A Review of campomelic dysplasia syndrome

N Larasati1, P K Zahra2, E I Auerkari2

1Pediatric Dentistry Residency Program, Faculty of Dentistry, University of Indonesia, Jl. Salemba Raya no. 4, Jakarta, 10430. Indonesia.
2Department of Oral Biology, Faculty of Dentistry. University of Indonesia, Jakarta, Indonesia

Corresponding author: ei_auerkari@yahoo.com

Abstract. Campomelic dysplasia (CD) is a rare autosomal dominant genetic disorder and severe skeletal dysplasia. It is characterized by a variable relationship between skeletal and extra-skeletal abnormalities: congenital tightness and long bone arches, pelvic and chest abnormalities, eleven pairs of ribs instead of the usual twelve, facial deformities, cracks and sexual ambiguity. The appearance of pelvic joints, horseshoe inversion, pulmonary hypoplasia, abnormalities of the neck and cervical spine, as well as heart and kidney abnormalities also indicate this syndrome. Other findings of the CD include sexual reversals, in which males have chromosomes, but in some individuals have female genitalia and reproductive systems. The CD is caused by a de novo mutation in the SRY box containing gene 9 (SOX9), which is the main regulator of the development of the cartilage skeleton. It plays an important role in the selection and differentiation of mesenic cells of the chondrocyte lineage of all components of the cartilage skeleton. Most affected individuals have recognizable mutations. It has been reported that heterozigosity involves mutations involving missene, meaningless mutations, deletions in the coding area, and mutations that sometimes interfere with the reorganity of chromosomes in the SOX9 regulatory area. Loss or loss of control over this regulatory area around SOX9 may explain the level of craniophaasial defects described in CD syndrome. We outline the clinical picture, treatment and spectrum of mutations involved in CD syndrome. However, more research is needed to determine the effects of SOX9 on the binding of other genes that function well or are unknown on cartilage.

1. Introduction
Campomelic dysplasia (CD) is a rare form of bone dysplasia with many congenital abnormalities. The term "campomelic" comes from the Greek "campo" which means "curved" and "melic" meaning "body part". CDs are characterized by a variable relationship between skeletal and extra-bone abnormalities, including congenital tightness and long bone arches, pelvic and chest abnormalities, eleven pairs of ribs instead of the usual twelve, facial deformities, clefts, and sexual ambiguity [1]. Other images associated with CDs include relative macrocephaly, flat face and hip dislocation, scoliosis, club legs, hearing loss, and rarer heart abnormalities. Prevalence at birth between 1 / 40,000 and 1 / 80,000 CD patients died in newborns due to respiratory distress due to rib hypoplasia [2].

CD is the result of mutations in single copy of the SOX9 gene (Sex-Determining Region Y-Box 9, localized to 17q24.3) or disturbances in the regulation of this gene. SOX9 is essentially known for both sex and skeletal development. Aberrations in this gene can occur in a consequence of chromosomal recombination involving this locus or as a result of inherited heterozygous de novo mutation [1,3]. Diagnosis of CD is usually difficult due to its rare presentation and poor prognosis, yet
regularly can be obtained by clinical and radiograph examination. Nevertheless, the genetic testing is required in order to determine the prognosis of CD and establish the genotype and phenotype correlation [1,4]. It is also paramount to understand mutational spectrum involved in CD syndrome to aim the advancement of CD treatment and promote proper genetic counseling.

2. Campomelic dysplasia syndrome

2.1. Feature
Campomelic dysplasia (CD) is a rare form of autosomal dominant genetic disease and severe skeletal dysplasia, which characterizes the variable relationship between skeletal and extraskeletal diseases: congenital tightness and long bone arches, abnormal pelvis and chest, eleven pairs of ribs, not the usual twelve, facial deformities, cleft palate and sexual ambiguity [5]. Other possible symptoms in certain Campomelic syndrome patients include hip dislocation, horseshoe inversion, pulmonary hypoplasia, neck and chest spinal abnormalities, and heart and kidney disease. Some individuals with Campomelic syndrome experience a sexual reversal, in which they are male chromosomes but have female genitalia and reproductive system.

2.2. Prevalence
Campomelic dysplasia is not often found, and there is no specific prevalence data. CDs have no particular racial or gender advantage. Prevalence at birth ranges from 1 / 40,000 to 1 / 80,000, while the incidence ranges from 0.05 to 1.6 / 10,000 [2,5]. Infants with CD generally die shortly after birth due to respiratory insufficiency secondary to airway compromise or cervical spine instability. However, previous study conducted by Mansour, et al in 2002 among 36 patients has clearly shown that a small proportion of affected subjects survive with survival rate of 10% while 77% patients died in the neonatal period due to severe respiratory distress and the rest died before the age of 2 years [5].

2.3. Etiology → human chromosome 17. SOX9
Campomelic dysplasia results from by de novo mutations that encodes SRY-box containing gene 9 (SOX9), a key regulator of endochondral skeletal development [6–8]. In addition, SOX9 protein regulates the activity of other genes that plays a crucial role for development of skeleton and reproductive organs. In most cases, mutation within SOX9 gene perform inhibition of SOX9 protein production or result in a protein with impaired function [9,10]. CD syndrome is considered to be a lethal particularly in the first year of life [11].

