Molecular Syndromology

Novel Insights from Clinical Practice

Mol Syndromol
DOI: 10.1159/000545570

Received: February 21, 2025
Accepted: March 27, 2025
Published online: March 28, 2025

# A Novel Homozygous Missense *SCUBE3* Variant with Protein Modeling in a Patient Diagnosed as Short Stature, Facial Dysmorphism, and Skeletal Anomalies with or without Cardiac Anomalies 2

Burcu Yeter[a] Batın Ilgıt Sezgin[b] Yunus Emre Dilek[c]
Yasemin Kendir Demirkol[a] Arzu Selamioğlu[d] Heves Kırmızıbekmez[e]
Hande Kaymakçalan Çelebiler[f, g] Günseli Bayram Akçapınar[c]

[a]Department of Pediatric Genetics, Umraniye Training and Research Hospital, Istanbul, Turkey; [b]Department of Pediatric Dentistry, Faculty of Dentistry, Istanbul Galata University, Istanbul, Turkey; [c]Department of Medical Biotechnology, Institute of Health Sciences, Acıbadem University, Istanbul, Turkey; [d]Department of Pediatric Metabolic Diseases, Bagcilar Training and Research Hospital, Istanbul, Turkey; [e]Department of Pediatric Endocrinology, Umraniye Training and Research Hospital, Istanbul, Turkey; [f]Department of Translational Medicine, Acıbadem University, Istanbul, Turkey; [g]Neurosurgical Department, Yale University, New Haven, CT, USA

**Established Facts**

- Homozygous pathogenic variants in the *SCUBE3* gene are associated with short stature, facial dysmorphism, and skeletal anomalies with or without cardiac anomalies 2 (SSFSC2).
- The differential diagnosis for short stature, microcephaly, mild learning disability, distinctive facial traits, and parental consanguinity should include SSFSC2.

**Novel Insights**

- A homozygous missense variant, c.908G>C (p.Cys303Ser), in the *SCUBE3* gene has not been previously reported.
- SSFSC2 can be presented with learning disability.
- The C303S variant in the *SCUBE3* gene was predicted to damage the SCUBE3 protein, primarily by disrupting the C303–C316 disulfide bridge.

**Keywords**
Protein modeling · SCUBE3 · Short stature · SSFSC2 · Exome sequencing

karger@karger.com
www.karger.com/msy



Correspondence to:
Burcu Yeter, dr.byeter@gmail.com

Karger

## Abstract

***Introduction:*** Short stature, facial dysmorphism, and skeletal anomalies with or without cardiac anomalies 2 is a very rare genetic disorder caused by biallelic pathogenic variants in the *SCUBE3* gene and has been reported in approximately 20 patients to date. SCUBE3 protein exhibits significant expression in various tissues, including primary osteoblasts, long bones, and the cartilage of the axial skeleton throughout development, while also playing a regulatory role in the FGF, Hedgehog, and TGF-β signaling pathways. ***Case Presentation:*** We report a 13-year-old female patient from a consanguineous Turkish family with a novel homozygous missense variant, c.908G>C (p.Cys303Ser) in the *SCUBE3* gene identified, through exome sequencing. The patient exhibited prenatal growth retardation, short stature, microcephaly, distinctive facial traits, such as long face, high arched eyebrows, epicanthus, blepharoptosis, hypotelorism, high nasal bridge, micrognathia, and large ears, dental anomalies, and skeletal abnormalities, including scoliosis, eleven pairs of ribs, mild radial bowing, irregular endplates in the lower thoracic vertabrae, and narrow iliac wings. ***Conclusion:*** Protein modeling using AlphaFold3 revealed disruption of a critical disulfide bridge within the seventh epidermal growth factor-like repeat, likely affecting protein stability. In this study, we aimed to further characterize the clinical, radiological, and molecular features of this disorder with protein modeling. 

## Introduction

In 2021, Lin et al. [1] described a newly recognized genetic disorder in 15 patients from nine families with short stature, distinctive facial traits, dental anomalies, and skeletal findings associated with biallelic pathogenic variants of the *SCUBE3* gene. This syndrome known as short stature, facial dysmorphism, and skeletal anomalies with or without cardiac anomalies 2 (SSFSC2) (MIM #619184) has been reported in approximately 20 patients to date [1–3]. The *SCUBE3* (signal peptide, CUB and EGF-like domain-containing protein 3) gene is located on human chromosome 6 at position p21.3. Research on *SCUBE3* is relatively recent and remains limited in scope. Similar to other SCUBE family members, SCUBE1 and SCUBE2, SCUBE3 is highly conserved across zebrafish, mice, and humans [4–6]. These SCUBE proteins possess at least five major domains: a signal peptide, nine sequentially arranged EGF-like domains, a spacer region, three cysteine-rich motifs, and a single CUB domain. These proteins exhibit significant expression in a variety of tissues throughout development, suggesting their possible involvement in developmental processes [1].

Here, we report a female patient with a novel homozygous missense variant, c.908G>C (p.Cys303Ser), in the *SCUBE3* gene. We also present the clinical, radiological, and molecular features, along with in silico structural modeling, to elucidate the potential pathogenic mechanism of this variant.

