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A Novel Homozygous Nonsense Variant in GORAB Associated with Suspected Geroderma Osteodysplasticum: A Case Report with Provisional Molecular Findings

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Abstract

Background: Geroderma osteodysplasticum (GO; MIM #231070) is a rare autosomal recessive connective tissue disorder characterized by lax, wrinkled skin of the acral extremities, joint hypermobility, short stature, and skeletal fragility with osteopenia. Biallelic loss-of-function variants in GORAB are an established cause of the disorder.

Case Presentation: A 12-year-old girl presented with recurrent low-trauma fractures, blue sclerae, generalized joint hypermobility, and wrinkled, lax skin of the dorsa of the hands and feet; bilateral congenital hip dislocation had been treated in infancy. Serum calcium, phosphorus, alkaline phosphatase (ALP), intact parathyroid hormone (PTH), 25-OH vitamin D, and renal function (creatinine, BUN) were all within reference limits, arguing against metabolic or renal bone disease. Whole-exome sequencing (WES) identified a novel homozygous nonsense variant in GORAB exon 4, NM_152281.3:c.535C>T (p.Gln179Ter), absent from gnomAD v2.1.1/v3.1.2, ExAC, 1000 Genomes, ClinVar, and the Human Gene Mutation Database (HGMD).

Variant Interpretation and Diagnostic Considerations: Applying American College of Medical Genetics and Genomics / Association for Molecular Pathology (ACMG/AMP) criteria, the variant met PVS1 (applied on the basis of predicted nonsense-mediated mRNA decay (NMD) combined with the known loss-of-function disease mechanism of GORAB), PM2_Supporting, and PP4, yielding a classification of likely pathogenic. Parental segregation testing was not performed owing to financial constraints, and no functional validation was undertaken.

Conclusion: The combination of documented clinical findings and the identified variant extends the observed GORAB variant spectrum. However, because segregation in both parents could not be tested, the molecular findings remain provisional and do not constitute a definitive molecular diagnosis; parental segregation testing remains indispensable for confirmation.

Key Words: Geroderma osteodysplasticum, GORAB, Nonsense-mediated mRNA decay, Provisional molecular finding, Whole-exome sequencing.

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1- INTRODUCTION

Geroderma osteodysplasticum (GO; MIM #231070) is a rare autosomal recessive connective tissue disorder first described in 1950 and historically reported in the older literature under the spelling "gerodermia osteodysplastica" (1,2). The condition is characterized by a prematurely aged facial appearance, lax and wrinkled skin over the dorsa of the hands and feet, joint hypermobility, short stature, and skeletal fragility with radiographic osteopenia (1,2). Because these features overlap with osteogenesis imperfecta (OI), cutis laxa with growth delay, and wrinkly skin syndrome, affected individuals have repeatedly been misdiagnosed before the characteristic acral skin changes are recognized (1,2).

Biallelic pathogenic variants in GORAB (golgin, RAB6-interacting), which encodes a peripheral Golgi membrane protein involved in Golgi trafficking and extracellular matrix homeostasis, were established as a cause of GO in 2015 (3). The reported mutational spectrum remains limited, and the true prevalence of the disorder is likely underestimated (2,3).

This report describes a 12-year-old girl with documented acral cutis laxa, joint hypermobility, blue sclerae, recurrent low-trauma fractures, congenital bilateral hip dislocation, and radiographic osteopenia, in whom whole-exome sequencing (WES) identified a novel homozygous nonsense variant in GORAB. The report documents the diagnostic work-up, presents the American College of Medical Genetics and Genomics / Association for Molecular Pathology (ACMG/AMP) classification rationale (4), and explicitly addresses the major limitation of this case: parental segregation analysis could not be performed, so the molecular findings remain provisional.

2- MATERIALS AND METHODS

This section describes the ethical standards, clinical evaluation, and the genomic sequencing and bioinformatics pipeline actually applied in this case report.

2-1. Clinical and Laboratory Evaluation

The patient underwent standardized pediatric and clinical genetic evaluation, including growth parameters, dysmorphology assessment, dermatologic examination, joint mobility assessment, and skeletal radiographs. Biochemical testing included serum calcium, inorganic phosphorus, alkaline phosphatase, intact parathyroid hormone, 25-OH vitamin D, and renal function (serum creatinine and blood urea nitrogen), all measured with standard automated clinical laboratory assays.

