CASE REPORT

# Classical cleidocranial dysplasia in an adult, due to a novel frameshift pathogenic variant in *RUNX2*

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## SUMMARY

Cleidocranial dysplasia (CCD) is a rare genetic disorder of bone, characterised by hypoplastic/aplastic clavicles, delayed closure of fontanelles and sutures of the cranium and dental abnormalities. We describe a novel frameshift pathogenic variation—c.470dupT (p.M157Ifs*4, NM_001024630) in the runt-related transcription factor 2 (*RUNX2*) gene—that adds to the spectrum of mutations in this gene. The current case also illustrates the clinical and radiological findings in an adult with CCD.

## BACKGROUND

Cleidocranial dysplasia (CCD; MIM 119600) is an autosomal dominant skeletal dysplasia that predominantly affects the bones undergoing intramembranous ossification, especially the cranium and the clavicles. CCD is caused by mutations in the runt-related transcription factor 2 (*RUNX2*) gene.[1] The prevalence of this condition is one in a million live births.[2] It is inherited in an autosomal dominant manner with no sex predilection. CCD is usually diagnosed at an early age due to the presence of wide open anterior fontanelles, dental abnormalities, recurrent upper airway infections, especially sinusitis, conductive hearing loss, skeletal abnormalities and mild motor delay. We report an adult case of CCD with a novel frameshift pathogenic variant c.470dupT (p.M157Ifs*4, NM_001024630) in exon 3 of the *RUNX2* gene.

## CASE PRESENTATION

The proband, a woman, was evaluated at 27 years for facial dysmorphism and short stature. There were multiple similarly affected members in the family, depicting an autosomal dominant mode of inheritance (figure 1I). On examination, she had short stature (148 cm, 3 SDs below the mean), brachycephaly, patent anterior fontanelle, metopic depression, downslanting palpebral fissure, telecanthus and midface hypoplasia. Narrow and drooping shoulders that could be approximated anteriorly (figure 1A, B) were noted. She had small hands with brachydactyly and tapering fingers. Clinodactyly of the fifth finger was noted. Thumbs and great toes were broad. There was partial cutaneous syndactyly of the second and third toes and a proximally placed fourth toe (figure 1C–E). She had normal intelligence.

## INVESTIGATIONS

Radiograph of the skull showed wide and patent anterior fontanelle (figure 1F). Chest radiograph revealed hypoplasia of clavicles (figure 1G). Sanger sequencing of the *RUNX2* gene revealed a novel heterozygous pathogenic variation, c.470dupT (p.M157Ifs*4, NM_001024630), in exon 3 in the proband (figure 1H).

## DIFFERENTIAL DIAGNOSIS

Presence of clavicular hypoplasia and wide open sutures are also observed in Yunis-Varon syndrome, CDAGS syndrome, parietal foramina with CCD and pycnodysostosis.[1] However, absence of other associated features and presence of characteristic findings suggested CCD as the most likely diagnosis.

## TREATMENT

Currently there is no treatment available for this condition. Secondary complications can be prevented by regular surveillance for orthopaedic complications, dental abnormalities, upper airway obstruction, ear infections, conductive hearing loss and osteoporosis. Prophylactically, vitamin D and calcium treatment can be started. Pregnant women should be monitored for cephalopelvic disproportion. For these patients, helmets and protective measures are recommended if performing high-risk activities.[2]

## DISCUSSION

Early diagnosis of classic CCD occurs due to the characteristic facial appearance of brachycephaly, flat forehead, metopic groove, hypertelorism, midface hypoplasia and short stature with narrow drooping shoulders that can be opposed at the midline. The clinical severity may vary from isolated dental anomalies to severe forms complicated by osteoporosis and recurrent fractures.[3] Intrafamilial variable expression is seen in members harbouring the same genetic variation.[2 4] The most prominent skeletal abnormalities in classic CCD include widely open sutures and fontanelles, hypoplastic or absent clavicles, cone-shaped thorax and crowding of teeth. However, in the absence of any secondary complications, there may be delay in presentation and diagnosis, as evident in the present case. The other skeletal abnormalities that may be present include scoliosis, short middle and distal phalanges, cone-shaped epiphyses and large femoral neck. Osteoporosis can occur in a few individuals.

