

Evidence that Rieger syndrome maps to 4q25 or 4q27

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Abstract

We report a baby with the features of Rieger syndrome and a de novo interstitial deletion of 4q which includes band 4q26 and an adjoining GTL light band, either q25 or q27. Rieger syndrome is provisionally mapped to 4q23→q27 but band 4q26 has been excluded as a possible site, suggesting that Rieger syndrome must map to a band, either 4q25 or 4q27, adjoining 4q26.

Rieger syndrome is characterised by hypodontia and malformation of the anterior chamber of the eye. Failure of involution of the periumbilical skin is considered to be a cardinal feature of the syndrome.¹ It is generally inherited as an autosomal dominant trait. Infrequently it has been associated with chromosomal abnormality but no consistent chromosomal abnormality has been involved to date.

Ligutic *et al*² described a case of interstitial deletion 4q23→q27 with Rieger syndrome. On the basis of this case and a report of apparent linkage between anterior segmental ocular dysgenesis, which resembles Rieger syndrome, and the blood group system MNSs, which is located on chromosome 4q, McKusick³ has provisionally mapped Rieger syndrome to 4q23→27.

Case report

The baby (fig 1) was born after a normal pregnancy complicated by intrauterine growth retardation. The pregnancy was induced at 39 weeks and the cord was said to have ruptured during labour. She was well at birth with a birth weight of 2850 g. At 4 weeks of age she developed jerking movements of the legs and later of the arms, and was noticed to be staring vacantly. The seizures lasted between 20 and 30 seconds, occurring six to seven times a day over the first four weeks of life. No abnormality was detected on cranial ultrasound or CT scan, but the EEG was abnormal when recorded from the cranial vertex. The general development seemed quite good with normal head control but the muscle tone seemed to be increased.

The facies were not remarkable; however, each ear had a thin superior helix and a prominent anthelix. The head circumference was between the 50th and 90th centiles. The upper gums were very irregular (fig 1B). In the right eye the pupil was displaced laterally (corectopia), while on the left side the pupil was central but Schwalbe's line was very prominent. Two

months later the left pupil was found to be ectopic (fig 1C), presumably owing to contraction of abnormal tissue in the angle of the anterior chamber. On each little finger there was an extra skin crease over the first phalanx and the finger nail was small. Failure of involution of the periumbilical skin was obvious. The anus was anteriorly placed, being about 0.5 cm behind the vulva.

When reviewed at 14 months her height was 73 cm (<10th centile), weight was 8.5 kg (<10th centile), and head circumference was 47 cm (50th centile). She had had no further seizures since initial admission. Phenobarbital therapy had continued but was being reduced. Physical milestones were within normal limits; she had sat alone at 7 months, crawled at 10 months, and was walking with support. Conductive hearing loss after several ear infections was treated with insertion of tubes at 14 months. Receptive language was good, and she was saying "dada" and "mum". Her vision was quite good: binocular vision 6/24, left eye 6/100, right eye 6/36. Eruption of the teeth was normal.

CYTOGENETIC STUDIES

Metaphase chromosomes were obtained from phytohaemagglutinin stimulated lymphocytes. Chromosome analysis was carried out on GTL and RBG banded preparations (fig 2) by standard methods.⁴ The proband was found to have a deletion in one chromosome 4 that involved loss of the GTL dark band q26 and also some GTL light band material, which on RBG banding appeared to be 4q25. Her karyotype can be described as 46,XX,del(4)(q2500q2700), and in the detailed nomenclature as 46,XX,del(4)(4pter→4q2500::4q2700→4qter). The parental chromosomes were normal. An EBV transformed lymphocyte cell line from this patient is available from the Murdoch Institute (cell code MI-AQI).

Discussion

The presence of corectopia and a prominent Schwalbe's line together with failure of involution of the umbilicus in the proband suggest a diagnosis of Rieger syndrome. At birth, unevnt gums suggested that the teeth might erupt abnormally, but at 14 months of age tooth development was normal.

