JCRMHS

Journal of Clinical Case Reports, Medical Images and Health Sciences

Volume 14 Issue 4, 2026

Article Information

Received date: 09/04/2026
Published date: 20/04/2026

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Key Words:

Geroderma osteodysplastica; GORAB gene, progeroid appearance, Osteopenia, Metaphyseal peg.

Case Report

Geroderma Osteodysplastica

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Abstract

Geroderma osteodysplastica (GO) is a rare autosomal recessive connective tissue disease characterized by wrinkled skin and osteoporosis, two distinct ageing-related features. It comes under the group of hereditary connective tissue disorder that includes cutis laxa syndrome and wrinkly skin syndrome. A loss-of-function mutation in GORAB results in the disease. This gene encodes a member of the golgin family, a group of coiled-coil proteins on golgin that maps to chromosome 1q24. GO is reported primarily in countries of the Middle East, where most patients have consanguineous parents. Herein, we describe the clinical presentation of a young male patient who was diagnosed with Ehler-Danlos syndrome and, after genetic testing, was finally diagnosed as Geroderma osteodysplastica.

Introduction

Geroderma osteodysplastica (GO; OMIM 231070) is a rare autosomal recessive disorder characterized by loose, wrinkled skin that is particularly noticeable on the dorsal surfaces of the hands and feet. Affected individuals typically show a prematurely aged appearance, hyperextensible joints, distinctive facial features, osteoporosis, and several other musculoskeletal abnormalities. The condition was first described by Bamatter and colleagues in five members of a Swiss family, who referred to them as “Walt Disney dwarfs.” The clinical features of GO overlap with a heterogeneous group of skin disorders, including the cutis laxa syndromes and wrinkly skin syndrome (WSS; MIM #278250).[1]

Geroderma osteodysplastica (GO) results from loss-of-function mutations in the GORAB gene located on chromosome 1q24. This gene encodes a golgin protein that plays a crucial role in maintaining normal Golgi apparatus activity and the cellular secretory pathway. When this gene is mutated, Golgi-dependent glycosaminoglycan synthesis becomes defective, leading to abnormalities in connective tissue matrix remodelling. As a result, patients develop fragmented elastic fibres that cause loose skin (cutis laxa) and severe early-onset osteoporosis.

The GORAB protein normally localizes to the Golgi apparatus and interacts with the small GTPase RAB6. It participates in vesicular transport within the Golgi complex and ensures proper modification of carbohydrate chains on proteins passing through this organelle. In GO, defective GORAB disrupts COPI-mediated vesicular trafficking in the Golgi apparatus, which leads to abnormal glycosylation of extracellular matrix proteins and ultimately causes the skin and skeletal manifestations of the disease.

The occurrences of GO and WSS have been described in different races, but most of the reports are from the countries of the Middle East, and this is linked to the high incidence of consanguineous marriages in this region.[1]. Based on five children from two consanguineous Arab families with overlapping features [Al-Gazali et al., 2001] suggested that GO and WSS may represent variable manifestations of the same disorder.[3]

Patient Information:

A 14-year-old male patient presented with the chief complaint of irregularly aligned teeth in both the maxillary and mandibular anterior and posterior

regions, along with concerns regarding facial esthetics. He was born to consanguineous but otherwise healthy parents, with no significant family history of similar conditions. The patient had attained normal developmental milestones and demonstrated normal intelligence, performing well academically.

Approximately one year earlier, his parents had consulted a general physician because of his low body weight, lean body habitus, and short stature compared with peers of the same age. Clinical examination at that time revealed hyperextensible skin and hypermobile joints, leading to a provisional diagnosis of Ehlers–Danlos syndrome. A spine radiograph demonstrated diffuse osteopenia with a prominent trabecular pattern and multiple vertebral body compressions, with less than 50% reduction in vertebral body height in the thoracic vertebrae. Subsequent genetic analysis confirmed a definitive diagnosis of Geroderma osteodysplastica, and the patient has been under follow-up for this condition for the past year.

The patient has a younger brother who is reportedly healthy and does not exhibit similar clinical features. On general physical examination, the patient appeared thin-built and undernourished. His height was 137 cm and weight was 27 kg, both of which were below the expected values for his age. Despite this, he demonstrated normal intellectual function with no evidence of cognitive impairment.

Generalized joint hypermobility was assessed using the Beighton scoring system. The patient showed positive findings for bilateral passive dorsiflexion of the fifth fingers, passive apposition of the thumbs to the forearm, and hyperextension of the knees, resulting in a total Beighton score of 6. Additionally, the patient demonstrated a positive Gorlin's sign, defined by the ability to touch the tip of the nose with the tongue.

