



**Manchester
Metropolitan
University**

Keeling, SL, Lee-Jones, L ORCID logoORCID: <https://orcid.org/0000-0003-1255-3545> and Thompson, P (2001) Interstitial deletion 4q32-34 with ulnar deficiency: 4q33 may be the critical region in 4q terminal deletion syndrome. *American Journal of Medical Genetics Part A*, 99 (2). pp. 94-98. ISSN 0148-7299

Downloaded from: <https://e-space.mmu.ac.uk/629777/>

Version: Accepted Version

Publisher: Wiley

DOI: [https://doi.org/10.1002/1096-8628\(2000\)9999:999<00::AID-AJMG1134>3.0.CO;2-D](https://doi.org/10.1002/1096-8628(2000)9999:999<00::AID-AJMG1134>3.0.CO;2-D)

Please cite the published version

<https://e-space.mmu.ac.uk>

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

S.L. Keeling,¹ L. Lee-Jones,² and P. Thompson²

¹ Victorian Clinical Genetics Service, Murdoch Childrens Research Institute, Royal Children's Hospital, Parkville, Victoria, Australia

² Institute of Medical Genetics for Wales, University Hospital of Wales, Heath Park, Cardiff, UK

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.

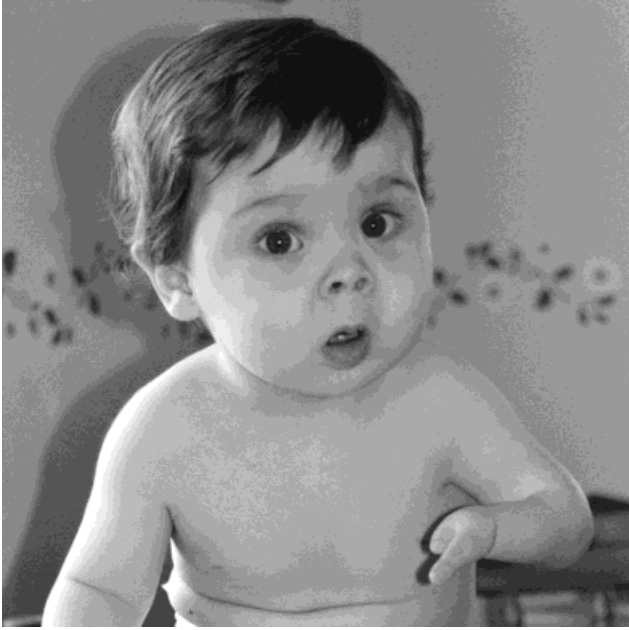


Fig. 1. The proband at 12 months of age. The features of note are the rounded face, epicanthic folds, small nose with anteverted nares, micrognathia, and an ulnar ray defect of the left arm resulting in absence of the third, fourth and fifth digits of the left hand, with a rudimentary left thumb and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



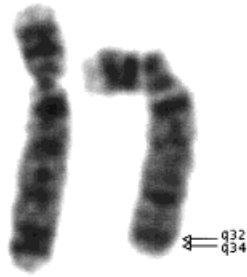
Fig. 2. A close-up view of the right hand showing its usual posture with the fourth digit flexed.



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].



normal chromosome 4 deleted chromosome 4

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]	

^a4q32-qter-4 patients, [this report, del 4q33-4q35; Mitchell et al., 1981; Tuchman et al., 1983; Lin et al., 1988, patient 2].

^b4q33-4qter-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].

^c4q34-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 2 nd and 3 rd toes [Stanberg et al., 1982] Overlapping toes [Tomkins et al., 1982] patient 1 Syndactyly of the 2 nd 3 rd fingers bilaterally [Tomkins et al., 1982] patient 2 Stiff, bilateral 5 th 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 5 th and left 2 nd and 5 th digits, cleft left hand between 4 th and 5 th fingers, camptodactyly of the right 5 th finger [Tomkins et al., 1982, patient 2]	1/6 partially duplicated left fifth finger [Tsai et al., 1999]

^a4q32-qter-4 patients, [this report del 4q33-4q35; Mitchell et al., 1981; Tuchman et al., 1983; Lin et al., 1988, patient 2].

^b4q33-4qter-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].

^c4q34-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.

ACKNOWLEDGMENTS

The authors thank Dr. Helen Hughes and Dr. Sally Davies of the Institute of Medical Genetics for Wales for their critical reading of the manuscript.