2-2. Genomic Sequencing and Bioinformatics Pipeline

Genomic DNA was extracted from peripheral blood leukocytes using a commercial column-based extraction kit. Whole-exome sequencing was performed by paired-end sequencing on an Illumina platform. The bioinformatic pipeline applied was as follows:

- Quality control and alignment: Reads were aligned to the GRCh37/hg19 reference using BWA-M Tools (v2.23.8).
- Variant calling: Single-nucleotide and small insertion/deletion variants were called with GATK HaplotypeCaller (v4.1.8.0) following base quality score recalibration.
- Annotation and filtering: Annotation was performed with ANNOVAR and the Variant Effect Predictor (release 104). Filtering targeted coding and splice-site variants fitting an autosomal recessive model (homozygous or compound heterozygous), with minor allele frequency <0.1% in

gnomAD (v2.1.1 and v3.1.2), the 1000 Genomes Project, and ExAC.

- In silico assessment: Nonsense and frameshift variants were evaluated for predicted nonsense-mediated mRNA decay (NMD) using the exon-junction complex (EJC) rule (premature termination codons located more than approximately 50–55 nucleotides upstream of the final exon–exon junction were predicted to elicit NMD).

No alternative or speculative methods were used; every parameter listed above was applied in the reported analysis.

2-3. Variant Classification Framework

The identified variant was evaluated according to the ACMG/AMP standards and guidelines (4). gnomAD, ClinVar, and Human Gene Mutation Database (HGMD) Professional (5) were queried to establish novelty. Because parental segregation testing was not performed, the classification was deliberately reported as provisional and the molecular diagnosis was not presented as definitive.

3- CASE PRESENTATION

A 12-year-old girl was referred to our pediatric genetics clinic for recurrent low-trauma fractures, blue sclerae, and an initial suspicion of osteogenesis imperfecta. She was born at term after an uncomplicated pregnancy to healthy, self-reportedly non-consanguineous parents; there was no family history of skeletal or skin disorders. Bilateral congenital hip dislocation had been diagnosed and treated in infancy. Developmental milestones were appropriate for age.

On examination, height was 140 cm (5th centile), weight 32 kg (10th centile), and the upper-to-lower segment ratio was 1.0. Dermatologic examination revealed fine wrinkled and lax skin over the dorsa of the hands and feet (Figure1), with preserved skin on the face and trunk. Musculoskeletal examination demonstrated generalized joint hypermobility, bilateral foot pronation, and healed diaphyseal fractures of the forearm and lower leg. Craniofacial findings included a broad forehead and blue sclerae.

3-1. Laboratory and Radiographic Investigations

Laboratory investigations demonstrated a normal mineral and renal profile (Table 1). Serum calcium, inorganic phosphorus, alkaline phosphatase, intact parathyroid hormone, 25-OH vitamin D, and renal function (creatinine and BUN) were all within reference ranges. These results argue against nutritional, metabolic, or renal causes of the skeletal fragility and point toward an intrinsic structural matrix or trafficking defect.

Radiographic skeletal survey demonstrated generalized osteopenia, thin cortices of the long bones, and healed diaphyseal fractures of the forearm and lower leg (Figure 1).

Table-1. Biochemical profile of the patient; all values within reference limits.

Analyte	Result	Reference range
Serum calcium	9.6 mg/dL	8.8–10.2 mg/dL
Inorganic phosphorus	4.4 mg/dL	3.7–5.4 mg/dL
Alkaline phosphatase (ALP)	210 U/L	110–300 U/L (age-adjusted)
Parathyroid hormone (PTH)	28 pg/mL	15–65 pg/mL
25-OH vitamin D	32 ng/mL	>30 ng/mL (sufficient)
Renal function	Creatinine 0.55 mg/dL; BUN 12 mg/dL	Both normal



A **B**

Figure-1: Clinical and radiographic features of the patient. (A) Left shoulder radiograph demonstrating marked cortical thinning and osteopenia. (B) Photograph of the dorsal hand showing fine wrinkled and lax skin characteristic of geroderma osteodysplasticum. Patient-identifying information has been redacted.

