Acampomelic campomelic dysplasia with de novo 5q;17q reciprocal translocation and severe phenotype

Ravi Savarirayan, Agnes Bankier

Abstract

Campomelic dysplasia (CD) is a rare skeletal malformation syndrome caused by mutations in the SRY related gene SOX9, mapped to 17q24.3-q25.1. A small proportion of cases are associated with structural rearrangements involving 17q and it has been proposed that this subgroup have a milder phenotype and better prognosis compared to those with mutations in the SOX9 gene.

We report a severely affected infant with the acampomelic form of campomelic dysplasia, who died at 11 days and was found to have a de novo reciprocal translocation, 46,XX,t(5;17)(q15;q25.1). This is the second reported case of severe campomelic dysplasia associated with a structural rearrangement involving 17q and suggests that this subgroup of patients may not significantly differ from those without chromosomal rearrangements with regards to phenotype or prognosis.

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Campomelic dysplasia (CD) is a rare skeletal disorder initially delineated with the documentation of six patients by Maroteaux *et al*¹ in 1971. The condition derives its name from the Greek translation of the most striking clinical and radiographic feature, namely "bent limbs", even though it is now well recognised that campomelia is not a mandatory feature of the disorder.²⁻⁴ The condition is characterised by variable additional clinical and radiographic features including macrocephaly, cleft palate, micrognathia, flat nasal bridge, low set ears, hypoplastic scapulae, non-mineralised thoracic pedicles, vertically narrow iliac wings, pretibial skin dimples, and talipes equinovarus.^{3,4}

Sex reversal is found in approximately two thirds of genotypic males.⁵ Most cases, including those with sex reversal, have mutations in the SRY (Sex determining Region Y) related gene SOX9,⁶ mapped to 17q24.3-q25.1 by the study of three cases with CD and de novo reciprocal translocations.⁷

The mode of inheritance of the condition has now been established as autosomal dominant owing to de novo mutations. Haploinsufficiency of the SOX9 product results in cases where a loss of function mutation has been identified in one SOX9 allele.^{6,8} The SOX9 protein has been recently shown to regulate the

expression of the gene encoding type II collagen (COL2A1), implicating abnormal regulation of COL2A1 during chondrogenesis as a cause of the skeletal manifestations associated with CD.⁹

The small proportion of cases in which CD has been associated with chromosomal rearrangements of 17q continue to be of great importance in the ongoing elucidation of SOX9 gene transcription and expression control and also the role it plays in the transcriptional regulation of other genes critical to osteochondrogenesis. We report another case in this select subgroup.

Case report

The patient was the product of the fifth pregnancy of healthy, non-consanguineous, white parents, born by unassisted vaginal delivery after induction of labour for maternal pregnancy induced hypertension at 36 weeks. The pregnancy had been normal apart from the isolated finding of right talipes equinovarus on a routine antenatal ultrasound scan performed at 19 weeks. The couple's previous four pregnancies had yielded three healthy children

Figure 1 The proband aged 1 day. Note flat nasal bridge, micrognathia, short neck, short thorax, and straight limbs.

Victorian Clinical
Genetics Service,
Royal Children's
Hospital, Parkville,
Victoria 3052,
Australia
R Savarirayan
A Bankier

Correspondence to:
Dr Savarirayan.

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Figure 2 Chest radiograph. Note hypoplastic scapulae and marked thoracic kyphoscoliosis at T4/5.

and a spontaneous miscarriage at 7 weeks. There was no family history of skeletal abnormality.

The child was born in poor condition with immediate respiratory distress, hypotonia, and bradycardia (heart rate 80 per minute). Apgar scores were 3 at one minute and 5 at five minutes and the child required aggressive resuscitation by endotracheal intubation and assisted ventilation by bag and mask.

Birth weight was 3042 g (75th centile), length 43 cm (<3rd centile), and head circumference 34.5 cm (75th centile). External abnormalities noted comprised midline cleft soft palate, micrognathia, flat, broad nasal bridge, low set and posteriorly angulated ears, short neck with redundant posterior skin folds, short thorax with kyphoscoliosis, and bilateral (right greater than left) talipes equinovarus (fig 1). The external genitalia were unambiguously female and all four limbs were clinically straight with bilateral pretibial dimples present. Radiology showed severe hypoplasia of the scapulae, hypoplastic distal cervical vertebrae, upper thoracic vertebrae, and left hemithorax (fig 2), marked thoracic kyphoscoliosis at T4/5, straight long bones (fig 3), bilateral talipes, and abnormal pelvic ossification, with underossification of the ischia and normally formed ilia.

The patient continued to require increasing mechanical ventilation support and any attempts at reducing this level of support were not successful. She was not considered a candidate for survival without lifelong artificial ventilation. Because of her poor prognosis it was agreed, with the family, to withdraw artificial ventilation and she died aged 11 days.

Internal examination at necropsy showed congested and oedematous lungs (histologically normal) and left pelviureteric junction

Figure 3 Radiograph of the lower limbs showing acampomelia.

obstruction with mild dilatation of the left ureter. Internal genitalia were normal female both macroscopically and on histology.

Analysis of cultured blood lymphocytes obtained before death showed a female karyotype with an apparently balanced reciprocal translocation involving the long arm of one chromosome 5 and the long arm of one chromosome 17 in all cells examined. The breakpoints were identified as 5q15 and 17q25.1 (fig 4) respectively, that is, 46,XX,t(5;17)(q15;q25.1). Parental karyotypes were normal.

Discussion

The patient reported displayed the clinical, radiographic, and pathological features typical of severe campomelic dysplasia, with the notable exception of campomelia itself. The finding of a *de novo* reciprocal translocation involving 17q in this patient is the eleventh reported case of CD associated with a structural rearrangement of the distal long arm of chromosome 17^{3 7 10 14} (our case). Two of these cases have involved an apparently balanced paracentric inversion involving 17q,^{10 12} with the remainder comprising apparently balanced reciprocal translocations involving 17q and another autosome^{3 7 11 13 14} (our case). In five translocation cases, the breakpoint on 17q has been shown to lie outside the SOX9 gene by up to 130 kb or greater^{6 8 13} and various explanations have been proffered to explain how these breakpoints may affect SOX9 function.¹³

Several authors^{3 6 8 13} have commented that the group of patients with CD associated with a chromosomal rearrangement are less severely affected than the non-translocation cases and thus have a better prognosis. This case report, however, is of a severe phenotype with death at 11 days from respiratory failure consequent to thoracic cage deformities and pulmonary insufficiency. Our case resembles a case

Figure 4 Partial karyotype with ideogram showing translocation between chromosomes 5 and 17. The breakpoints are indicated by arrows; the normal homologues are on the left of each pair.

reported by Maraia *et al.*,¹⁰ who also had severe CD associated with a 17q chromosome rearrangement and died at 3 months from respiratory failure, a common cause of death in CD owing to deficient cartilage within the tracheo-bronchial tree.⁵

These cases show that not all patients with CD associated with chromosomal rearrangements of 17q survive infancy and suggest that they may not significantly differ from the non-translocation group with regards to severity of phenotype or prognosis.

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