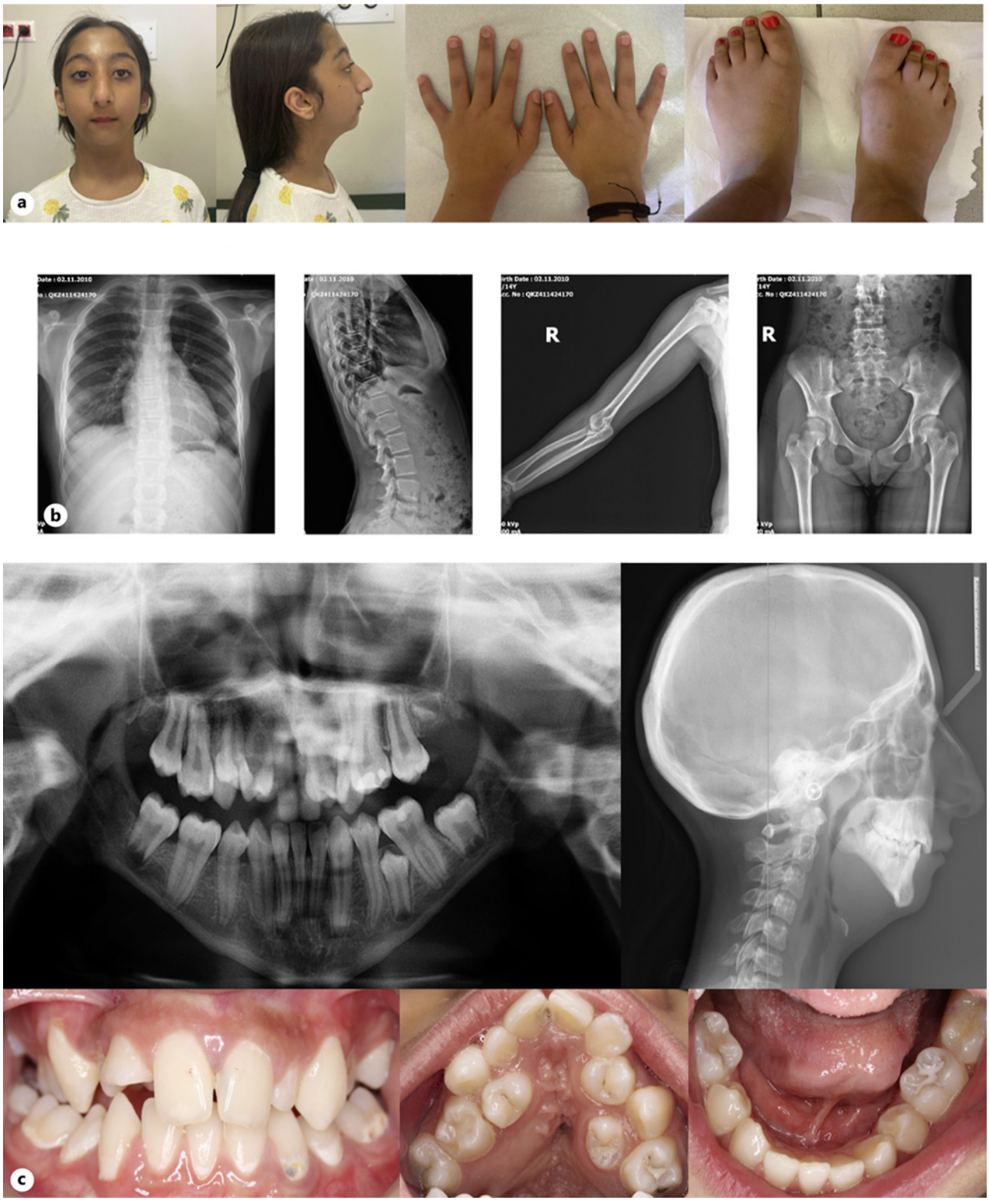
## Case Presentation

A 13-year-old female patient was admitted to our genetics clinic due to her short stature and distinctive facial traits. She was the third child of a Turkish consanguineous couple. The maternal history revealed intrauterine growth retardation detected through ultrasonographic examinations, leading to a cesarean delivery of a full-term infant. Fetal mobility and amniotic fluid were normal. Birth weight was 1,800 g (−3.7 standard deviation score [SDS]). The birth length and head circumference were unknown. After birth, she stayed in the neonatal intensive care unit for 2 months due to low birth weight and feeding difficulties. The medical history revealed that the patient had a cleft palate, which was surgically corrected at 12 months of age. A conductive hearing loss was detected during the hearing examination. The neuromotor developmental milestones were appropriate for her age. She was receiving special education due to learning difficulties. Her mother, father, and two brothers were healthy. There were no notable features in the family history. On physical examination, her body weight was 36.5 kg (−2.62 SDS), height was 138 cm (−3.61 SDS), and head circumference was 51 cm (−3 SDS). Long face, high forehead, high arched eyebrows, epicanthus, blepharoptosis, hypotelorism, high nasal bridge, long arched nose, high-narrow palate, low columella, micrognathia, and large ears were noted as distinctive facial traits. Maxillary transverse deficiency was identified, potentially resulting from the cleft palate surgery. She had mesomelic shortening, which was prominent in the upper extremities, brachydactyly, and hallux valgus. Joint movements were normal. Her pubertal stage was Tanner stage-4, with completed epiphyseal fusion on left wrist graphics. Routine laboratory tests results for growth retardation including whole blood count, biochemical tests, thyroid hormones, tissue transglutaminase antibodies were all within the reference ranges. Serum insulin-like growth factor-1 (IGF-1) level was 325 μg/L (N: 140–485 μg/L). Further endocrinologic evaluation was not performed since the patient had completed linear growth at presentation and IGF-1 level was within upper normal limits. X-rays revealed

