CASE REPORT

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Novel *SOX9* Gene Variant Associated with Campomelic Dysplasia: Effects on Sex Phenotypes

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ABSTRACT

Campomelic dysplasia (CD) is a rare autosomal dominant genetic disorder primarily caused by mutations in the *SOX9* gene. While this condition can affect multiple organ systems, it mainly influences skeletal and sexual development, leading to skeletal malformations and gonadal dysgenesis. We present two cases of CD diagnosed at an early age. Their clinical presentations were characteristic of this disorder, including bowing of the lower extremities, pretibial dimples, Pierre Robin sequence, and bilateral clubfoot. Both cases exhibited delays in motor skills and speech. The first case involved a 46,XY sex-reversed infant with a novel heterozygous *SOX9* gene substitution of p.Arg107Gly (NM_000346.4:c.319C>G). The second case involved a 1.5-year-old boy with typical male external genitalia carrying a heterozygous p.Ala116Val variant (c.347C>T) in the *SOX9* gene. Both variants were located in the high mobility group domain of the gene. Two variants, the novel p.Arg107Gly and the p.Ala116Var, in the *SOX9* gene were reported to be associated with CD. Despite being in the same domain, these variants lead to different sex phenotypes.

Keywords: Campomelic dysplasia, differences in sex development, 46,XY sex reversal, *SOX9* gene

What is already known on this topic?

Campomelic dysplasia is a rare genetic disorder caused by heterozygous variants in the *SOX9* gene. Its clinical manifestations involve various organ systems, primarily skeletal malformations and gonadal dysgenesis.

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What this study adds?

This study identifies two variants in the high mobility group domain of the *SOX9* gene: p.Arg107Gly and p.Ala116Val. These variants were detected in two unrelated cases presenting classical campomelic dysplasia phenotypes while exhibiting opposite sex characteristics. The p.Arg107Gly variant is reported for the first time. Although p.Ala116Val is classified as a variant of uncertain significance according to American College of Medical Genetics and Association for Molecular Pathology guidelines, this report provides additional information on p.Ala116Val as a variant associated with campomelic dysplasia. To our knowledge, these are the first reported cases of campomelic dysplasia from our country.

Introduction

Campomelic dysplasia (CD; OMIM #114290) is a rare genetic condition primarily caused by mutations in the *SOX9* gene and following an autosomal dominant inheritance pattern. Due to the expression of the *SOX9* gene in different tissues, this disorder impacts skeletal development and has consequences for sexual development and other organ systems (1,2).

The *SOX9* gene encodes a transcription factor essential for the development of the skeleton. Genetic variations of *SOX9* impair its function, causing a variety of clinical outcomes, from significant malformations that can be fatal during the neonatal period to less severe forms that show subtler skeletal abnormalities (2-4).

In addition to its effects on skeletal tissues, about three-fourths of XY individuals with CD experience male-to-female sex reversal due to the impaired SOX9 function in the testis-determining pathway. This highlights the multifaceted effects of *SOX9* mutations and the complexity of their clinical presentations (2,4,5). This report presents two unrelated cases of CD, characterized by varying degrees of phenotypic features resulting from different mutations in the *SOX9* gene. These cases were our initial encounters with CD.

Case Report

The first case involved a two-week-old baby girl who presented with facial dysmorphism (Figure 1), macrocephaly, micrognathia, high-arched palate, laryngomalacia, bilateral bowing limbs, pretibial dimple, and bilateral congenital talipes equinovarus (CTEV). Her external genitalia exhibited typical female characteristics, lacking palpable gonads and having two openings. She was the fourth child of non-consanguineous parents, and no other family members showed similar symptoms. Initially, trisomy 18 was suspected, but her karyotype revealed 46,XY without any additional chromosomal abnormalities. Further molecular testing of the *SRY* and *AR* genes showed no pathological variants. However, we detected the novel heterozygous p.Arg107Gly [NM_000346.4:c.(319C>G)] variant in the *SOX9* gene leading to a diagnosis of CD (Figure 2). At follow-up, at 5 years and 8 months, her body weight and height were 16.6 kg [standard deviation score (SDS) -1.20] and 103.5 cm (SDS -1.85), respectively. She could already walk and speak but experienced delays in gross motor skills, poor concentration, and inconsistent responses to simple commands. She continues to receive therapy from a medical rehabilitation team. Her parents remained reluctant to undergo laparoscopic exploration to search for the presence of gonads in her abdomen.

The second case involved a 1.5-year-old boy brought to medical attention after his parents noticed similarities between his condition and the first case they had seen on social media. His birth weight was 3200 g, and his length at birth was 45 cm. His facial features included a large head, a broad forehead, retrognathia, a cleft palate, a flat face, and low-set ears (Figure 3A). At the time of examination, he weighed 9.4 kg (SDS -1.36) and measured 74 cm (SDS -3.06) in length. He displayed bowed lower extremities (Figure 3B), 11 ribs, and bilateral CTEV.

