LETTER TO JMG

The phenotype of survivors of campomelic dysplasia

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Five patients with campomelic dysplasia who have survived (age range 7 to 20 years) are described, all of whom have molecular or cytogenetic evidence of campomelic dysplasia. The phenotype and radiological features of these cases are consistent. Complications in this group include recurrent apnoea and upper respiratory infections, progressive kyphoscoliosis, mild to moderate learning difficulties, short stature, and dislocation of the hips. All five had very similar facial features. The radiological features include hypoplastic scapulae, defective ischiopubic ossification, absent or hypoplastic patellae, and spinal dysraphism.

Campomelic dysplasia (CMD) is a rare skeletal dysplasia resulting from mutations in *SOX9*. It is usually lethal in the first year of life. Three-quarters of the cases with a male karyotype have complete or partial sex reversal.[1] The skeletal changes in the neonatal period are well recognised and include hypoplastic scapulae, bowing of the long bones, vertical narrow iliac bones, and absence of ossification of the thoracic pedicles.

The case histories of five children who share a number of clinical and radiological features are presented.

CASE REPORTS

Case 1

A mother was diagnosed at the age of 18 years after giving birth to a daughter with the classical features of campomelic dysplasia.[2]

The daughter had shortening of all four limbs, tibial bowing, with skin dimpling over the apex of each tibia. There was bilateral talipes equinovarus and relative macrocephaly (head circumference on the 50th centile, length <3rd centile). She had micrognathia and a depressed nasal bridge. The karyotype was normal female. She had the classical radiological features of campomelic dysplasia with hypoplastic scapulae and absent pedicles in the mid-thoracic region, 11 pairs of ribs, shortening of the long bones with bowing, narrow iliac bones with dislocation of the hips, short first metacarpals, and short phalanges in the hands and feet.[2] She died of respiratory problems in the neonatal period.

At that time her mother was examined and found to have some skeletal abnormalities. She was below the 3rd centile for height (1.5 m) with a flat face, long philtrum, depressed nasal bridge, small mouth, and micrognathia (fig 1). A right fibula osteotomy was required at the age of 11 years because of a 4 cm asymmetry of her lower limbs. The halluces on both sides were short. Both thumbs and little fingers were short and the nails were hypoplastic. She had conductive hearing loss of the left ear and was myopic. Intelligence was normal but seizures began at the age of 13 requiring treatment with sodium valproate. Radiographs showed a small left iliac bone with non-ossification of the inferior pubic rami and short ischia on both sides, hypoplastic scapulae, 11 pairs of ribs, short first metacarpals, short middle phalanges of the index and little fingers, and thoracic scoliosis. The patellae were small and there was mild bowing of the tibia (see fig 1A and B in Lynch *et al*[2] and Offiah *et al*[3]).

Mutation analysis of *SOX9* confirmed deletion at C155 resulting in a frameshift and truncation of the product at amino acid 59 (A J Schafer, personal communication). The *SOX9* mutation was found in the mother and daughter.

Figure 1 Patient 1 aged 18 years.

Case 2

This affected boy is currently 11 years old. He was born to Pakistani consanguineous parents (half first cousins) who had a termination of pregnancy for a fetus which was also affected by campomelic dysplasia. He has one normal older sister and a brother who died at 1 day of age from congenital heart disease.

This baby was born at 37 weeks' gestation by caesarean section for previous sections. He weighed 2400 g at birth. Immediate resuscitation by intubation was required for respiratory distress.

Clinical features included short long bones and marked bilateral talipes equinovarus. He was dysmorphic (fig 2) with macrocephaly, hypertelorism, depressed nasal bridge, low set ears, micrognathia, and a posterior submucous cleft of the palate. He had marked tracheomalacia and recurrent apnoea and required a tracheostomy until the age of 6 years. He also required a gastrostomy for poor feeding.

At 3½ years, his height was 92 cm (<3rd centile) and head circumference was 54 cm (>97th centile). There was moderate global developmental delay. His gross motor development was very delayed and he did not walk until he was 3½ years old. Hearing was impaired but vision was normal. There was marked joint laxity and a progressive, moderate kyphoscoliosis, dislocation of one hip, and unstable knees.