thoracic scoliosis, eleven pairs of ribs, mild radial bowing, irregular endplates in the lower thoracic vertabrae, and narrow iliac wings. The lateral cephalogram demonstrated maxillary and mandibular retrognathia (bimaxillary retrusion), with a sella-nasion-A point angle of 69° and a sella-nasion-B point angle of 64°, respectively. Mandibular micrognathia, glossoptosis, and upper airway obstruction were also observed in conjunction with the cleft palate, indicating the presence of Pierre-Robin sequence (PRS). Cone-beam computed tomography and panoramic radiography identified the agenesis of three permanent teeth (hypodontia) and evident taurodontism in all permanent molars. Severe dental crowding, particularly in the maxilla, along with the ectopic eruption of the maxillary left first premolar and the maxillary right first and second premolars, was noted. Additionally, dental caries were observed. Echocardiogram and abdominal ultrasound results were normal. Karyotyping was normal 46, XX at standard resolution, and chromosomal microarray analysis was normal. Subsequently, exome sequencing was performed, found a homozygous variant c.908G>C;(p.Cys303Ser) in the *SCUBE3* (NM_152753.3) gene. The variant was confirmed in the patient and her parents through Sanger sequencing. AlphaMissense, EIGEN, FATHMM-MKL, M-CAP, Mutation Assessor, PROVEAN, REVEL, and SIFT computational algorithms predicted the missense variant as deleterious. This missense variant has not been previously reported in the literature or variant databases such as ClinVar, HGMD, and LOVD and has not been found in population databases, including ESP, 1000G, gnomAD Exomes, and Genomes v2.1.1. The variant met the PM2_moderate and PP3_strong (REVEL score: 0.962) criteria according to American College of Medical Genetics (ACMG) guidelines [7] and modifications recommended by ClinGen's Sequence Variant Interpretation working group (https://clinicalgenome.org/working-groups/sequence-variant-interpretation). Ultimately, the variant has been classified as likely pathogenic according to the ACMG guidelines. In the segregation analysis, the parents and an older healthy brother were found to be heterozygous for this variant. Photographs and images of the patient, pedigree, and Sanger sequencing are shown in Figure 1. Based on the clinical, radiological, and molecular findings, our patient was diagnosed with SSFSC2.

## Discussion

The primary characteristics of SSFSC2 include prenatal growth retardation, short stature, microcephaly, skeletal abnormalities such as brachydactyly, thin-short long bones, coxa valga, and narrow iliac wings, joint involvement, dental anomalies, and distinctive facial traits, including a long face, high forehead, prominent nasal bridge, long nose, and micrognathia. Our patient had all these findings except for joint limitation or hypermobility. In rare cases, SSFSC2 has been associated with congenital heart defects such as atrial septal defect, pulmonary hypertension, patent foramen ovale, and cardiac arrhythmias, as well as cleft palate, conductive hearing loss, scoliosis, missing costae, hypospadias, cryptorchidism, nystagmus, and strabismus. Short stature is a consistent feature of the disease, with reported patient heights in the literature ranging from −2.5 to −5.8 standard deviations [1]. In the literature, 1 patient only has been reported with learning difficulties, behavioral problems such as attention deficit and hyperactivity, and speech delay in SSFSC2 [1]. Our patient also had mild learning difficulties. However, our patient did not exhibit any behavioral disorders. A detailed evaluation of the etiology of our patient's learning difficulty revealed no history of teratogen exposure during the prenatal period, no hypoxic birth history, no neonatal infections or severe neonatal jaundice, and no exposure to traumatic brain injury. The patient's metabolic tests, chromosomal analysis, and microarray analysis for detecting copy number variations also yielded normal results. ES did not identify any significant variants in other genes that could account for this condition. Nevertheless, there is a possibility of a gene that has not yet been discovered. However, since prematurity and low birth weight, both present in our patient's history, are significant risk factors for learning difficulties, it is challenging to determine whether the learning difficulty is a feature of the syndrome. We believe that future studies will help clarify this issue. As a result, learning difficulties may represent a rare manifestation of this disorder or could be attributed to an accompanying condition. Developmental delay also appears to be a rare finding in this syndrome. In the study by Lin et al. [1], congenital hypotonia and speech delay were reported in only 1 patient. Similarly, our patient exhibited age-appropriate developmental milestones. Lin et al. [1] reported that all patients exhibited dental findings, some of which were less commonly observed and others were less specific. Notably, dental involvement was recognized as a consistent feature in individuals with biallelic inactivating *SCUBE3* variants. PRS is a rare congenital condition, primarily characterized by the triad of micrognathia, glossoptosis, and upper airway obstruction, and it may present either as an isolated anomaly or as a component of a syndrome or a complex disorder involving multiple anomalies [8]. This anomaly may also involve cleft palate as a common and additional feature;




