Identification and Functional Characterization of a Novel De Novo RUNX2 Frameshift Mutation Associated With Cleidocranial Dysplasia

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Research

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Abstract

Background

Cleidocranial dysplasia (CCD) is a rare genetic disorder affecting bone and cartilage development. Clinical features of CCD comprise short stature, delayed ossification of craniofacial structures with numerous Wormian bones, underdeveloped or aplastic clavicles and multiple dental anomalies. Several studies have revealed that CCD development is strongly linked with different mutations in Runt-related Transcription Factor 2 (RUNX2) gene. In this study, we report a case with typical CCD presentations.

Methods

We performed genetic testing of participants and found a novel RUNX2 frameshift mutation: c.1550delT in a sporadic case. We also compared the functional activity of the mutant and wild-type RUNX2 through immunofluorescence microscopy and osteocalcin promoter luciferase assay.

Results

Both mutant RUNX2 and wild-type RUNX2 protein were similarly confined in the nuclei. The novel mutation caused abrogative transactivation activity of RUNX2 on osteocalcin promoter.

Conclusions

We explored a novel RUNX2 deletion/frameshift mutation in a sporadic CCD patient. This finding emphasizes on crucial role of VWRPY domain in RUNX2 transactivation ability.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the latest manuscript can be downloaded and accessed as a PDF.

Figures

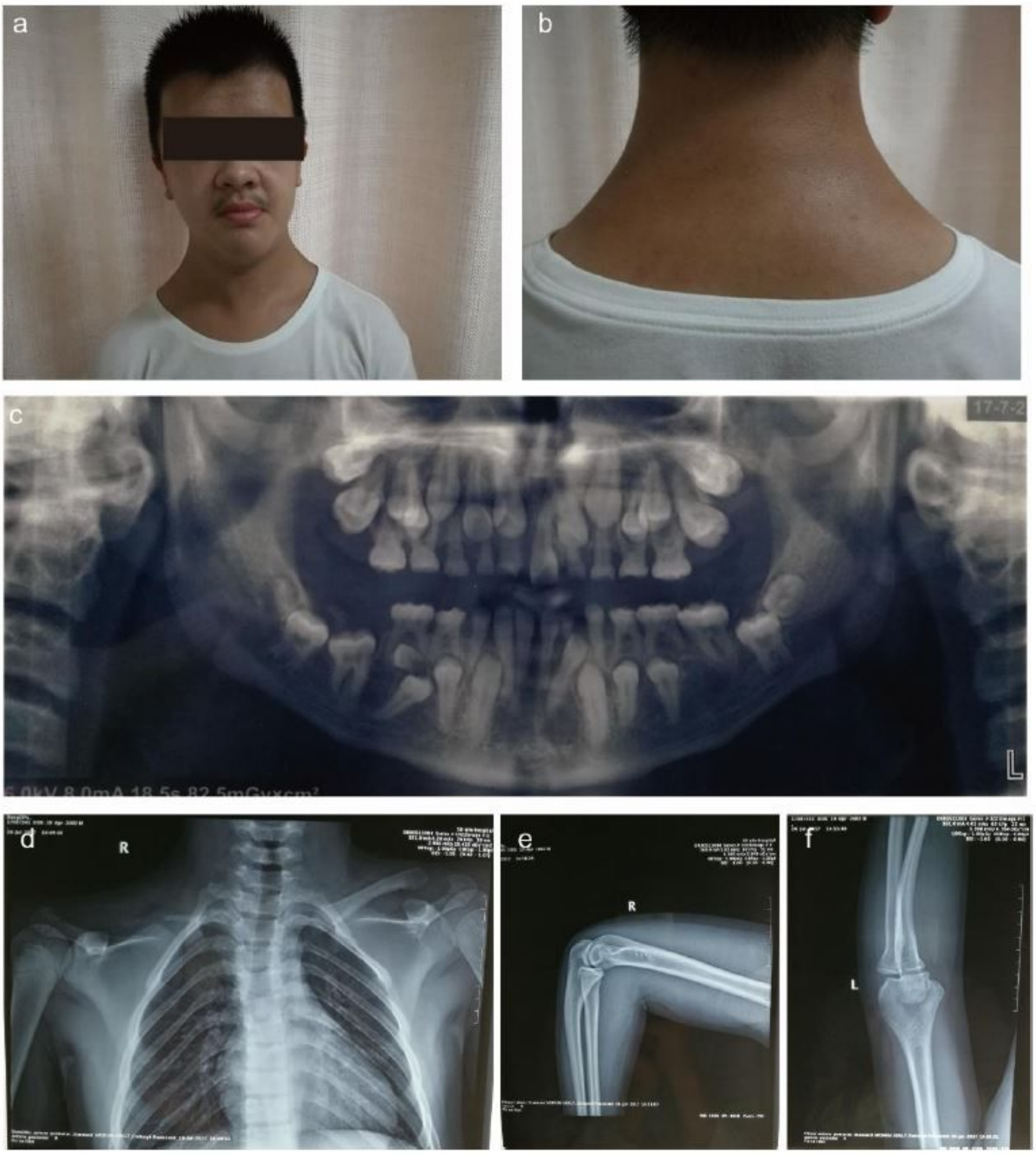

Figure 1

Typical and radiological findings in the CCD patient. (a) Frontal facial view of patient representing midline depression of forehead. (b) Hypoplasia of the clavicles abnormal facility in the opposing shoulders (c) Panoramic radiography revealed primary teeth retention, numerous impacted permanent teeth in both maxilla and mandible. (d) Chest X-ray showed bilateral hypoplastic clavicles hypoplasia of iliac bones,