Radiographs showed a double curve scoliosis with lumbar spine dysraphism (fig 3) and an exaggerated lumbar lordosis with short pedicles and pronounced scalloping of the lumbar vertebral bodies. Both scapulae were hypoplastic (fig 4). There was also defective ischiopubic ossification, narrow iliac bones, and hypoplastic patellae (fig 2A and fig 1C, Offiah *et al*[3]).

A *SOX9* mutation (H65Y) has been found in this case which has previously been shown greatly to reduce the DNA binding activity of the SOX9 protein (McDowall *et al*,[4] patient 10).

Figure 2 Patient 2 aged 3.5 years.

Figure 4 Case 2: AP chest (aged 7.5 years) showing hypoplastic scapulae with absent scapular wings and lateral clavicular hooks.

Figure 3 Case 2: AP thoracolumbar spine (aged 9 years) showing double curve scoliosis and lumbar spinal dysraphism.

Case 3

This child is now 7 years old but was reviewed at the age of 1 year. She was born at 42+ weeks by normal vaginal delivery to unrelated parents who had a previous normal child. The pregnancy had been uneventful apart from hyperemesis and antenatal scans were reported as normal at 19 and 41 weeks. At birth, intubation and ventilation were required immediately but she was successfully extubated after 24 hours. She required a nasopharyngeal tube for five weeks and there was marked hypotonia.

She had a variable degree of stridor and recurrent apnoea usually associated with feeding. There was a progressive

kyphoscoliosis from the age of 3 months requiring spinal fusion and brace. Her hips were not dislocated but she had dislocatable knees. There was mild conductive hearing loss but vision at one year was normal. There was mild global developmental delay but gross motor skills were more markedly delayed. On examination, she was short with a height of 68 cm (<3rd centile) at 11 months, but not asymmetrical. She was dysmorphic with macrocephaly (98th centile), depressed nasal bridge, hypertelorism, epicanthic folds, micrognathia, and a cleft of her soft palate. There was a significant pectus carinatum and bilateral metatarsus varus. She had some bowing of the long bones in her lower limbs with bilateral pretibial dimples. There was complete sex reversal with normal female external genitalia.

Radiographic findings include defective ischiopubic ossification (fig 2B, Offiah *et al*[5]), narrow iliac bones, anterior bowing of the tibia, disproportionately short fibulae, and hypoplastic distal tibial epiphyses (fig 5). There was a double curve scoliosis with segmentation defects of the mid-dorsal spine, narrow iliac bones, and hypoplastic scapulae.

Chromosome analysis showed a male karyotype with a de novo paracentric inversion of chromosome 17 (46,XY, inv(17)(q11.2,q24.3-q25.1).

Case 4

This 11 year old girl was the first child of healthy, unrelated parents. She was born by emergency caesarean section for failure to progress at 42 weeks' gestation. During the neonatal period her breathing was noted to be noisy and she required observation but no ventilation.

On examination at the age of 4 years, she was dysmorphic (fig 6) with relative macrocephaly (between the 50th and 90th centile), frontal bossing, depressed nasal bridge, hypertelorism, micrognathia, and low set ears. There was disproportionate short stature (<3rd centile) with a short trunk and relatively long limbs.

She had a severe and progressive kyphoscoliosis for which she has had unsuccessful corrective surgery. There have been recurrent upper and lower respiratory infections and persistent mild stridor. There was mild developmental delay, particularly affecting gross motor development.

The radiological findings showed marked kyphoscoliosis, with spina bifida of the lower cervical and mid-thoracic spine. There were hypoplastic scapulae (fig 7) and bilateral dislocation of the radial heads. There was defective ossification of the inferior pubic rami with dislocation of the left hip and narrow, vertical iliac wings (fig 8).

Chromosome analysis showed a female karyotype but with a de novo balanced translocation, 46,XX, t(4;17)(q21.3;q23.3).

Figure 5 Case 3: lateral tibia and fibula (aged 1 year) showing disproportionately short fibula, hypoplastic distal tibial epiphysis, and anterior bowing of the tibia.

Figure 7 Case 4: AP chest (aged 5.5 years) showing spina bifida of the lower cervical spine, hypoplastic scapular wings, long acromian processes, and a thoracic scoliosis concave to the left.

Figure 8 Case 4: AP pelvis (aged 9 years) showing short ischia, defective ossification of the inferior pubic rami, dislocated left hip, narrow vertical iliac wings, and slender superior pubic rami.