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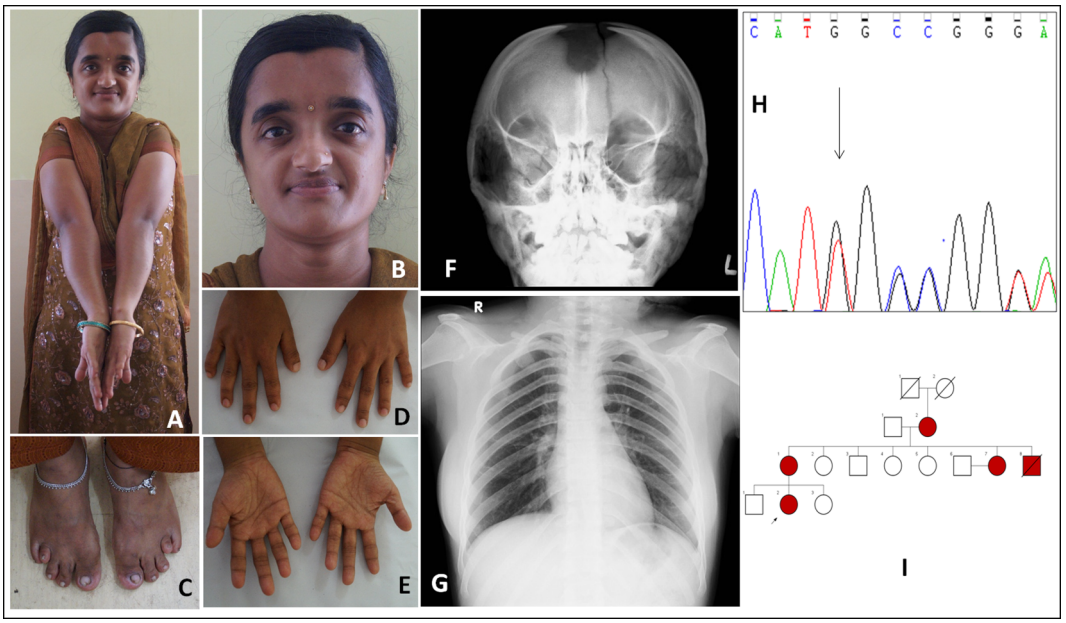


**Figure 1** The proband at 27 years showing brachycephaly, narrow, drooping shoulders that can be approximated anteriorly (A), metopic depression, downslanting palpebral fissure, telecanthus and midface hypoplasia (B). Hands showing tapering of fingers, broad thumbs and clinodactyly. Brachydactyly in upper and lower limbs, partial cutaneous syndactyly of the second and third toes and a proximally placed fourth toe were also noted (C–E). Radiograph of the skull showing wide and patent anterior fontanelles (F). Radiograph of the chest showing hypoplasia of clavicles (G). Sanger sequencing identified the pathogenic variant, c.470dupT (p.M157Ifs*4; NM_001024630), in exon 3 of the *RUNX2* gene (H). Pedigree showing multiple affected members in the family (I).

The only gene known to be associated with this condition is *RUNX2* (MIM 600211) gene, also known as core binding factor A1. It is a transcription factor involved in osteoblast differentiation from mesenchymal cells.[5] Mutations in this gene are found in 60–70% of the participants clinically diagnosed with the condition and include missense, non-sense, deletions/insertions and splice site variations leading to premature termination.[2 6 7]

The variant observed in our patient, c.470dupT, is a novel truncating frameshift variant leading to a premature stop codon (p.M157Ifs*4, NM_001024630). The same variant was also observed in her maternal aunt (blood samples of other affected members of the family were not available for testing) (figure 1I). The truncated protein product is likely to undergo non-sense-mediated messenger RNA decay.[8] Also, this variation is present in the RUNT domain of the protein, which is known to disrupt DNA binding. Another frameshift variant has been reported at the same amino acid position, methionine to aspargine, by Ott *et al*[5] (p.M157Nfs*4; HGMD ID: CI104816), due to duplication of nucleotide 'A' (c.469dupA). Frameshift pathogenic variants in *RUNX2* gene are observed in 27% of patients with CCD.

A critical gene dosage of 70% of the wild-type *RUNX2* is essential for normal osteoblast differentiation, below which intramembranous bone tissue is hampered, leading to CCD. Levels above 79% are shown to produce a normal skeleton.[9] This implies that the range of bone phenotypes and variable expression in patients with CCD is attributable to quantitative reduction of *RUNX2* protein.

Appropriate management and surveillance for orthopaedic, dental and airway-related problems can be provided with early diagnosis of CCD. Special care must be taken for anaesthetic management. Protective devices to prevent head trauma should be used by those affected with CCD. Appropriate molecular diagnosis helps in genetic counselling in these families.

## Learning points

- Classical cleidocranial dysplasia (CCD) is usually detected in early childhood, due to characteristic craniofacial dysmorphism, widely open fontanelles/sutures and absent/hypoplastic clavicles.
- Mutations are detected in 60–70% of those with clinical diagnosis of CCD. Molecular diagnosis can help to confirm the atypical presentations of the disease.
- Early detection of the condition aids in appropriate management of dental and orthopaedic complications, including osteoporosis.
- Pregnancy should be monitoring for cephalopelvic disproportion in these participants.
- Appropriate anaesthetic management is warranted in these participants.

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