wide symphysis pubis with a bell-shaped thoracic cavity and scoliosis. (e,f) No abnormalities were seen in the bones of the bilateral elbow joints, and the epiphyseal line showed closure.

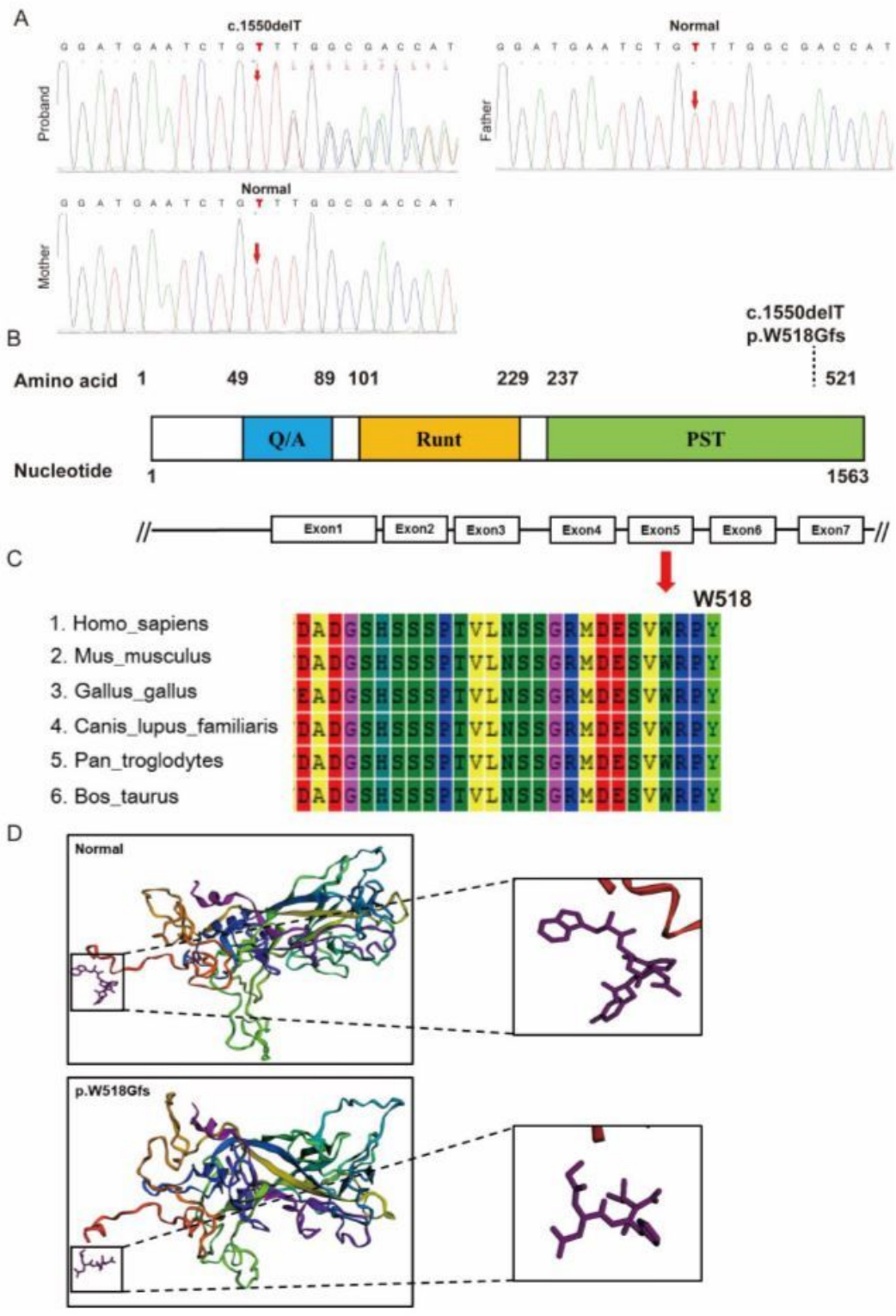

Figure 2

Partial sequence diagram of RUNX2 and biochemical characterization of the RUNX2 (c.1061G>T) variant (A) Partial sequence diagram of RUNX2. A heterozygous c.1550delT transition mutation is shown using an arrow (GenBank accession number: NM_001024630). This frameshift mutation resulted in changes in

amino acid synthesis starting from amino acid Trp 518 (p.Trp518Glyfs). (B) RUNX2 structural domains. Mutations at the protein level are indicated below the PST domain. (C) Cross-species conservation of Trp518-RUNX2. (D) Protein structure prediction of the RUNX2 (WT and Trp518Glyfs).