Figure 6 Patient 4.

Case 5

This woman is now 21 years old (she has four normal sibs). Birth was at term by emergency caesarean section for fetal distress. She had respiratory distress in the neonatal period but was not ventilated. At birth, she was noted to be short limbed and had bilateral pretibial dimples. There was bilateral talipes equinovarus which was more severe on the right.

She was dysmorphic with a depressed nasal bridge, hypertelorism, micrognathia, and low set ears (fig 9). There was a high arched palate but no cleft palate. On examination, her height was 119 cm (<<3rd centile) with a relatively large head circumference of 53 cm (10th centile). She had disproportionate short stature, with a short trunk and relatively long limbs. Supination of her forearms was restricted owing to bilateral dislocation of the radial heads.

The left hand had long index and middle fingers but the ring and little fingers were short with contractures at the distal interphalangeal phalanges. There was bilateral hallux valgus and pes planus.

She had many complications with recurrent apnoea and chest infections. The apnoea improved following adenoidectomy at the age of 2 years. A severe, progressive kyphoscoliosis developed from the age of 9 months. This required two major but unsuccessful operations. Conductive hearing loss required grommets and hearing aids and there was myopia. There was marked dental caries and irregular teeth. She had moderate learning difficulties and attended a special needs school.

The radiological features included bowing of the long bones and delayed ossification of the epiphyses (fig 10), short first metacarpals with short middle and distal phalanges, and dislocated radial heads. There was defective ischiopubic ossification (fig 2D, Offiah *et al*[5]) and small patellae. The spine showed a significant scoliosis with cervical and lumbar dysraphism (fig 11).

The karyotype was normal female and *SOX9* mutation analysis showed a de novo cytidine to thymidine transition at nucleotide 509, which results in substitution of proline 170 with leucine. This mutation has not been previously reported.

DISCUSSION

Campomelic dysplasia is generally considered to be a lethal skeletal dysplasia. However, it is clear from published reports that a small proportion of affected subjects survive. In a previously reported series of 36 patients, there were three survivors, giving a survival rate of between 5% and 10%.[1] However, it is possible that some surviving patients with a milder phenotype are not diagnosed, so the survival rate may be higher.

Figure 9 Patient 5 aged 21 years.

Figure 10 Case 5: AP left tibia and fibula (aged 2 years) showing a short fibula, bowing of the tibia and fibula, small distal femoral and proximal tibial epiphyses, and delayed ossification of the distal tibial and fibular epiphyses.

The dysmorphic features of all five cases are consistent and distinctive (table 1). Characteristically there is relative macrocephaly, depressed nasal bridge, hypertelorism, long philtrum, micrognathia with or without a cleft palate, and hypotonia.

The main clinical problems in the neonatal period are respiratory. These include recurrent apnoea, chest infections, and stridor, sometimes requiring tracheostomy. Later complications include conductive hearing loss, developmental delay, (especially gross motor), and dental caries with irregular teeth. Myopia was present in the two oldest patients (cases 1 and 5) and may be a complication in later life.

Other complications have been reviewed in orthopaedic publications.[5-7] These reports emphasise the presence of a severe and progressive kyphoscoliosis associated with increased morbidity. Other orthopaedic problems include talipes equinovarus, congenital subluxation or dislocation of the hips, and dislocation of the radial heads causing limitation in supination.

There is a striking change in the disproportion of the short stature with age. At birth there are short limbs with normal length of the trunk, but with the progression of the kyphoscoliosis the trunk becomes relatively shorter than the limbs (fig 9).

Sex reversal was only present in one of these cases (case 3) and was associated with a paracentric inversion of the long arm of chromosome 17. The other male in this series was not sex reversed (case 2). In a previously reported series, 73% of patients with a male karyotype had female or ambiguous genitalia. Only four patients had a male karyotype with normal male genitalia. One of these cases is described here, another survived for four months, and two were terminated in pregnancy because of a prenatal diagnosis of a lethal skeletal dysplasia. From these small numbers it is impossible to postulate that sex reversal is associated with a more severe phenotype.

There are two possible explanations for the survival of these patients with CMD. The first explanation is mosaicism of the *SOX9* mutation. This is the most likely reason for survival in case 1. This woman had clinical and radiological evidence of asymmetry and gave birth to a girl with classical lethal CMD. The father of case 2 was also shown to carry the same *SOX9* mutation as his affected son but was clinically unaffected.[4] He also had a further fetus affected by CMD. It is likely that he is also mosaic for the mutation.