The proband was found to have an interstitial deletion in the long arm of chromosome 4. The deletion included the GTL dark band 4q26 and on RBG banding it could be seen that a RBG dark band was also partially deleted. Comparison of the normal and deleted chromosomes suggested that this was probably

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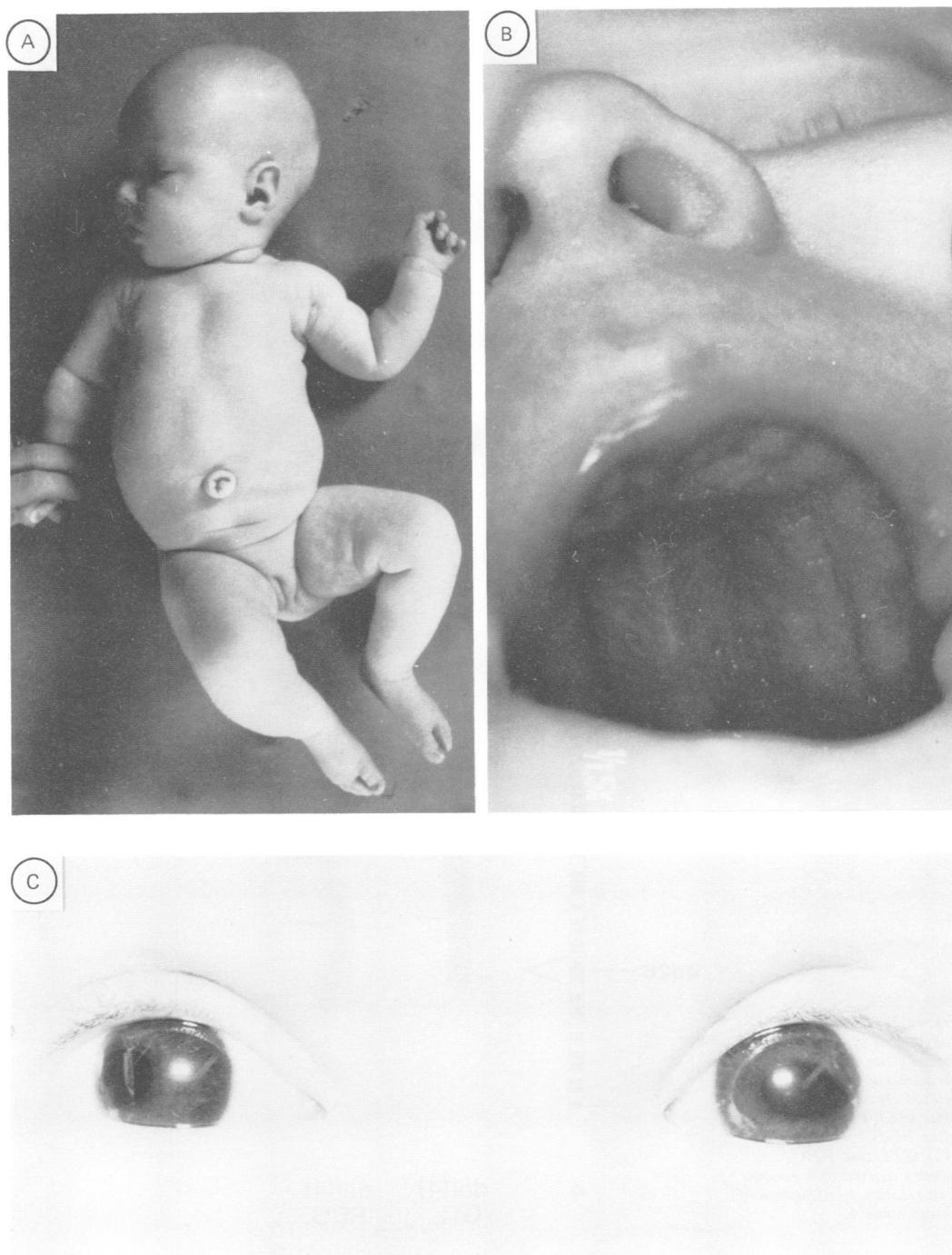


Figure 1 The proband at 2 months of age showing (A) the protuberant umbilicus, (B) the mouth with irregular gums, and (C) the eyes showing corectopia.

band 4q25, but it is possible that it was band 4q27. As the parental chromosomes were normal this is an apparently *de novo* chromosomal abnormality.

Epidermal growth factor (EGF) has been mapped to band 4q25.³ Urinary EGF levels in the proband were studied using a radio-immune assay and a radioreceptor assay at 29 to 31 weeks of age and showed normal levels compared with age matched controls (L Read, personal communication).

