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A novel *SOX9* mutation, 972delC, causes 46,XY sex-reversed campomelic dysplasia with nephrocalcinosis, urolithiasis, and dysgerminoma ☆

Nicholas G. Cost [a,*], Aaron T. Ludwig [a], Duncan T. Wilcox [a], Dinesh Rakheja [b], Steven J. Steinberg [c], Linda A. Baker [a]

[a] *Department of Urology, University of Texas-Southwestern Medical Center and Children's Medical Center at Dallas, Dallas, TX 75390-9110, USA*
[b] *Department of Pathology, University of Texas-Southwestern Medical Center and Children's Medical Center at Dallas, Dallas, TX 75390-9110, USA*
[c] *Department of Neurology and Institute of Genetic Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA*

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Abstract An 8-year-old phenotypic female with campomelic dysplasia (CD) and 46,XY sex-reversal presented with renal colic. Medullary nephrocalcinosis, urolithiasis, and renal malrotation were diagnosed by computed tomographic scanning. Pelvic sonogram identified an enlarged left gonad. Genetic testing revealed a novel *SOX9* heterozygous deletion of a cytosine at nucleotide 972 (972delC), causing a frameshift at codon 200, introducing a stop codon 18 codons further downstream (P200fsX218). At laparoscopic gonadectomy, a left dysgerminoma was removed. This first reported case of dysgerminoma in a sex-reversed patient with CD who also had urolithiasis stresses the importance of prophylactic gonadectomy and urologic evaluations in this susceptible population.

1. Introduction

Campomelic dysplasia (CD, OMIM #114290 [http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=114290]) is an autosomal dominant skeletal malformation syndrome typically caused by mutations in the *SOX9* gene on chromosome 17q24.3-25.1 [1-3]. Congenital angulation of long bones, hypoplastic scapulae, hypoplastic pelvic bones, 11 rib pairs, narrowed thorax, tracheobronchiomalacia, hypoplastic lungs, and cutaneous dimpling of the extremities are seen along with the Robin sequence as follows: micrognathia, glossoptosis, and cleft palate. In 65% to 75% of the XY patients, male-to-female sex-reversal occurs, typically with streak gonads. Campomelic dysplasia is generally lethal in the neonatal period because of respiratory distress, with only 5% to 10% surviving infancy [1,3].

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* Corresponding author. Department of Urology, UT Southwestern Medical Center and Children's Medical Center at Dallas, Dallas, TX 75390-9110, USA. Tel.: +1 214 648 2278; fax: +1 214 648 8786
E-mail address: nicholas.cost@sbcglobal.net (N.G. Cost).

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2. Case report

A phenotypic female was born at 31 weeks of gestation to healthy nonconsanguineous white parents. Prenatal testing demonstrated lower extremity skeletal abnormalities, polyhydramnios, and a 46,XY karyotype. At birth, physical examination demonstrated micrognathia, a cleft palate, angulated lower extremities with overlying skin dimpling, and normal female external genitalia. She was intubated because of respiratory distress, and subsequent imaging revealed a narrowed thorax and 11 rib pairs.

The patient has required long-term ventilator support because of her tracheobronchiomalacia and pulmonary hypoplasia. In addition, she is gastrostomy tube fed, has bilateral hearing loss requiring aids, and has severe kyphoscoliosis. At 8 years of age, hematuria and flank pain led to the computed tomographic scan diagnosis of severe medullary nephrocalcinosis, bilateral nephrolithiasis, and bilateral renal malrotation without hydronephrosis. After spontaneous passage of one stone, ureteroscopy with laser lithotripsy for a 5 × 7-mm stone was performed, demonstrating a renal stone composition of 50% calcium phosphate and 50% calcium oxalate dihydrate. A 24-hour stone risk analysis demonstrated mild hypocitraturia (111 mg/d), hyperuricosuria (17 mg/kg per day), and supersaturation for calcium phosphate (4.0 mg/d).

A pelvic ultrasound done during her workup noted a midline prepubertal uterus, an undetectable right gonad, and a concerning left 1.4 × 1.8 × 1.0-cm gonad. Radiologic metastatic workup was negative. Serum α-fetoprotein was normal at 0.6 (normal, 0-8), β-human chorionic gonadotropin was high at 1.2 (normal, 0-0.8), and cancer antigen-125 (CA-125) was high at 62 (normal, 0-35). Bilateral laparoscopic salpingogonadectomy revealed a right-sided streak gonad and a left-sided dysgerminoma with lymphovascular invasion, the first reported to our knowledge (Fig. 1). Peritoneal washings and lymph node sampling were negative.