Clinical Images

Extraoral examination revealed a dolichocephalic head shape with wrinkled skin over the hands and feet, while the skin over the face and trunk appeared relatively normal. The patient exhibited a progeroid facial appearance with drooping cheeks, mild malar hypoplasia, and deviation of the nasal septum. Generalized hyperextensible skin was noted, along with prominent veins visible over the dorsum of the hands and the abdominal region.

Intraoral examination revealed a Class I molar relationship with both anterior and posterior dental crowding. Tooth 25 was palatally displaced, while teeth 14 and 15 were rotated. Teeth 13, 23, and 47 were in the process of eruption. A high-arched palate was also observed, along with the presence of supra- and subgingival calculus deposits.

Radiographic evaluation of the hand and wrist demonstrated normal wrist and carpal bones with no evidence of fractures or new bone formation. Orthopantomogram (OPG) revealed erupting teeth 18, 28, 38, 48, 17, 27, and 37 and retention of the deciduous tooth 74. Anterior crowding was also noted. Lateral cephalometric radiography demonstrated malar hypoplasia and deviation of the nasal septum.

As the patient had previously been diagnosed with Geroderma osteodysplastica, he was kept under regular supervision to monitor for potential pathological fractures. The patient was advised extraction of the retained deciduous tooth 74 and supragingival scaling, and was subsequently referred to the Department of Dentofacial Orthopaedics for further orthodontic management.

Discussion

Geroderma Osteodysplastica (GO) is a rare hereditary connective tissue disorder inherited in an autosomal recessive pattern. It is caused by a loss-of-function mutation in the GORAB gene located on chromosome 1q24. Under normal conditions, the GORAB protein plays a crucial role in maintaining Golgi apparatus structure and facilitating vesicular trafficking, which is essential for the proper processing and transport of extracellular matrix (ECM) proteins.

In the presence of a defective GORAB gene, Golgi architecture becomes disrupted, resulting in impaired protein trafficking from the Golgi to the extracellular space. This dysfunction adversely affects post-translational modifications, particularly glycosylation, of key extracellular matrix components such as collagen, elastic fibers, and proteoglycans. Additionally, osteoblast function is compromised, contributing to both cutaneous and skeletal manifestations observed in GO.

Importantly, Geroderma Osteodysplastica does not involve primary mutations in collagen-encoding genes. Instead, defective Golgi-mediated processing leads to abnormal organization of predominantly type I and type III collagen. Although these collagen types are structurally present, they are improperly arranged rather than intrinsically defective at the genetic level.

Clinically, GO is characterized by lax, wrinkled skin, particularly over the dorsum of the hands and feet, along with distinctive facial features such as a broad forehead, underdeveloped maxillary and malar regions, mandibular prognathism, and prominent ears. Skeletal manifestations include joint laxity, hyperextensibility, frequent hip dislocation, osteoporosis, kyphoscoliosis, and a reduced upper-to-lower segment ratio.

Pathophysiology of Skin Manifestations

Dermal fibroblasts rely on an intact Golgi apparatus for proper synthesis, modification, and secretion of extracellular matrix proteins, including type I collagen and elastin, which are essential for maintaining skin strength and elasticity. In GO, Golgi dysfunction leads to defective post-translational modification and secretion of these proteins. Consequently, collagen and elastic fibers within the dermis become disorganized and functionally deficient.

This structural compromise of the dermal extracellular matrix results in decreased الجلد elasticity and support, producing the characteristic features of loose, wrinkled, and prematurely aged skin, commonly referred to as a “geroderma” appearance.