2.4. Inheritance pattern
Campomelic dysplasia is the main autosomal feature. Most cases are recent sporadic incidents in the family. It has been reported that the recurrence was caused by a mosaic of gonads [12]. However, legacy models are being discussed. Evidence of autosomal recessive inheritance has been provided through the description of siblings in this situation. However, there have been some reports of CMD patients born to slightly affected parents, suggesting autosomal deviation is dominant.

2.5. Genetic mutation in campomelic dysplasia
The sox gene (Sry HMG-box) is part of the high mobility protein (HMG) group and is characterized by its electrophoretic mobility in SDS-PAGE. The sox protein binds to DNA through its HMG domain, allowing it to act as a transcription factor. These domains compete fiercely in sox factors that typically recognize similar DNA patterns: (A/T)(A/T) CAA(A/T)G. Since most Sox factors are expressed in more than one cell line, a special cell cofactor is also required to provide different promoter specifications [13,14]. Based on homology of its sequences inside and outside the HMG domain, the Sox protein has been divided into 10 groups, from A to J, Sry belongs to the SoxA group [15,16].
Sox9 belongs to the SoxE group, which also includes Sox8 and Sox10. SOX9 was first described as a candidate gene for Campomo dysplasia (CD), which is characterized by skeletal abnormalities, skull deformities, and sexual reversals.[6,8] The fact proves that Sox9 is the main regulator of cartilage growth. It plays a key role in the selection and differentiation of mesenic cells into chondrogenic lineages of all emerging bone components. Sox9 binds to and regulates the specific chondrocyte-enhancing function of many genes essential for chondrocyte differentiation, including type II collagen, Col2a1 (the main matrix protein in adult cartilage) [17,18].

The CD is caused by a haplotype of the SOX9 transcription factor on the chromosome 17q24.3. First, SOX9 was identified as a CD candidate gene for patients with newly translocated upstream from the SOX9 encoding sequence. [6–8,10,19,20] Nonsense of the SOX9 encoding region, missense and frameshift mutations account for about 90% of CD cases. The remaining cases are the result of removal, translocation, or inversion of SOX9 upstream SOX9. Chaotic SOX9 and frameshift mutations are distributed throughout the encoding region, while missing mutations converge in hmg domains, which interfere with DNA binding [10,21] or prevent dimer formation in the dimerization. [22,23] Mutations that are unreasonable and dominated by frameshift in C-terminus produce sox9 proteins by cutting the transactivation domain. Generally, some or more HMG domains do not exist in terminal-N mutations. The corresponding mutant protein loses the transactivation domain, and the HMG domain is a loss of function allion, and the mutant protein that retains the HMG domain can serve as the dominant negative [21,24].

SOX9 transcription rules include cis ~1 Mb upstream regulation domain SOX9. Translocation and breakpoint inversions that interfere with upstream sequences differ, but they belong to the same breakpoint cluster: the distance between the proximal and distal clusters is about 400 kb. [25] Compared to mutations in the SOX9 encoding region, long-term survivors of CD de novo translocation or inversion with breakpoints in upstream SOX9 are more likely to be found, suggesting that they are usually no more severe than intragenic mutations. [25,26] The discovery of mutations on both sides of SOX9 associated with craniofacial defects in CD patients suggests that the SOX9 regulatory sequence covers a much broader genome than originally expected. These findings further support the presence of certain network enhancers that can control sox9 expression remotely during craniofacial development. This loss or loss of control of the accommodation area around SOX9 may explain the range of craniofacial defects described in CDs and ACDs. Recently, many good reviews have discussed these results [27].

Previous research has reported, 73% patients with male chromosomes had female genitalia but sex reversal with XX genotypes did not perform [5]. As mentioned before, there are patients who survived with CD syndrome. It is suggested due to the mosaicism of the SOX9 mutation occur in which one parent carry SOX9 mutation without clinically affect the children. It is also suggested that chromosomal rearrangements involving chromosome 17q cause CD syndrome without disrupting the SOX9 gene. The rearrangements may somehow decrease but not eradicate the expression of the gene resulting in a milder phenotype [11].

2.6. Management
It is difficult for a newborn to survive, therefore, support is mainly for comfort. Attention should be paid to the cervical spine of the sufferer, as it may be unstable. Ultrasound and gender examinations can be performed on chromosomes and pelvis to check internal genitalia. In the case of survivors, those who can be fed orally can fix the gap and may require plastic surgery or correction.

