al., 1992; Jefferson et al., 1986; Fagan and Morris, 1989; Curtis et al., 1989, del 4q33q35.1 mother and 2 sons; Stanberg et al., 1982; Tomkins et al., 1982, 2 patients; Calabrese et al., 1997, patient 1, 4q33–q35; Mitchell et al., 1981, patient 5; Grammatico et al., 1997; Ho and Ng, 1993; Evers et al., 1993].
[c]4q34-qter-6 patients [Lin et al., 1988, patient 4; Tsai et al., 1999; Caliebe et al., 1997; Descartes et al., 1996, mother and 2 sons].

Therefore, genes involved in facial, limb, cardiac and central nervous system development must reside at 4q33. In particular, we propose that this region plays a role in the development of ulnar rays.

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