Pathophysiology of Skeletal Manifestations

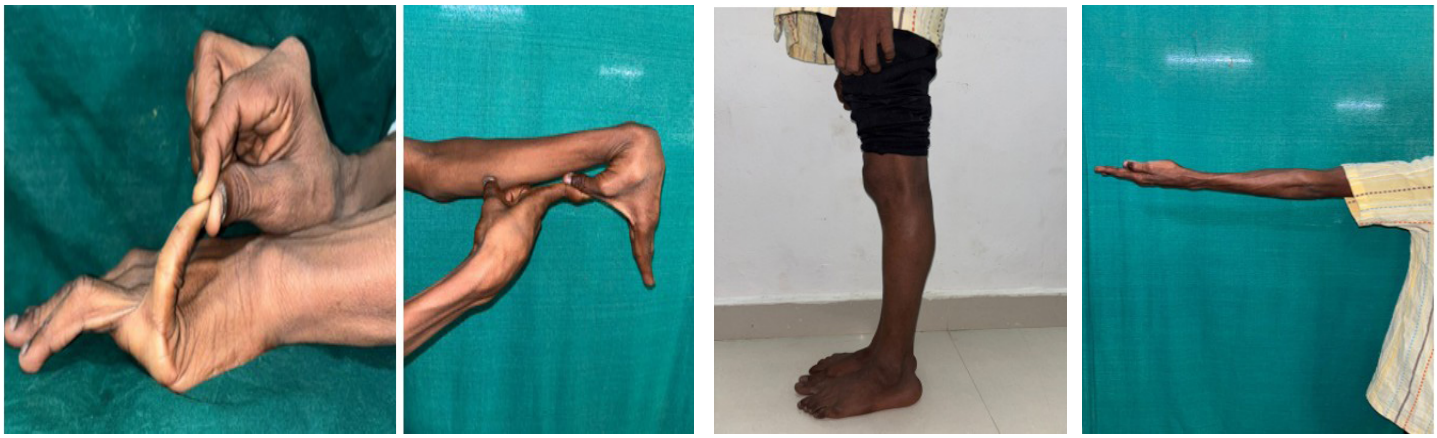
The GORAB mutation also disrupts the processing and secretion of critical bone matrix proteins, including type I collagen, osteocalcin, and osteonectin. Impaired glycosylation and defective protein handling lead to poor collagen fibril organization and inadequate osteoid matrix formation.

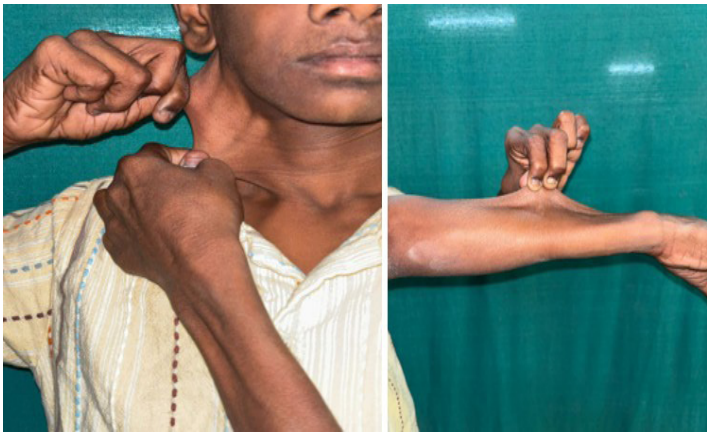
As osteoblasts depend on proper extracellular matrix production for bone formation and mineralization, their dysfunction results in reduced bone density and structural weakness. This ultimately manifests as osteopenia, skeletal deformities, and increased bone fragility.

Overlap with Other Connective Tissue Disorders

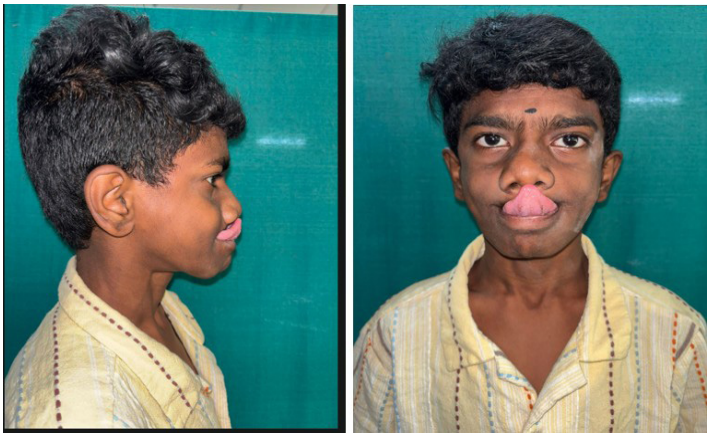
The clinical presentation of GO overlaps with a heterogeneous group of disorders affecting collagen and

Disorder	Defective Gene/Protein	Basic Defect	Pathophysiology
Ehlers-Danlos syndrome	Collagen genes (e.g., COL5A1, COL3A1)	Defective collagen synthesis and structure	Abnormal collagen fibril formation leads to reduced tensile strength of connective tissue → hyperextensible skin, joint laxity, fragile vessels
Osteogenesis imperfecta	COL1A1, COL1A2 (Type I collagen)	Quantitative/qualitative defect in type I collagen	Poor osteoid formation and weak bone matrix → bone fragility, fractures, blue sclera
Cutis laxa syndrome	ELN, FBLN5, ATP6V0A2	Defective elastin or elastic fiber assembly	Impaired elastic fiber formation → loss of recoil in skin and organs → loose, sagging skin and systemic involvement (lungs, vessels)
Wrinkly skin syndrome	ATP6V0A2, PYCR1	Defective Golgi function and glycosylation	Abnormal processing of ECM proteins → defective collagen and elastin organization → wrinkled skin, growth retardation, developmental delay
Marfan syndrome	FBN1 (fibrillin-1)	Defective microfibril formation	Weak connective tissue + increased TGF-β activity → aortic dilation, long bones, lens dislocation