He had typical male external genitalia, with both testes in the scrotum. There were no similar phenotypic traits in other family members. Despite his physical deformities, he was an active

Figure 1. Facial appearances of the first case at 4 months old

child who could already walk and had started to speak, although he experienced delays in motor skills and speech. Molecular analysis revealed a heterozygous p.Ala116Val [NM_000346.4:c.(347C>T); ClinVar accession ID VCV001497400.5] variant in the *SOX9* gene (Figure 2).

Both identified *SOX9* variants are absent in gnomAD v.4.1.0, and subsequent *in silico* analysis with SIFT, CADD, MutationTaster, and Polyphen-2 software predicted that both are likely damaging. However, based on American College of Medical Genetics and Association for Molecular Pathology (ACMG-AMP) guidelines (6), we classified the p.Arg107Gly variant as likely pathogenic (PM1, PM2, PM5, and PP3) and p.Ala116Val as a variant of uncertain significance (VUS; PM2, PM1, and PP3).

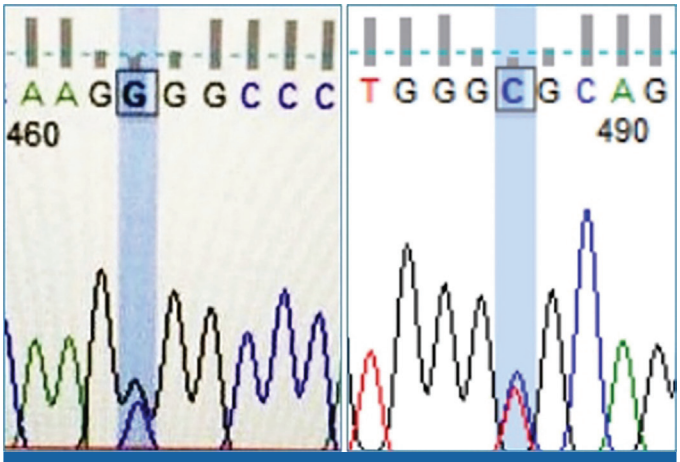

Figure 2. The electropherograms of the first (left) and second cases (right), which demonstrate heterozygous substitutions of p.Arg107Gly [NM_000346.4:c.(319C>G)] and p.Ala116Val [NM_000346.4:c.(347C>T)] in the *SOX9* gene

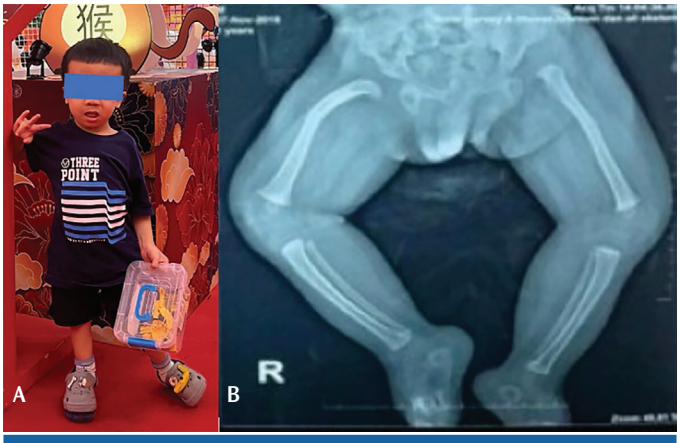

Figure 3. The second case, at 5.5 years old, his right foot was 3 cm shorter than the left one (A). The radiograph of the lower extremities in the second case shows bowing of the femurs, tibiae, and fibulae (B)

Molecular analysis for both cases was conducted using Sanger sequencing on all coding regions of the *SOX9* gene with previously published primers (7). Modifications were applied to Exon 3A (Forward 5'-CCTGATAAAAGGGGGCTGTCCAG-3'; Reverse 5'-GTGCTGCTGCTGCTCGCTGTA-3') and Exon 3B (Forward 5'-CAGGCGCACACGCTGACCAC-3'; Reverse 5'-CGGCCATCTTCGCCCTTCGT-3'). However, parental molecular analysis was not performed because DNA samples were unavailable.

Discussion

We documented two cases of CD, each presenting with different sex phenotypes. As these were our initial experiences with the condition, establishing the diagnosis was particularly challenging. We initially failed to recognize the simultaneous presence of bone deformities and male-to-female sex reversal, leading us to test for other genes. CD is a rare disorder, occurring in approximately 1 in 200,000 births. However, as demonstrated in our cases, it is likely underreported. It may often be misdiagnosed as other syndromes or skeletal dysplasia, or it might go undiagnosed because the severely affected cases may die in the perinatal period (1,2,8).