REFERENCES

- Bamshad M, Lin RC, Law DJ, Watkins WC, Krakowiak PA, Moore ME, Franceschini P, Lala R, Holmes LB, Gebuhr TC, Bruneau BG, Schinzel A, Seidman CE, Seidman CE, Jorde LB. 1997. Mutations in human TBX3 alter limb, apocrine and genital development in ulnar-mammary syndrome *Nat Genet* 16:311-315.
- Calabrese G, Giannotti A, Mingarelli R, Di Gilio MC, Piemontese MR, Palka G. 1997. Two newborns with chromosome 4 imbalances: deletion 4q33-q35 and ring r(4)(pterq35.2-qter). *Clin Genet* 51:264-267.
- Caliebe A, Waltz S, Jenderny J. 1997. Mild phenotypic manifestations of terminal deletion of the long arm of chromosome 4: clinical description of a new patient *Clin Genet* 52:116-119.
- Curtis MA, Smith RA, Sibert J, Hughes HE. 1989. Interstitial deletion, del(4)(q33q35.1), in a mother and two children. *J Med Genet* 26:652-654.
- Descartes M, Keppler-Noreuil K, Knops J, Longshore JW, Finley WH, Carroll AJ. 1996. Terminal deletion of the long arm of chromosome 4 in a mother and two sons. *Clin Genet* 50:538-540.
- Dutrillaux B, Jansson J, Lauren K, Lejeune J, Lindsten J, Petersen GB, Saldana P, Garcia. 1973. An unbalanced 4q/21q translocation identified by the R but not by the G and Q chromosome banding techniques. *Ann Genet* 16:11-16.
- Evers LJM, Schrandt-Stumpel CTRM, Engelen JJM, Mulder H, Borghgraef M, Fryns JP. 1993. Terminal deletion of long arm of chromosome 4: patient report and literature review. *Genet Counsel* 4:139-145.
- Fagan KA, Morris RB. 1989. Del(4)(q33qter): Another case report of a child with mild dysmorphism. *J Med Genet* 26:776-784.
- Ferrier S, Freund M. 1974. A propos d'un cas de deletion du bras ling du chromosome B4 (B4q-). *Arch Genet* 47:16-26.
- Grammatico L, Spaccini L, Di Rosa C, Cupilari F, Del Porto G. 1997. Del(4)(pter-q33): case report and review of the literature. *Genet Counsel* 8:39-42.
- Ho NK, Ng ISL. 1993. Deletion of the terminal segment of the long arm of chromosome 4 with aortic stenosis. *J Paediatr Child Health* 29:473-475.
- Jefferson RD, Burn J, Gaunt KL, Hunter S, Davison EV. 1986. A terminal deletion of the long arm of chromosome 4 (46,XX,del(4)(q33)) in an infant with phenotypic features of Williams syndrome. *J Med Genet* 23:474-480.
- Lin AE, Garver KL, Diggans G, Clemens M, Wenger SL, Steele MW, Jones MC, Israel J. 1988. Interstitial and terminal deletions of the long arm of chromosome 4: further delineation of phenotypes. *Am J Med Genet* 31:533-548.
- Lurie IW. 1995. Further study of genetic interactions: Loss of short arm material in patients with ring chromosome 4 changes developmental pattern of del(4)(q33). *Am J Med Genet* 56:308-311.
- Menko FH, Madan K, Baart JA, Beukenhorst HL. 1992. Robin sequence and a deficiency of the left forearm in a girl with a deletion of chromosome 4q33-qter. *Am J Med Gen* 44:696-698.
- Mitchell JA, Packman S, Loughman WD, Fineman RM, Zackai E, Patil SR, Emanuel B, Bartley JA, Hanson JW. 1981. Deletions of different segments of the long arm of chromosome 4. *Am J Med Genet* 8:73-89.

- Mitchell LE, Healey SC, Chenevix-Trench G. 1995. Evidence for an association between nonsyndromic cleft lip with or without cleft palate and a gene located on the long arm of chromosome 4. *Am J Hum Genet* 57:1130–1136.
- Ockey CH, Feldman GV, Macaulay ME, Delaney MJ. 1967. A large deletion of the long arm of chromosome no.4 in a child with limb abnormalities. *Arch Dis Child* 42:428–434.
- Pierpont JW, Storm AL, Erikson RP, Kohn BR, Pettijohn L, DePaepe A. 1995. Lack of linkage of apparently dominant cleft lip (palate) to two candidate chromosomal regions. *J Craniofac Genet Dev Biol* 15: 66–71.
- Roberts DJ, Tabin C. 1994. The genetics of human limb development. *Am J Med Genet* 55:1–6.
- Robertson SP, O'Day K, Bankier A. 1998. The 4q- syndrome: delineation of the minimal critical region to within band 4q31. *Clin Genet* 53: 70–73.
- Sandig KR, Mucke J, Trautmann U. 1982. The partial 4q monosomy. Report of a 5-year-old boy with deletion 4q31.3 leads to 4qter. *Eur J Pediatr* 138:254–257.
- Sarda P, Lefort G, Fryns JP, Humeau C, Rieu D. 1992. Interstitial deletion of the distal long arm of chromosome 4. *J Med Genet* 29:259–261.
- Seabright M. 1971. A rapid banding technique for human chromosomes. *Lancet* ii:971–972.
- Stanberg J, Jabs EW, Elias E. 1982. Terminal deletion (4)(q33) in a male infant. *Clin Genet* 21:125–129.
- Tegada MI, Lizarraga MA, Mendoza BS, Escudero F, Carbonero K, Benito JA. 1990. Deletion of chromosome 4: 46,XY,del(4)(q31.3) after gamete intrafallopian transfer and in vitro fertilization-embryo transfer. *Fertil Steril* 54:953–954.
- Tomkins DJ, Hunter AGW, Uchida IA, Roberts MH. 1982. Two children with deletion of the long arm of chromosome 4 with breakpoint at band q33. *Clin Genet* 22:348–355.
- Townes PL, White M, DiMarzo SV. 1979. 4q- syndrome. *Am J Dis Child* 133:383–385.
- Tsai C, Van Dyke DL, Feldman GL. 1999. Child with velocardiofacial syndrome and del(4)(q34.2): another critical region associated with a velocardiofacial syndrome-like phenotype. *Am J Med Genet* 82:336–339.
- Tuchman M, Ebrahimi J, Gorlin RJ. 1983. Deletion of chromosome 4q33-qter. Is it different from 4q31-qter deletion syndrome? *Am J Med Genet* 14:391–393.
- Wheater RF, Roberts SH. 1987. An improved lymphocyte culture: deoxycytidine release of a thymidine block and use of a constant humidity chamber for slide making. *J Med Genet* 24:113–114.
- Yu CW, Chen H, Baucum RW, Hand AM. 1981. Terminal deletion of the long arm of chromosome 4. Report of a case of 46,XY,del(4)(q31) and review of 4q- syndrome. *Ann Genet* 24:158–161.