Stathacopoulos *et al*⁶ reviewed the association of Rieger syndrome and chromosome abnormality. They found seven possible cases of Rieger syndrome associated with a chromo-

somal abnormality. The chromosomal abnormalities seen were not consistent except for two cases with deletions of 13q that overlapped for the region 13q14→13q22. Interstitial deletion of 4q apparently involving bands 4q25, 4q26, or 4q27 has been previously reported in five cases.^{2,7,8} One case (patient 7 in the report of Mitchell *et al*⁷) with deletion 4q21.1→4q25 had generalised seizures that responded to phenobarbital treatment and an anteriorly placed anus, both features seen in our patient. This case differed from our patient in having diffused hypotonia and not having Rieger syndrome. The case of Ligutic *et al*² with deletion 4q23→4q27 had Rieger syndrome. A recent

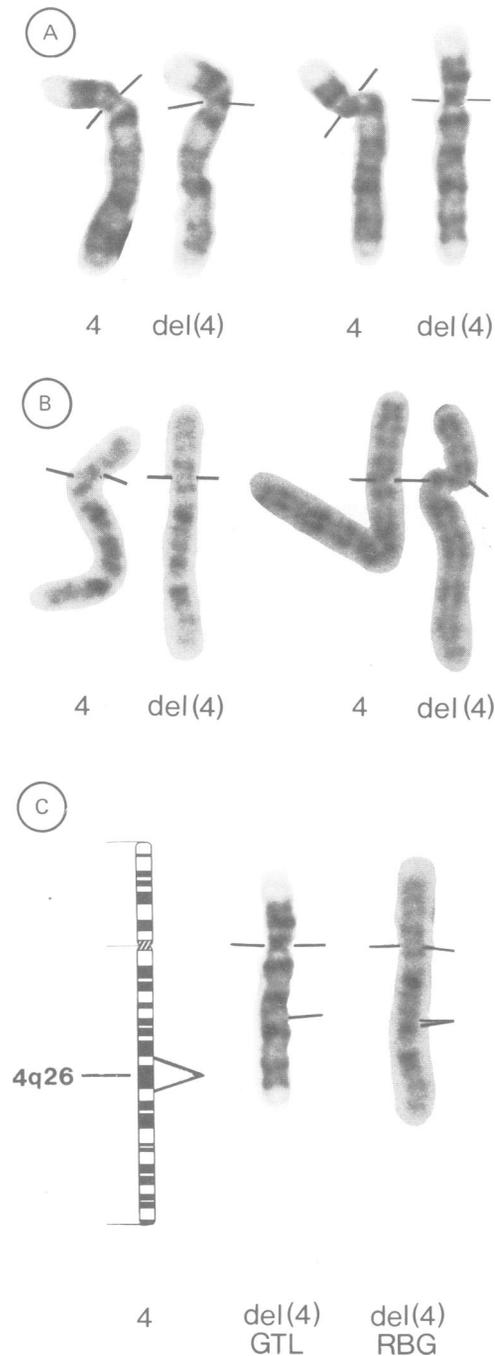


Figure 2 Partial karyotypes of the proband showing the normal chromosome 4 and the deleted chromosome 4 (A) after GTL banding, (B) after RGB banding, and (C) GTL and RGB banded deleted chromosome 4 in relation to ideogram of chromosome 4.

report found that deletion of band 4q26 was not associated with Rieger syndrome.⁸ The finding in this case together with those previously reported suggest that Rieger syndrome must map to a GTL light band adjoining the more readily identifiable band 4q26.

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- 1 Jorgensen RJ, Levin LS, Cross HE, Yoder F, Kelly TE. The Rieger syndrome. *Am J Med Genet* 1978;2:307-18.
- 2 Ligutic I, Brecevic L, Petkovic I, Kalogjera T, Rajic Z. Interstitial deletion 4q and Rieger syndrome. *Clin Genet* 1981;20:323-7.
- 3 McKusick VA. *Mendelian inheritance in man*. 8th ed. Baltimore: Johns Hopkins University Press, 1988:662-3.
- 4 Verma RS, Babu A. *Human chromosomes—manual of basic techniques*. New York: Pergamon Press, 1989.
- 5 Cox R, Murray JC, Buetow KH. Report of the committee on the genetic constitution of chromosome 4. *Human Gene Mapping 10. Cytogenet Cell Genet* 1989;51:121-36.
- 6 Stathacopoulos RA, Bateman JB, Sparkes RS, Hepler RS. The Rieger syndrome and a chromosome 13 deletion. *J. Pediatr Ophthalmol Strabismus* 1987;24:198-203.
- 7 Mitchell JA, Packman S, Loughman WD, et al. Deletions of different segments of the long arm of chromosome 4. *Am J Med Genet* 1981;8:73-90.
- 8 Motegi T, Nakamura K, Terakawa T, et al. Deletion of a single chromosome band 4q26 in a malformed girl; exclusion of Rieger syndrome associated gene(s) from the 4q26 segment. *J Med Genet* 1988;25:628-33.