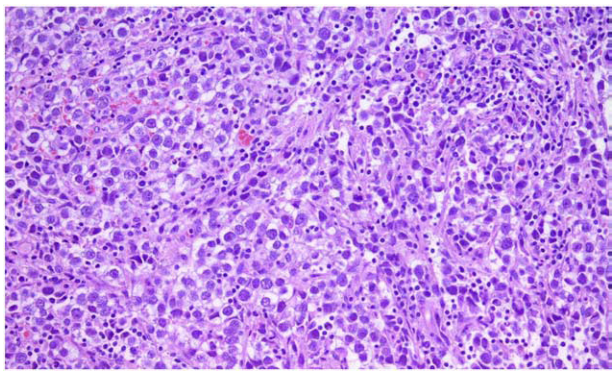

Fig. 1 Left gonad (H&E, ×200)—the cellular neoplasm completely replaces the gonad and shows the classic features of a dysgerminoma. It is composed of sheets of relatively monomorphic round to oval cells, with uniform nucleus, finely granular chromatin, 1 to 2 discrete nucleoli, moderate amount of clear to eosinophilic cytoplasm, and well-defined cell borders. The sheets of tumor cells are interrupted by thin fibrovascular septa that contain a lymphocytic infiltrate.

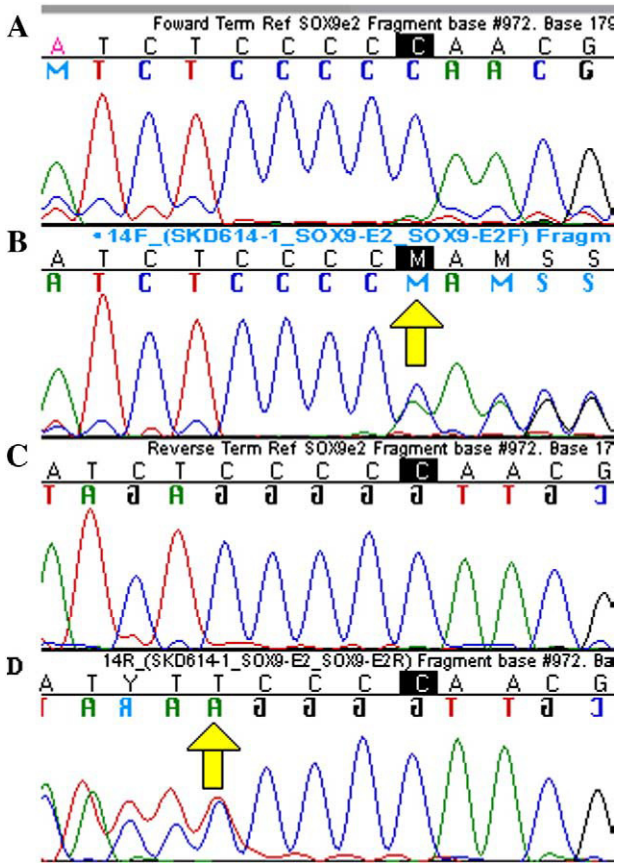

Fig. 2 Electropherograms of bidirectional PCR sequencing of patient sample vs consensus reference *SOX9* sequence. A, Reference forward sequence without 972delC. B, Patient forward sequence with heterozygous 972delC (arrow). C, Reference reverse sequence without 972delC. D, Patient reverse sequence with heterozygous 972delC (arrow).

3. Genetic study

Further genetic testing was done given the clinical diagnosis of CD, and after obtaining informed consent, blood samples were collected and sent to the Johns Hopkins DNA Diagnostic Laboratory (Baltimore, MD). Genomic DNA was extracted from whole blood using a standard method. Amplification of the coding sequence of *SOX9* by polymerase chain reaction (PCR) was carried out using 6 overlapping primer pairs as has been described previously [3,4]. Cycle sequencing of each segment was carried out in the forward and reverse directions. Each sequence was analyzed by capillary electrophoresis, and these data were reviewed by multiple staff members of the Johns Hopkins DNA Diagnostic Laboratory. A novel heterozygous *SOX9* deletion, 972delC, was discovered (Fig. 2) by PCR