3. Conclusion
CDs become abnormally rare and fatal bone development associated with genetic mutations, and have low survival rates. Therefore, the treatment of these patients requires an organized multidisciplinary approach and stable monitoring in these patients, which has been discussed in this review article. The main purpose of this article is to uncover the etiology, incidence, and genetic mutations associated with Campomelic dysplasia syndrome. This article also provides additional details about CD
syndrome. Since the SOX9 mutation is associated with camphoric dysplasia, extensive research has been conducted to find trace genes in the chondrocyte lineage. So far, although more research is needed to determine the influence of SOX9 on other gene combinations whose functions have been determined or unknown in cartilage, people still have a relative understanding of the function of SOX9 in some stages of chondrocyte differentiation.

References

[1] Carvajal N, Martínez-García M, Chagoyen M, Morcillo N, Pino A, Lorda I and Trujillo-Tiebas M J 2016 Gene 577 289–92
[2] Unger S, Scherer G and Superti-Furga A. Campomelic Dysplasia (Seattle: GeneReviews®)
[3] Scherer G, Zabel B and Nishimura G 2013 Eur. J. Hum. Genet. 21 792
[4] Jain V and Sen B 2014 Campomelic dysplasia J. Pediatr. Orthop. B 23 485–8
[5] Mansour S, Hall C M, Pembrey M E and Young I D 1995 J Med Genet. 32 415–20
[6] Foster J W, Dominguez-Steglich M A, Guioli S, Kwok C, Weller P A, Stevanović M, Weissenbach J, Mansour S, Young I D, Goodfellow P N, Brook J D and Schafer A J 1994 Nature 372 525–30
[7] Kwok C, Weller P A, Guioli S, Foster J W, Mansour S, Zuffardi O, Punnett H H, Dominguez-Steglich M A, Brook J D, Young I D, Goodfellow P N and Schafer A J 1995 Am. J. Hum. Genet. 57 1028–36
[8] Wagner T, Wirth J, Meyer J, Zabel B, Hertert E, Wolf U, Tommerup N, Schempw and Scherer G 1994 Cell 79 1111–20
[9] Antonakopoulos N, Vrachnis D, Loukas N, Iliodromiti Z and Vrachnis N 2019 HJOG 18 3 67–70
[10] Meyer J, Südbbeck P, Held M, Wagner T, Schmitz M L, Dagna Bricarelli F, Eggemont E, Friedrich U, Haas O A, Kobelt A, Leroy J G, Van Maldergem L, Michel E, Mitulla B, Pfeiffer R A, Schinzel A, Schmidt H and Scherer G 1994 Nature 372 525–30
[11] Mansour S, Offiah A C, McDowall S, Sim P, Tolmie J and Hall C 2002 J Med Genet 39 597–602
[12] Smyk M, Obersztyn E, Nowakowska B, Bocian E, Cheung S W, Mazurczak T and Stankiewicz P 2007 Am. J. Med. Genet. 15 143A(8) 866–870
[13] Kamachi Y, Uchikawa M and Kondoh H 2000 Trends Genet. 16 181–7
[14] Wilson M and Koopman P 2002 Curr. Opin. Genet. Dev. 12 4 441–446
[15] Bowles J, Schepers G and Koopman P 2000 Dev. Biol. 227 239–55
[16] Schepers G E, Teasdale R D and Koopman P 2002 Dev. Cell 3 167–70
[17] Lefebvre V and de Crombrugghe B 1998 Matrix Biol. 16 529–40
[18] Lefebvre V and Smits P 2005 Birth Defects Res. Part C - Embryo Today Rev. 75 3 200–212
[19] Tommerup N, Scheppe W, Meinecke P, Pedersen S, Bolund L, Brandt C, Goodpasture C, Gulberg P, Held K R, Reinwein H, Saugeat O D, Scherer G, Skjeldal O, Toder R, Westvik J and Wolf U 1993 Nat. Genet. 4 170–174
[20] Young I D, Zuccollo J M, Malthby E L and Broderick N J 1992 J. Med. Genet. 29 251–2
[21] McDowall S, Argentaro A, Ranganathan S, Weller P, Mertin S, Mansour S, Tolmie J and Harley V 1999 J. Biol. Chem. 274 24023–30
[22] Bernard P, Tang P, Liu S, Dewing P, Harley V R and Vilain E 2003 Hum. Mol. Genet. 12 1755–65
[23] Sock E, Pagon R A, Keymolen K, Lissens W, Wegner M and Scherer G 2003 Hum. Mol. Genet. 12 1439–47
[24] Preiss S, Argentaro A, Clayton A, John A, Jans D A, Ogata T, Nagai T, Barroso I, Schafer A J and Harley V R 2001 J. Biol. Chem. 276 27864–72
[25] Leipoldt M, Erdel M, Bien-Willner G A, Smyk M, Theurl M, Yatsenko S A, Lupsik J R, Lane A H, Shanske A L, Stankiewicz P and Scherer G 2007 Clin. Genet. 71 67–75
[26] Pfleifer D, Kist R, Dewar K, Devon K, Lander E S, Birren B, Korniszewski L, Back E and
Scherer G 1999 *Am. J. Hum. Genet.* **65** 111–24

[27] Amiel J, Benko S, Gordon C T and Lyonnet S 2010 *Ann. N. Y. Acad. Sci.* **1214** 34–46