1

*(Figure continued on next page.)*

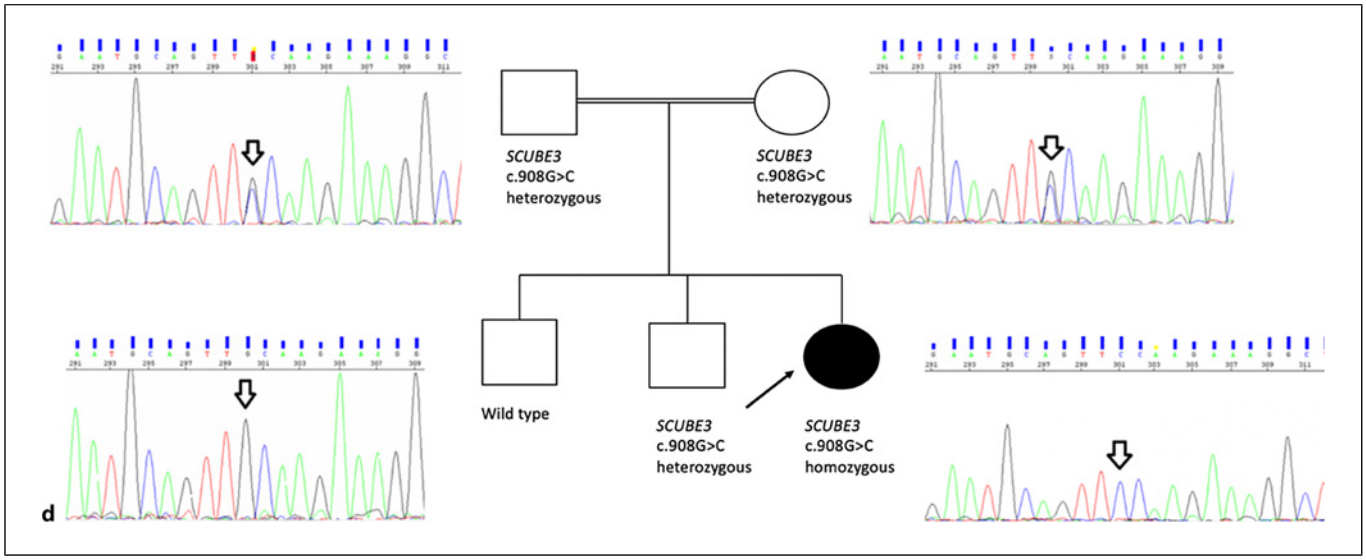
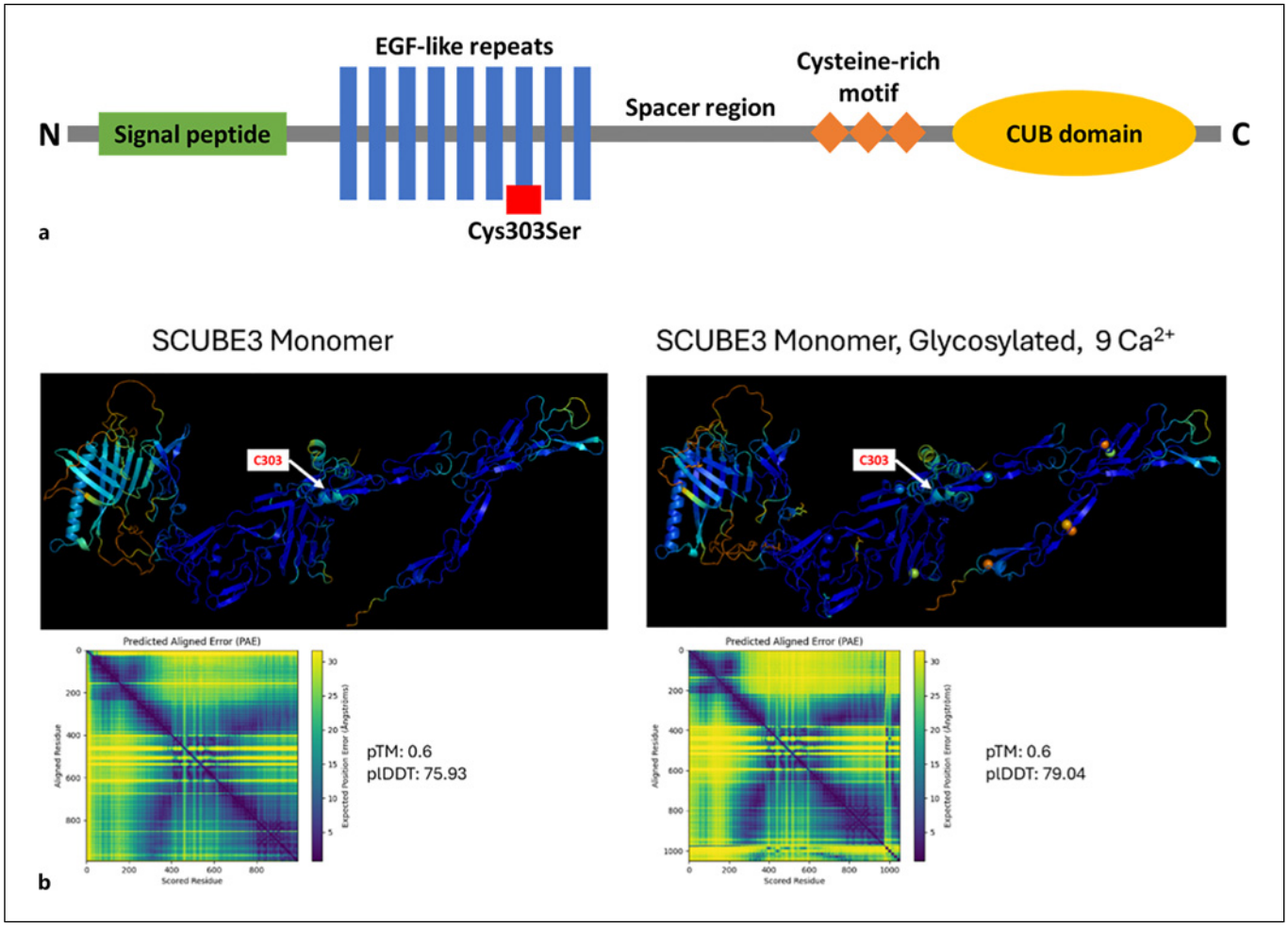