Secondly, chromosomal rearrangements involving chromosome 17q have been shown to cause CMD without disrupting the *SOX9* gene. Two of the patients reported here had a de novo chromosomal translocation involving chromosome 17q. A previous study described three patients with campomelic dysplasia and a chromosomal translocation (involving 17q); two of these patients were 2.5 years old and one was still alive at the age of 26 years.[8] These rearrangements may somehow

Table 1 A comparison of the clinical facial features and complications in the five patients presented

Facial features

Flat face	5/5
Hypertelorism	5/5
Long philtrum	5/5
Depressed nasal bridge	5/5
Micrognathia	5/5
Relative macrocephaly	5/5

Complications

Kyphoscoliosis	Mild thoracic scoliosis	Yes, moderate, progressive	Yes, severe and progressive	Yes, severe and progressive	Yes, severe and progressive
Developmental delay	No	Moderate	Gross motor delay only	Mild to moderate, global	Mild to moderate, global
Short stature	<3rd centile	<3rd centile	<3rd centile	<3rd centile	<3rd centile
Recurrent apnoea and respiratory problems	No	Yes, required tracheostomy	Yes	Mild	Yes
Conductive hearing loss	Yes (left side)	Yes	Yes	?	Yes
Dislocation of hips	No	Yes	No	Yes	No

+ = feature present, ? = not known.

reduce but not abolish the expression of the gene resulting in a milder phenotype.[9] [10] Two of these patients had sex reversal, again suggesting that this feature is not a significant feature in terms of prognosis in this condition.

The SOX9 protein has been shown directly to regulate the *COL2A1* (type II collagen) gene.[11] [12] It is also a transcription factor that is essential for chondrocyte differentiation and cartilage formation.[13] [14] This may explain the overlapping features with spondyloepiphyseal dysplasia congenita, Stickler syndrome, and Kniest syndrome, such as facial dysmorphism (depressed nasal bridge, micrognathia, cleft palate), epiphyseal, and spinal involvement.

There is considerable radiological overlap with ischiopubic-patella syndrome (IPP).[3] This suggests that some of the cases

reported as the more severe form of IPP may be surviving campomelic dysplasia. The radiological features in these five patients are characteristic and described in detail by Offiah *et al.*[3] All five of the patients described here have the characteristic radiological features of IPP but have genetic or cytogenetic evidence of CMD. We believe that the IPP syndrome is a heterogeneous group. The more severe cases are probably survivors of CMD and may have mosaic or mild mutations in *SOX9* or cytogenetic rearrangements of chromosome 17. The milder forms of IPP with radiological changes confined to the pelvis and patella are a separate entity and are probably not related to *SOX9,* although further studies on these patients would be required to prove this. We suggest that this "mild" group is called "small patella syndrome", as originally described.[15]

Surviving CMD is a distinct and recognisable entity; the complications appear to be consistent within this group and overlap with the type II collagenopathies.

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Figure 11 Case 5: AP thoracolumbar spine (aged 11 years) showing significant scoliosis, cervical and lumbar spinal dysraphism, defective ischiopubic ossification, and "drumstick" proximal femora.

REFERENCES
1 **Mansour S**, Hall CM, Pembrey ME, Young ID. A clinical and genetic study of campomelic dysplasia. *J Med Genet* 1995;**32**:415-20.
2 **Lynch SA**, Gaunt ML, Minford AMB. Campomelic dysplasia: evidence of autosomal dominant inheritance. *J Med Genet* 1993;**30**:683-6.
3 **Offiah AC**, Mansour S, McDowall S, Tolmie J, Sim P, Hall CM. Surviving campomelic dysplasia has the radiological features of the previously reported ischio-pubic-patella syndrome. *J Med Genet* (in press).
4 **McDowall S**, Argentaro A, Ranganathan S, Weller P, Mertin S, Mansour S, Tolmie J, Harley V. Functional and structural studies of wild type SOX9 and mutations causing campomelic dysplasia. *J Biol Chem* 1999;**274**:24023-30.
5 **Ray S**, Bowen JR. Orthopaedic problems associated with survival in campomelic dysplasia. *Clin Orthop Rel Res* 1984;**185**:77-82.