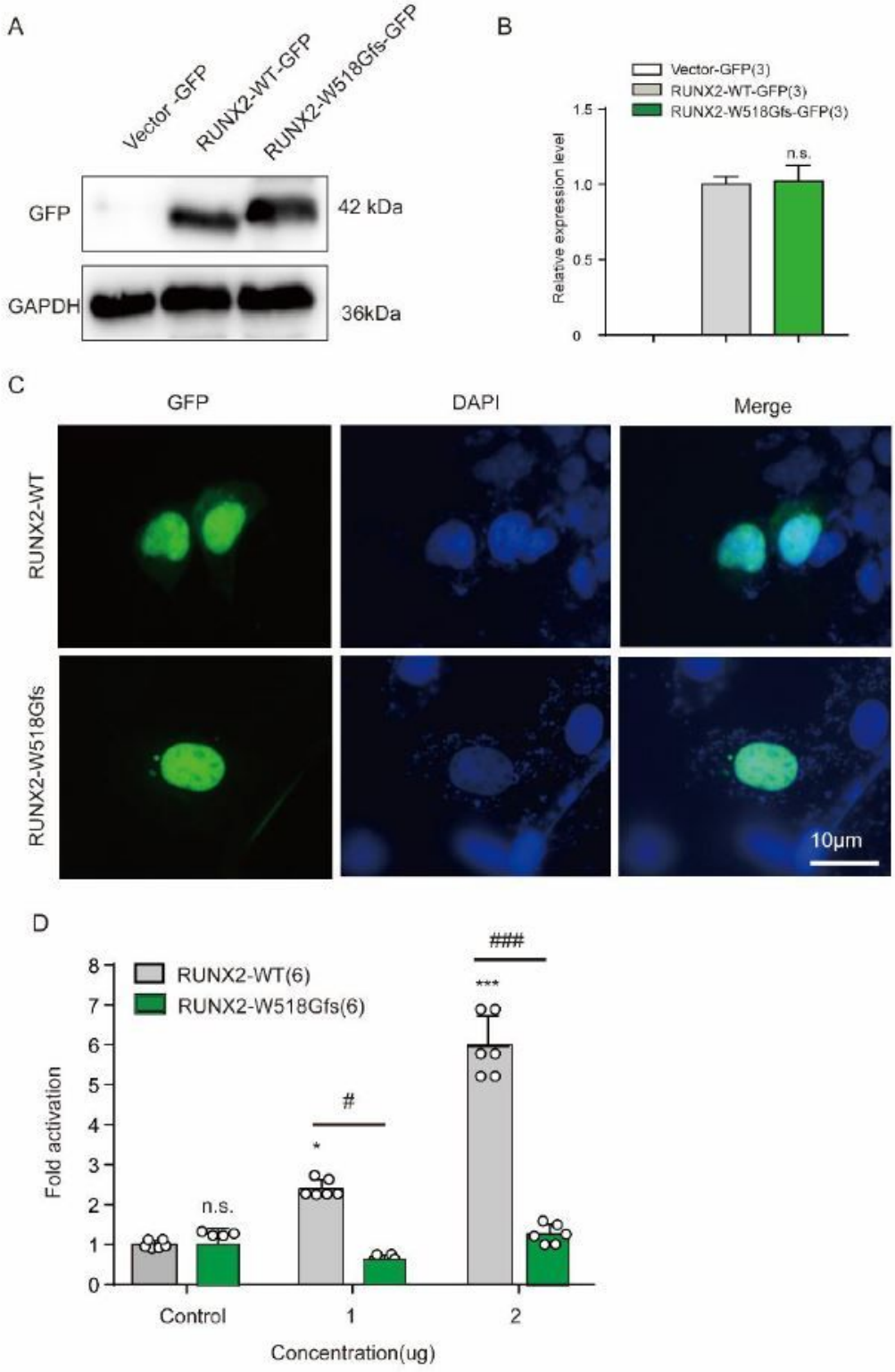

Figure 3

Functional characterization of the RUNX2 (c.1061G>T) variant (A) Protein expression of RUNX2 (WT and Trp518Glyfs). (B) The Histogram of the RUNX2 protein expression level analysis. n.s., denotes RUNX2

Trp518Glyfs compare with the empty denotes p□0.05. (C) Nuclear localization of WT and mutant RUNX2. (D) Luciferase results of HEK293 cells were transfected with each RUNX2 expression vector (WT and Trp518Glyfs). *, denotes RUNX2 WT plasmid compare with the empty plasmid, p□0.0; #, denotes RUNX2 Trp518Glyfs compare with RUNX2 WT, p□0.05