CD presents with variable symptoms, frequently including key features, such as the bowing of long bones, especially the femur and tibiae. These signs are often detected through prenatal ultrasounds (2,8), although they were not identified in our cases. Additional skeletal abnormalities include underdeveloped shoulder blades, 11 ribs, and a narrow chest. Individuals with this condition typically show distinctive facial features, including a flattened nasal bridge, micrognathia, glossoptosis, cleft palate, and airway obstruction associated with the Pierre Robin sequence (1,9). Our cases presented with these classic clinical manifestations, with varying degrees of motor and speech delay. However, of the cases presented herein were both aged almost six years at the most recent examinations.

Over 200 variants of the *SOX9* gene have been documented, mostly leading to diverse clinical presentations of CD (10). Multiple studies have failed to establish any genotype-phenotype relationships (11,12). Both *SOX9* variants identified in our cases were located within the high mobility group (HMG) domain of the gene. Meyer et al. (11) conducted a functional study of four missense mutations (p.Pro108Leu, p.Trp143Arg, p.Arg152Pro, and p.Pro170Arg) occurring in the HMG domain of *SOX9*, showing that these substitutions diminished or reduced DNA binding capability. These amino acid substitutions led to severe phenotypes and early death. Conversely, a sex-reversed 46,XY case carrying an HMG domain non-sense mutation, p.Gln117Ter, which led to an 80% loss of the protein structure, still survived at 12 years old (11).

Another notable feature of CD is XY sex reversal, as observed in the first case presented here. The sex reversal associated with CD is linked to gonadal dysgenesis since *SOX9* is involved in male sex determination (2). It is recognized that individuals with dysgenetic gonads and a Y chromosome are at significant risk for developing germ cell malignancy (13,14), and therefore, surgical removal before puberty is widely recommended. Consequently, we strongly advised the parents of the first case to consider a laparoscopic evaluation for the abdominal gonads. Nevertheless, the parents remained hesitant to approve any invasive procedures.

Despite being only nine amino acids apart, the *SOX9* variants in our cases located in the same domain resulted in different sex phenotypes. Adjacent reported missense variants in the HMG domain, the p.Lys106Glu (8) and p.Pro108Leu (11), have been associated with severe CD. One case involved a 46,XX fetus terminated at 21 weeks of gestation, and another a 46,XY sex-reversed infant who died at 6 months.

The p.Arg107Gly mutation likely causes protein conformation changes due to the amino acid switch from a positively charged hydrophilic residue to a non-polar hydrophobic residue. Conversely, the heterozygous p.Ala116Val mutation may result in less severe phenotypes since both amino acids involved in the transformation are non-polar and hydrophobic. Arg107 and Ala116 are located in helix-1 of *SOX9*, with the p.Arg107Ala variant located explicitly in the *SOX9* nuclear localization domain. The amino acid substitution in p.Arg107Ala may disrupt the nuclear import of *SOX9*, thereby impairing its function. However, functional analysis is needed to confirm this.

Furthermore, the helix regions of *SOX9* play a crucial role in DNA binding and bending, which is essential for *SOX9* regulatory activity. It was previously described that helix-1 contains key residues responsible for *SOX9*-mediated DNA bending (15). A change in the hydrophobic packing of a previously described variant, p.Phe154Leu, was shown to reduce DNA binding activity by 20-fold (16). However, the p.Ala116Val variant observed in this study would be less disruptive to this hydrophobic packing as alanine and valine residues share similar biochemical properties. Although the p.Ala116Val variant is currently classified as a VUS according to ACMG-AMP guidelines, this report may provide valuable information regarding its association with CD.

Two variants of the *SOX9* gene, p.Arg107Gly and p.Ala116Val, confirmed the diagnosis of CD in two children. The clinical presentation of CD may vary and may go unrecognized due to lack of clinical awareness. The specific location in the HMG domain and the alteration of biochemical properties may contribute to the clinical variations observed in these cases.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the Health Research Ethics Committee, National Research and Innovation Agency (NRIA), No. 25/KE.03/SK/12/2023.

Informed Consent: Parental written informed consent was obtained before enrolling the cases.

Footnotes

Authorship Contributions

Medical Practices: Nanis Sacharina Marzuki, Concept: Nanis Sacharina Marzuki, Hannie DH Kartapradja, Firman Pratama Idris, Design: Nanis Sacharina Marzuki, Hannie DH Kartapradja, Data Collection or Processing: Nanis Sacharina Marzuki, Hannie DH Kartapradja, Analysis or Interpretation: Nanis Sacharina Marzuki, Hannie DH Kartapradja, Firman Pratama Idris, Literature Search: Nanis Sacharina Marzuki, Hannie DH Kartapradja, Firman Pratama Idris, Writing: Nanis Sacharina Marzuki, Hannie DH Kartapradja, Firman Pratama Idris.

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