**Fig. 1. a** Distinctive facial traits of the patient. Microcephaly, long face, high-arched eyebrows, epicanthus, blepharoptosis, hypotelorism, high nasal bridge, long arched nose, low columella, micrognathia, and large ears, brachydactyly, and bilateral hallux valgus. **b** X-rays of the patient. Eleven pairs of costae and thoracic scoliosis, irregular endplates of lower thoracic vertebrae, mesomelic shortening, mild radial bowing, and narrow iliac wings. **c** Panoramic dental X-ray, lateral cephalogram, and intraoral features of the patient. Evident taurodontism, hypodontia, bimaxillary retrusion, severe dental crowding, dental caries, maxillary transverse deficiency and ectopic erupted teeth, and intraoral view showing hypodontia in the mandible. **d** Pedigree and Sanger sequencing electropherograms. *SCUBE3* gene c.908G>C variant is homozygous in the patient, heterozygous in the mother, father, and older brother. This variant was not found in the other brother.

however, there is no consensus on whether it constitutes a part of PRS [9]. In the study cohort by Lin et al. [1], among 14 patients in whom PRS and cleft palate were evaluated, PRS was detected in only 2 patients, neither of whom exhibited cleft palate. Conversely, cleft palate was observed in 1 patient who, nonetheless, was not diagnosed with PRS. Our patient displayed the defining features of this rare condition, particularly during infancy, including the primary triad of mandibular micrognathia, glossoptosis, and upper airway obstruction, along with feeding and respiratory difficulties and a surgically corrected cleft palate. Tooth agenesis (TA) refers to the congenital absence of one or more teeth in either the deciduous or permanent dentition. It is classified based on the number of missing teeth as hypodontia (fewer than six teeth missing), oligodontia (six or more teeth missing), and anodontia (the total absence of all teeth) [10]. TA can occur in isolation or as part of various syndromes, including non-syndromic or syndromic cleft lip or cleft lip and palate [11]. The previous report indicated that 4 patients had hypodontia/oligodontia, but only one also had a cleft palate [1]. Our patient exhibited hypodontia and cleft palate, consistent with this phenotype. Taurodontism is another dental abnormality that seems to be linked to more severe forms of TA and is also a defining feature of the amelogenesis imperfecta phenotype resulting from *DLX3* mutations [12]. Additionally, taurodontism is more frequently observed in individuals with cleft lip and palate, affecting a greater number of teeth than in those without clefts. Taurodontism was not noted in any patients in Lin et al.'s [1] cohort, whereas our patient demonstrated pronounced taurodontism in all permanent molars, particularly in the maxillary molars, a feature that may be linked to a novel finding in this syndrome.

The *SCUBE3* gene shows high expression levels in primary osteoblasts, the long bones, and the cartilage of the axial skeleton, while exhibiting lower expression in human umbilical vein endothelial cells and the heart [13]. SCUBE3 protein regulates FGF, Hedgehog, and TGF-β signalling pathways, although the exact molecular mechanisms involved in this modulation remain largely unexplored [14, 15]. In the study by Lin et al. [1], *SCUBE3* knockdown was shown to impair BMP-mediated chondrogenesis and ossification, leading to disrupted endochondral bone growth. The *SCUBE3* gene is suggested to play a crucial role in skeletal development and growth. Also, *SCUBE3* might serve as a key upstream regulator of




2

*(Figure continued on next page.)*

fast fiber myogenesis by influencing FGF8 signaling during zebrafish embryonic development [14].

