

# Cleidocranial dysplasia. A molecular and clinical review

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## Abstract

Cleidocranial dysplasia (CCD) is a rare autosomal dominant disorder characterized by skeletal and dental abnormalities primarily, short stature, aplasia or hypoplasia of clavicles, open fontanelles and supernumerary teeth. Heterozygous mutations of the runt-related transcription factor 2 (*RUNX2*) gene have been found in approximately 60-70% of cases, leaving a large number of cases with no defined genetic cause which led us to delve into molecular mechanisms underlying CCD and thus to detect potential target genes to be explored in these patients. In this review, we also highlight very broadly the phenotypic characteristics of previously reported patients with CCD.

**Keywords:** Cleidocranial dysplasia, *RUNX2* gene, supernumerary teeth

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## Introduction

Cleidocranial dysplasia (CCD, OMIM #119600) is an autosomal dominant dysplasia of skeletal and dental tissues, characterized by aplasia or hypoplasia of clavicles, multiple Wormian bones, failure of midline ossification, delayed tooth eruption, supernumerary

teeth and other skeletal abnormalities. CCD was accurately described at the end of the 18th century. Nevertheless, a hundred years later it was coined as “dysostosis cleidocranial hereditary” (1, 2). Hesse was first to describe dental defects in patients with CCD (3). Since then a lot of information has been published, in particular a comprehensive study was carried out in

order to describe skeletal abnormalities, these observations lead researchers to propose the term cleidocranial dysplasia (1, 4). CCD is a congenital disorder with an incidence of 1 in 1.000.000 newborns and more than 1.000 cases have been reported so far. Mutations in runt-related transcription factor 2 gene (*RUNX2*, OMIM #600211) have been associated with the molecular basis of this disorder. *RUNX2* codify for a core-binding transcription factor protein (CBFA1 or *RUNX2*), which plays an important role in the differentiation of osteoblasts, chondrocyte maturation and regulation of bone metabolism (5, 6). This comprehensive review discusses insights into molecular pathways of the molecular mechanism causing CCD and the multiple phenotypes so far encountered and reported in literature underlining the importance of the dentist in the management of supernumerary teeth.

## RUNX2 role in Osteogenesis

*RUNX2* has an important role in both osteogenesis pathways and belongs to *RUNX* family, a transcription factor family, which forms heterodimers with *CBFB* and recognizes a consensus sequence in DNA (5). *RUNX2* is expressed only in chondrocyte and osteoblast progenitors and mature osteoblasts (7). *RUNX2*, *SP7*, and canonical Wnt signaling have been associated with the commitment of mesenchymal stem cells to the osteoblastic lineage during osteoblast differentiation. Likewise, *RUNX2* complex has been involved in the terminal chondrocytes differentiation, an essential step for ossification (6). Moreover, *RUNX2* upregulates *OSTERIX* gene and other such as *SPARC*, *SPP1*, and *COL1A1*, all of these are important for bone maturation. In the same way, classic Wnt pathway, bone morphogenetic protein (BMP) and fibroblast growth factors (FGFs) regulate *RUNX2* expression (8–10). *RUNX2* has also demonstrated controlling expression of mesenchymal tissue through differentiation of dental epithelium, which could lead to dental anomalies found in CCD patients (11). Recently, a group of miRNAs, have been demonstrated to regulate osteogenesis by targeting *RUNX2* (12–14).

## Genetics of CCD

Heterozygous mutations in *RUNX2* gene are widely recognized as the main cause of CCD. *RUNX2*, also called *CBFA1*, *AML3* and *PEBP2aA*, is composed of 8 exons and maps on the short arm of chromosome 6 (6p21) (15, 16). Mutations in *RUNX2* have a complete penetrance and some of these could present variable expressivity, the phenotype can range from single dental anomalies to a severe phenotype with all clinical features including osteoporosis (17). So far, more than

100 mutations have been reported, including, 80 point mutations, 11 affecting splicing, 47 small deletions, 28 small insertions, 2 small indels, 22 and 8 gross deletions and insertions, respectively, 4 chromosomal rearrangements and 4 mutations altering the number of polyglutamine repeated sequence located in Q/A domain (Human Gene Mutation Database, (<http://www.hgmd.cf.ac.uk>). However, mutations in *RUNX2* have only been reported in 60-70% of patients with CCD and microdeletions matching with contiguous gene deletions in 13-28% of cases, which could suggest an important role of other components not yet described, involved in the signaling pathway of *RUNX2* gene (18, 19).

## Clinical characteristics of CCD

CCD is a skeletal dysplasia, which is known to be associated with several bone defects such as, Wormian bones, hypoplasia or agenesis of clavicle, macrocephaly, frontal bossing, mid face hypoplasia, mandibular prognathism, delayed closure of the fontanels, the short stature, dental anomalies in the number and shape and wide pubic symphysis (7, 17, 18). Other common characteristics were hypoplasia of maxilla and hypertelorism, short middle phalanx of the fifth finger and brachycephalic head (20). Recently, two previously reported patients and one of our patients showing a clear CCD phenotype shared a remarkable clinical finding such as some blood malignancies, leading us to propose a correlation between some mutations in *CBFA1* domain of *RUNX2* gene and acute myeloid leukemia and acute lymphoid leukemia (21–24).

## Oral manifestations of CCD

The most important dental features include altered eruption patterns: usually in these patients primary teeth are retained and an eruption of permanent teeth is delayed, the presence of supernumerary teeth, misshapen teeth and tooth agenesis (21). Severe dental anomalies have been associated with mutations located in runt domain (20). However, we have reported the p.R131C mutation located in runt domain, in which patients carrying this mutation did not present supernumerary teeth (18, 25). Other cases with no supernumerary teeth have been reported, but the mutation is not located in runt domain, considering that mutations in an extra-runt region are usually associated with mild phenotypes, the clinical finding is not surprising (20). Moreover, intrafamilial variations have been frequently reported in dental features, mainly in the number of supernumerary teeth, ranging from 1 to 20 teeth, indeed environmental and epigenetic factors have been

proposed as the mechanism mediating these phenotypes in CCD patients (20, 26). Also, patients with CCD displayed significant changes in dentin and inadequate mineralization, showing a reduction in calcium and phosphate and carbon and oxygen composition was increased (27).

## Orthodontic treatment in CCD

Radiological and clinical approaches are the most important and consistent signs and symptoms to confirm diagnosis, therefore, patients with CCD should be carefully evaluated by a dental multi specialist team due to the complexity of the treatment foreseen. Dental anomalies are one of the most important stigmata of these patients; unfortunately, guideline for management of CCD patients is scarce and depends on the severity of dental anomalies, however, basically, extractions of supernumerary (and their possible transplantation) teeth and to use removable or fixed orthodontic devices in order to align teeth after the extraction/autologous transplantation, and sometimes to guide the eruption and the subsequent alignment of teeth in order to improve life quality of patients (28–31).

## Conclusions

CCD is a disorder with intra and interfamilial clinical variability; several organs are affected in these patients, thus, a multidisciplinary specialist team constituted by radiologist, neurologist, geneticist, pediatricians, surgeon and pediatric dentist should evaluate patients in order to provide the best care. Oral manifestations could become a problem to develop a normal life, so it is important to start orthodontic treatments at an early age.

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