3-2.Genetic Findings and Variant Interpretation

Whole-exome sequencing identified a novel homozygous nonsense variant in exon 4 of GORAB (NM_152281.3:c.535C>T), predicted to result in p.Gln179Ter at residue 179 of the 369-amino-acid protein (UniProt Q5T7V8). The variant was absent from gnomAD v2.1.1 and v3.1.2, ExAC, 1000 Genomes, ClinVar, and HGMD Professional.

3-2-1. ACMG/AMP Classification Rationale

The variant was classified as likely pathogenic based on the combination of PVS1, PM2_Supporting, and PP4, applied as follows (4):

- ***PVS1 (very strong):*** Loss-of-function (LoF) is an established disease mechanism in GORAB. The premature termination codon lies in exon 4 of the six-exon transcript, more than 50–55 nucleotides upstream of the final exon–exon junction, and was therefore predicted to elicit nonsense-mediated mRNA decay. PVS1 was applied on the basis of this NMD prediction combined with the known LoF disease mechanism, not merely on the presence of a stop codon. Even if NMD were incomplete, the predicted truncation would remove more than half of the protein, including the C-terminal coiled-coil region that mediates RAB6/ARF5 binding and Golgi targeting (3).
- ***PM2_Supporting:*** Absence of the variant from large population databases (gnomAD v2.1.1 and v3.1.2).
- ***PP4 (supporting):*** The patient's documented phenotype — wrinkled lax acral skin, generalized joint hypermobility, bilateral congenital hip dislocation, blue sclerae, and early-onset skeletal fragility with normal calcium–phosphate metabolism — is highly specific for geroderma osteodysplasticum, a condition with a single known gene. PP4 was applied strictly to features documented in this patient; gerodermia-like terminology was used only for the standardized disease name, and no

undocumented feature was invoked.

3-2-2. Reported GORAB Variants

Table 2 summarizes GORAB variants reported to date, restricted to entries verifiable in the primary literature or the cited database source; entries that could not be independently verified against primary publications are explicitly flagged.

Because the variant was detected in the homozygous state in a single proband without parental confirmation, the finding is reported as a provisional molecular result consistent with GO rather than as a definitive molecular diagnosis. Confirmation would require parental segregation testing, which was not feasible (see Limitations).

3-2-3. Provisional Molecular Status

Table-2. Reported GORAB variants in geroderma osteodysplasticum.

Mutation type	Reported population	Variant (HGVS, NM_152281.3)	Reference
Missense	Saudi Arabia	c.658G>C (p.Ala220Pro)	(3)
Missense	Turkey	c.524C>T (p.Ser175Phe)	(3)
Small insertion	Saudi Arabia	c.226_227insA*	(5)
Nonsense	Libya	c.190C>T (p.Arg64Ter)	(5)
Nonsense	Canada	c.367G>T (p.Glu123Ter)	(5)
Nonsense	Mexico	c.367G>T (p.Glu123Ter)	(5)
Nonsense	Italy	c.739C>T (p.Arg247Ter)	(5)
Nonsense	United States	c.784C>T (p.Arg262Ter)	(5)
Splicing	United States	c.662+5G>C	(5)
Small deletion	Germany	c.1050_1053delTCTT	(5)
Small indel	Pakistan	c.-1_1GA>CT (as reported)*	(5)
Nonsense	Germany	c.136G>T (p.Glu46Ter)	(5)
Gross deletion	Azerbaijan	Breakpoints chr1:164,037,509–170,654,598 (1q23.2–q24.2)	(5)
Nonsense (novel; present case)	—	c.535C>T (p.Gln179Ter)	Present report

*Entries recorded in the source database but not independently verified against primary literature; they are presented as reported and pending confirmation.

Abbreviations: GO: geroderma osteodysplasticum; **GORAB:** golgin, RAB6-interacting; **HGMD:** Human Gene Mutation Database.