The protein sequence, domain architecture, and known binding sites of the SCUBE3 (UniProt ID: Q8IX30) [16] were obtained from the UniProt database (www.uniprot.org). SCUBE3 in the UniProt database is annotated with nine EGF-like repeats, six of which have calcium-binding function. EGF-like domains are commonly found in extracellular and membrane-bound proteins that participate in cell signaling [17]. Within SCUBE3, these domains can interact with ligands and other proteins. The missense mutation at residue 303 is located within the seventh EGF-like repeat, forming a disulfide bridge with C316 in close proximity to other disulfide bridges within this domain (Fig. 2a). SCUBE3 can bind $Ca^{2+}$ ions and interact with homologous proteins (SCUBE1 and SCUBE2) as well as other partners, such as TGFBR2 (transforming growth factor-β receptor II), FGF8 (fibroblast growth factor 8), and FGFR4 (fibroblast growth factor receptor 4) [18]. Because no crystal structure is currently available for SCUBE3, AlphaFold3 was employed to predict the structures of wild-type (WT) SCUBE3 and its C303S variant [19]. Several configurations were generated for these predictions, including the presence/absence of the signal peptide, the inclusion of potential glycosylation sites, varying numbers of bound $Ca^{+2}$ ions, and homodimerization scenarios (i.e., two SCUBE3 chains). Structure prediction scores were evaluated using the pLDDT (predicted local distance difference test) and PTM (predicted TM) score metrics. Overall, excluding the signal peptide increased confidence in the final predicted structures. Incorporating the five glycosylation sites also tended to improve prediction scores, whereas adding $Ca^{2+}$ ions – particularly six $Ca^{2+}$ ions – further increased confidence. In monomeric predictions, pLDDT and PTM scores were generally