6 **Thomas S**, Winter RB, Lonstein JE. The treatment of progressive kyphoscoliosis in camptomelic dysplasia. *Spine* 1997;**22**:1330-7.
7 **Coscia MF**, Bassett GS, Bowen JR, Ogilvie JW, Winter RB, Simonton SC. Spinal abnormalities in camptomelic dysplasia. *J Pediatr Orthop* 1989;**9**:6-14.
8 **Tommerup N**, Schempp W, Meinecke P, Pedersen S, Bolund L, Brandt C, Goodpasture C, Guldberg, Held KR, Reinwein H, Saugstad OD, Scherer G, Skjeldal O, Toder R, Westvik J, van der Hagen CB, Wolf U. Assignment of an autosomal sex reversal locus (SRA1) and campomelic dysplasia to 17q24.3-q25.1. *Nat Genet* 1993;**4**:170-4.
9 **Wunderle VM**, Critcher R, Hastie N, Goodfellow PN, Schedl A. Deletion of long-range regulatory elements upstream of SOX9 causes campomelic dysplasia. *Proc Natl Acad Sci USA* 1998;**18**:10649-54.
10 **Pfeifer D**, Kist R, Dewar K, Devon K, Lander ES, Birren B, Korniszewsk Back E, Scherer G. Campomelic dysplasia translocation breakpoints are

scattered over 1 Mb proximal to SOX9: evidence for an extended control region. *Am J Hum Genet* 1999;**65**:111-24.
11 **Bell DM**, Leung KK, Wheatley SC, Ng LJ, Zhou S, Ling KW, Sham MH, Koopman P, Tam PP, Cheah KS. SOX9 directly regulates the type-II collagen gene. *Nat Genet* 1997;**16**:174-8.
12 **Lefebvre V**, Huang W, Harley VR, Goodfellow PN, de Crombrugghe B. SOX9 is a potent activator of the chrondrocyte-specific enhancer the pro alpha1(II) collagen gene. *Mol Cell Biol* 1997;**17**:2336-46.
13 **Lefebvre V**, de Crombrugghe B. Toward understanding SOX9 function in chondrocyte differentiation. *Matrix Biol* 1998;**16**:529.
14 **Bi W**, Deng JM, Zhang Z, Behringer RR, de Crombrugghe B. Sox9 is required for cartilage formation. *Nat Genet* 1999;**22**:85-9.
15 **Scott JE**, Taor WS. The "small patella" syndrome. *J Bone Joint Surg Br* 1979;**69**:172-5.

ECHO ....

UGT1A7 and colorectal cancer susceptibility

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Direct evidence that sporadic colorectal cancers (CRCs) can arise from an interaction between genes and environment has come from a study of gene variation affecting the power of an enzyme to detoxify known carcinogens.

Identification of genetic polymorphisms of the human UDP-glucuronosyltransferase *(UGT)1A7* gene—a new risk factor—may also improve primary prevention of CRCs in some patients. *UGT1A7* is crucial in detoxifying environmental mutagens—cyclic aromatic compounds—by the action of its enzymic product.

Two polymorphisms in the *UGT1A7* gene in particular were related to CRC. The frequency of wild type alleles *UGT1A7*1/1* was much lower in patients with CRCs than controls (9% v 20%; odds ratio 0.39 (95% confidence interval 0.17 to 0.92)). The frequency of polymorphic alleles was significantly higher in patients than controls for *UGT1A7*3/1* (19% v 10%; 2.26 (1.09 to 4.68)), *UGT1A7*3/2* (19% v 9%; 2.39 (1.15 to 4.99)), and for *UGT1A7*3* alleles combined (50% v 27%; 2.75 (1.6 to 4.71)). CRCs were also significantly associated with *UGT1A7* polymorphisms —especially *UGT1A7*3*—when tested by logistic regression.

The activity of each of these *UGT1A7* polymorphisms in detoxifying a range of cyclic compounds in vitro was much lower than that of the wild type genotype, and *UGTA17*3* polymorphisms had no detectable activity.

The study included 210 healthy blood donors as controls and 78 patients with CRCs. *UGT1A7* genotypes were determined by PCR and sequence analysis of DNA extracted from blood samples. Enzyme activity was assayed with a human cell line transfected with plasmids containing polymorphic variant DNA.

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