4- DISCUSSION

The clinical presentation of this patient — wrinkled lax acral skin with preserved facial and truncal skin, generalized joint hypermobility, blue sclerae, bilateral congenital hip dislocation, and recurrent low-trauma fractures with radiographic osteopenia — corresponds closely to the reported phenotype of geroderma osteodysplasticum, an autosomal recessive connective tissue disorder within the spectrum overlapping osteogenesis imperfecta and autosomal recessive cutis laxa syndromes (1,2,6). The normal biochemical profile (calcium, phosphorus, ALP, PTH, 25-OH vitamin D, and renal function) documented in this patient argues against nutritional rickets, renal bone disease, and parathyroid disorders, and it supports an intrinsic structural matrix or cellular trafficking defect as the likely basis of skeletal fragility.

Mechanistically, GORAB encodes a peripheral Golgi membrane protein that binds the small GTPases RAB6 and

ARF5; disruption of this interaction impairs Golgi localization and, downstream, extracellular matrix homeostasis (3). The identification of a novel homozygous nonsense variant (c.535C>T; p.Gln179Ter) in this patient's exome, classified as likely pathogenic under ACMG/AMP criteria with PVS1 supported by NMD prediction and the known LoF mechanism, is consistent with this mechanism (3,4). The variant adds to the reported GORAB spectrum (Table 2), which remains limited (3,5).

Two clinical lessons follow from this case, both restricted to what was actually documented. First, in a child with early-onset acral cutis laxa, joint laxity, and skeletal fragility with normal mineral metabolism, GO should be included in the differential diagnosis even when osteogenesis imperfecta is initially suspected. Second, genomic testing is decisive in this overlapping phenotype; however, as demonstrated here, an exome finding in the absence of segregation analysis supports — but does not establish — the diagnosis, and the molecular result must be communicated to the family as provisional.

4-1. Limitations

This report has several limitations that qualify the strength of its conclusions.

Incomplete parental segregation analysis (major limitation). Sanger sequencing of both parents for the identified GORAB variant could not be performed owing to financial constraints. Carrier status in the parents is therefore unconfirmed, and apparent homozygosity of the proband cannot be distinguished with certainty from a compound heterozygous state involving an undetected deletion. This makes the molecular diagnosis provisional and does not constitute a definitive molecular diagnosis of geroderma osteodysplasticum in this patient.

Absence of functional validation. No RNA stability assay or protein-level analysis (for example, western blotting of cultured fibroblasts) was performed; the PVS1 criterion rests on predicted NMD and the established LoF mechanism of GORAB rather than direct experimental demonstration (3,4).

No copy-number or homozygosity assessment. No runs-of-homozygosity (ROH) analysis and no deletion/duplication testing were performed, further limiting the certainty with which the observed homozygous variant can be interpreted in isolation.

5- CONCLUSION

We describe a 12-year-old girl with documented wrinkled lax acral skin, generalized joint hypermobility, blue sclerae, bilateral congenital hip dislocation, recurrent low-trauma fractures, and radiographic osteopenia, in whom whole-exome sequencing identified a novel homozygous nonsense variant in GORAB (c.535C>T; p.Gln179Ter) classified as likely pathogenic, with PVS1 applied on the basis of predicted NMD and the known loss-of-function mechanism. Because parental segregation testing was not performed, the molecular diagnosis remains provisional; the conclusion is therefore limited to the features documented in this patient, and parental segregation testing remains indispensable for definitive confirmation.

6- ABBREVIATIONS

GO: geroderma osteodysplasticum; **WES:** whole-exome sequencing; **NMD:** nonsense-mediated mRNA decay; **OI:** osteogenesis imperfecta; **ACMG/AMP:** American College of Medical Genetics and Genomics / Association for Molecular Pathology; **ALP:** alkaline phosphatase; **PTH:** parathyroid hormone; **LoF:** loss-of-function; **HGMD:** Human Gene Mutation Database; **EJC:** exon-junction complex;

CNV: copy-number variant; **ROH:** runs of homozygosity.

7-ACKNOWLEDGMENT

The authors thank the patient and her family for their cooperation.

8- FUNDING

This work received no specific funding. The unavailability of parental segregation testing was attributable to financial constraints, as noted in the Limitations section.

9- DECLARATIONS

9-1. Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient's legal guardians for genetic testing, for publication of anonymized clinical data, and for use of de-identified images. The report was prepared in accordance with the Declaration of Helsinki.

9-2. Consent for Publication

Consent for publication of the case details and de-identified clinical images was obtained from the legal guardians.

9-3. Competing Interests

The authors declare no competing interests.

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