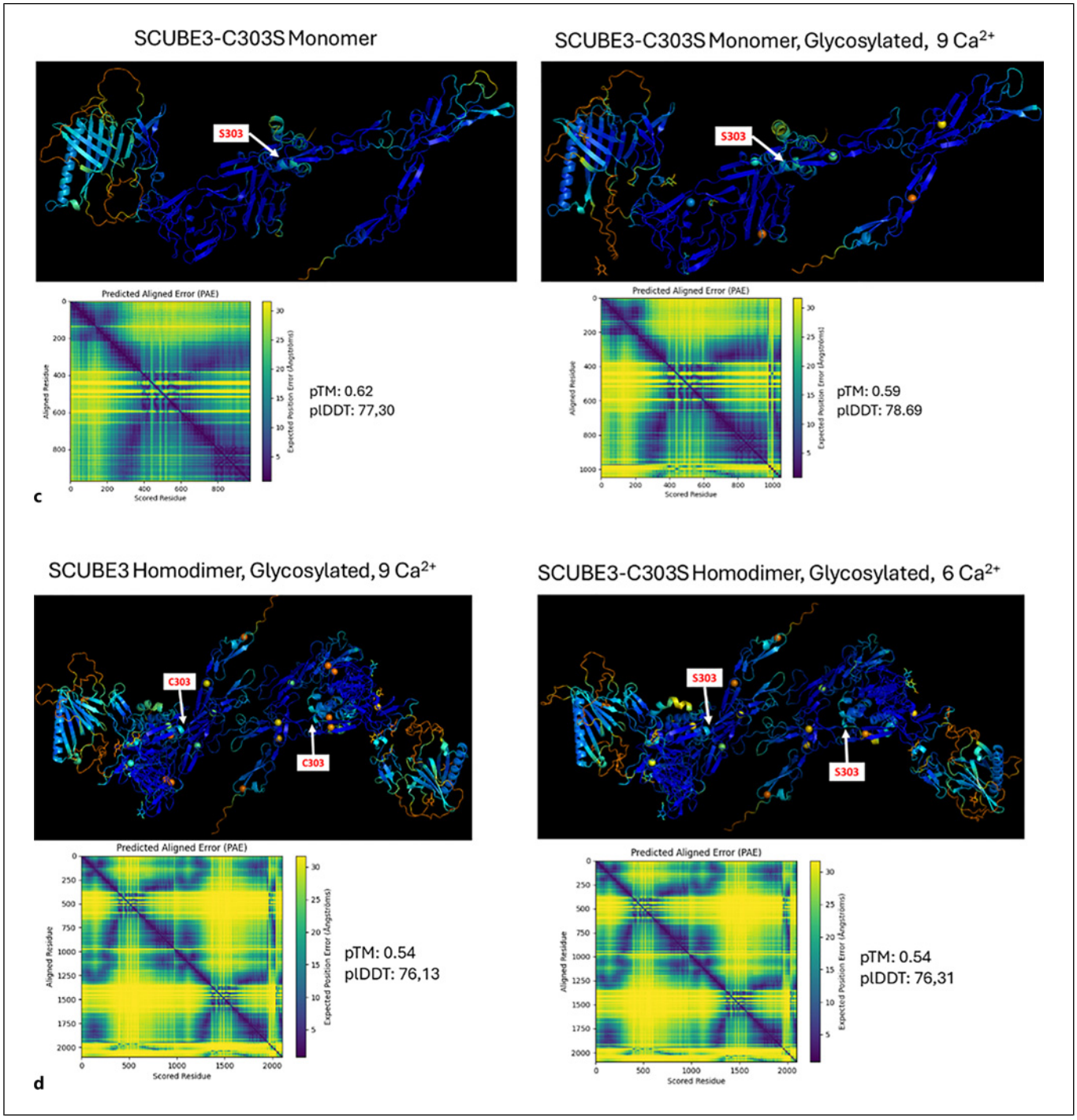



**Fig. 2. a** Schematic representation of SCUBE3 functional domains with C303C variant indicated (adapted from Lin et al. [1] [2020]). **b** SCUBE3 AlphaFold3 monomer model and predicted align scores for SCUBE3 without signal peptide, glycosylation, and $Ca^{2+}$ (left), SCUBE3 without signal peptide, glycosylated, and with 9 $Ca^{2+}$ added (right). **c** SCUBE3-C303S variant AlphaFold3 monomer model and predicted align scores for SCUBE3 without signal peptide, glycosylation, and $Ca^{2+}$ (left), SCUBE3-C303S without signal peptide, glycosylated, and with 9 $Ca^{2+}$ added (right). **d** SCUBE3 and SCUBE3-C303S variant AlphaFold3 homodimer models and predicted align scores for proteins without signal peptide, glycosylated, and with 9 or 6 $Ca^{2+}$ added.

higher than in homodimeric models (Fig. 2b–d). Additionally, the AlphaMissense Pathogenicity Heatmap [20] was used to investigate the potential pathogenicity of the SCUBE3-C303S variant. The AlphaMissense Pathogenicity Heatmap indicated a score of 0.999 for C303S, suggesting a high likely pathogenic potential. Likewise, all other missense mutations at the same position and at other cysteine residues within the EGF-like domains showed similarly high pathogenicity scores.

AlphaFold modeling predictions of SCUBE3 (WT and C303S) under varying conditions suggest that excluding the signal peptide and including the five glycosylation sites alongside six $Ca^{2+}$ ions yields the most confident structural models. Monomeric forms exhibited slightly higher pLDDT and PTM scores relative to homodimers. No marked structural variation was detected between the WT and C303S variant under these conditions, except for the broken disulfide bridge. The EGF-like and CUB domains in SCUBE3 appear critical for protein-protein interactions. Notably, the C303S mutation is predicted to be highly pathogenic, potentially due to its location within the seventh EGF-like domain. SCUBE3 contains numerous cysteine residues, primarily within the EGF-like and cysteine-rich domains, forming disulfide bridges crucial for structural stability [1]. The C303 residue participates in a disulfide bridge with C316, and replacing C303 with serine (C303S) disrupts this bond, potentially destabilizing the EGF-like repeat 7, thereby impacting SCUBE3 stability.

SSFSC2 was defined as Short Stature, Facial Dysmorphism, Skeletal and Dental Anomalies Syndrome, *SCUBE3* related (NOS 21–0240), under group 21, which includes primordial dwarfism and slender bones in the nosology of genetic skeletal disorders: 2023 revision [21]. Skeletal dysplasias constitute a significant portion of genetic disorders, and with advancing technology, an increasing number of new diseases are being identified. Despite the limited available data, we aimed to further characterize the clinical and molecular features of this disorder through protein modeling and patient features. The CARE Checklist has been filled in by all authors (online suppl. material; for all online suppl. material, see https://doi.org/10.1159/000545570).

## Conclusion

In summary, SSFSC2 is a newly identified and extremely rare skeletal dysplasia. We described a female patient affected with SSFSC2 who had distinctive facial traits, short stature, dental anomalies, and learning disability due to a novel homozygous variant in the *SCUBE3* gene. Modeling of the SCUBE3-WT and the C303S variant revealed a highly pathogenic and damaging effect of the mutation on the SCUBE3 protein, specifically through disruption of the C303–C316 disulfide bridge. Incorporation of metal ions and glycan residues improved the prediction confidence of AlphaFold3 in SCUBE3 modeling. Novel variants are crucial for extending the molecular spectrum of SSFSC2 and for gaining a clearer understanding of the genotype-phenotype correlation in larger patient populations.

## Acknowledgment

The authors thank the family for allowing them to publish this report.

## Statement of Ethics

Ethical approval was not required for this study by local/national guidelines. Written informed consent for genetic testing and publication of clinical findings, patient photographs, radiographic images, and molecular results was obtained from her parent.

## Conflict of Interest Statement

The authors declare no conflicts of interest.

## Funding Sources

The authors received no financial support for the research, authorship, and/or publication of this article.

## Author Contributions

Burcu Yeter conceived the study, wrote the manuscript, and studied the genetic analysis. Burcu Yeter and Heves Kırmızıbekmez performed the clinical evaluations and collected data. Burcu Yeter, Batın Ilgıt Sezgin, Yunus Emre Dilek, Yasemin Kendir Demirkol, and Heves Kırmızıbekmez wrote the manuscript. Yunus Emre Dilek and Günseli Bayram Akçapınar performed the protein modeling. Yasemin Kendir Demirkol, Arzu Selamioğlu, Hande Kaymakçalan Çelebiler, and Günseli Bayram Akçapınar reviewed the manuscript. All authors read and approved the final manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

## References


1 Lin YC, Niceta M, Muto V, Vona B, Pagnamenta AT, Maroofian R, et al. SCUBE3 loss-of-function causes a recognizable recessive developmental disorder due to defective bone morphogenetic protein signaling. Am J Hum Genet. 2021;108(1):115–33. https://doi.org/10.1016/j.ajhg.2020.11.015

2 Li JW, Qian YJ, Mao SJ, Chao YQ, Qin YF, Hu CX, et al. Clinical features associated with maternal uniparental disomy for chromosome 6. Mol Cytogenet. 2024;17(1):18. https://doi.org/10.1186/s13039-024-00688-y

3 Joustra SD, Isik E, Wit JM, Catli G, Anik A, Haliloglu B, et al. Genetic findings in short Turkish children born to consanguineous parents. Horm Res Paediatr. 2024:1–11. https://doi.org/10.1159/000539696

4 Lin YC, Sahoo BK, Gau SS, Yang RB. The biology of SCUBE. J Biomed Sci. 2023;30(1):33. https://doi.org/10.1186/s12929-023-00925-3

5 Grimmond S, Larder R, Van Hateren N, Siggers P, Hulsebos TJ, Arkell R, et al. Cloning, mapping, and expression analysis of a gene encoding a novel mammalian EGF-related protein (SCUBE1). Genomics. 2000;70(1):74–81. https://doi.org/10.1006/geno.2000.6370

6 Tsai MT, Cheng CJ, Lin YC, Chen CC, Wu AR, Wu MT, et al. Isolation and characterization of a secreted, cell-surface glycoprotein SCUBE2 from humans. Biochem J. 2009;422(1):119–28. https://doi.org/10.1042/BJ20090341

7 Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–24. https://doi.org/10.1038/gim.2015.30

8 Breugem CC, Evans KN, Poets CF, Suri S, Picard A, Filip C, et al. Best practices for the diagnosis and evaluation of infants with robin sequence: a clinical consensus report. JAMA Pediatr. 2016;170(9):894–902. https://doi.org/10.1001/jamapediatrics.2016.0796

9 Santoro M, Coi A, Barišić I, Pierini A, Addor MC, Baldacci S, et al. Epidemiology of Pierre-Robin sequence in Europe: a population-based EUROCAT study. Paediatr Perinat Epidemiol. 2021;35(5):530–9. https://doi.org/10.1111/ppe.12776

10 Yin W, Bian Z. The gene network underlying hypodontia. J Dent Res. 2015;94(7):878–85. https://doi.org/10.1177/0022034515583999

11 Williams MA, Letra A. The changing landscape in the genetic etiology of human tooth agenesis. Genes. 2018;9(5):255. https://doi.org/10.3390/genes9050255

12 Dong J, Amor D, Aldred MJ, Gu T, Escamilla M, MacDougall M. DLX3 mutation associated with autosomal dominant amelogenesis imperfecta with taurodontism. Am J Med Genet A. 2005;133A(2):138–41. https://doi.org/10.1002/ajmg.a.30521

13 Wu BT, Su YH, Tsai MT, Wasserman SM, Topper JN, Yang RB. A novel secreted, cell-surface glycoprotein containing multiple epidermal growth factor-like repeats and one CUB domain is highly expressed in primary osteoblasts and bones. J Biol Chem. 2004;279(36):37485–90. https://doi.org/10.1074/jbc.M405912200

14 Tu CF, Tsao KC, Lee SJ, Yang RB. SCUBE3 (signal peptide-CUB-EGF domain-containing protein 3) modulates fibroblast growth factor signaling during fast muscle development. J Biol Chem. 2014;289(27):18928–42. https://doi.org/10.1074/jbc.M114.551929

15 Yang M, Guo M, Hu Y, Jiang Y. Scube regulates synovial angiogenesis-related signaling. Med Hypotheses. 2013;81(5):948–53. https://doi.org/10.1016/j.mehy.2013.09.001

16 The UniProt Consortium. UniProt: the universal protein knowledgebase. Nucleic Acids Res. 2017;45(D1):D158–69. https://doi.org/10.1093/nar/gkw1099

17 Selander-Sunnerhagen M, Ullner M, Persson E, Teleman O, Stenflo J, Drakenberg T. How an epidermal growth factor (EGF)-like domain binds calcium. High resolution NMR structure of the calcium form of the NH2-terminal EGF-like domain in coagulation factor X. J Biol Chem. 1992;267(27):19642–9. https://doi.org/10.2210/pdb1ccf/pdb

18 Wu YY, Peck K, Chang YL, Pan SH, Cheng YF, Lin JC, et al. SCUBE3 is an endogenous TGF-beta receptor ligand and regulates the epithelial-mesenchymal transition in lung cancer. Oncogene. 2011;30(34):3682–93. https://doi.org/10.1038/onc.2011.85

19 Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, et al. Highly accurate protein structure prediction with AlphaFold. Nature. 2021;596(7873):583–9. https://doi.org/10.1038/s41586-021-03819-2

20 Cheng J, Novati G, Pan J, Bycroft C, Žemgulytė A, Applebaum T, et al. Accurate proteome-wide missense variant effect prediction with AlphaMissense. Science. 2023;381(6664):eadg7492. https://doi.org/10.1126/science.adg7492

21 Unger S, Ferreira CR, Mortier GR, Ali H, Bertola DR, Calder A, et al. Nosology of genetic skeletal disorders: 2023 revision. Am J Med Genet A. 2023;191(5):1164–209. https://doi.org/10.1002/ajmg.a.63132