Hyperextensibility of Skin



Positive Gorlin Sign

elastic fibers. Collagen fibers provide tensile strength and serve as a scaffold for mineralization in bone, while elastic fibers contribute to tissue elasticity and recoil, particularly in the skin.

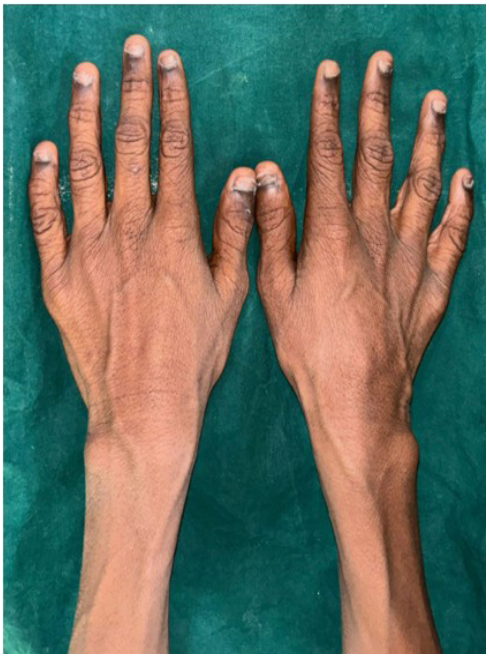
Conditions with overlapping features include Ehlers-Danlos syndrome, osteogenesis imperfecta, cutis laxa, wrinkly skin syndrome, and Marfan syndrome. These disorders share common underlying mechanisms involving abnormalities in extracellular matrix components such as collagen, elastin, or fibrillin, leading to compromised structural integrity of tissues, however differential diagnosis has to be made with the following diagnostic cues.

Differential Diagnosis

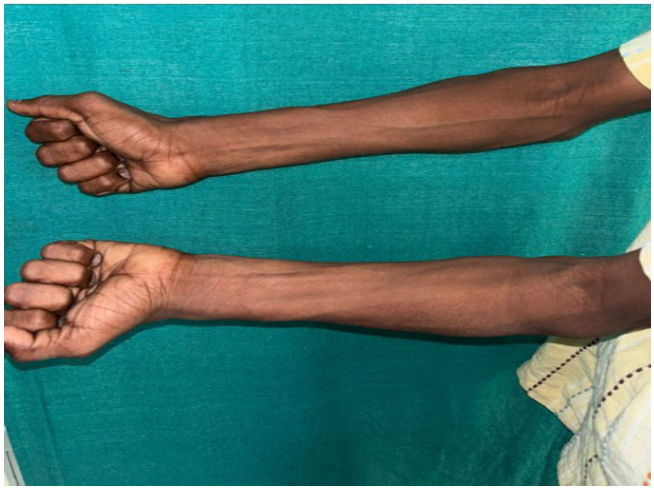
In the present case, the patient exhibited hyper elastic and wrinkled skin, suggesting involvement of both collagen (type I) and elastic fibers. Additional findings such as joint hypermobility and osteopenia further indicate a defect in collagen function within bone. Short stature attributed could be due to vertebral compression secondary to decreased bone density. Although the Gorlin sign which is seen is not a classical feature of GO, it may occasionally be observed due to generalised connective tissue laxity.

Ehlers-Danlos syndrome was excluded due to the absence of hallmark features such as easy bruising and atrophic scarring, along with the presence of significant osteopenia. Osteogenesis imperfecta was ruled out despite reduced bone density, as there were no associated findings such as blue sclera, hearing loss, or dentinogenesis imperfecta.

Cutis laxa was considered but excluded due to the absence of multisystem involvement, including pulmonary emphysema, hernias, and vascular abnormalities and the relatively greater skeletal involvement seen in this case. Wrinkly skin syndrome was also ruled out, as the patient demonstrated normal developmental milestones and lacked growth retardation typically associated with that condition.



Wrinkly skin on the dorsum of the hands



Prominent veins on the arm

Finally, Marfan syndrome was excluded based on the patient's short stature and absence of characteristic cardiovascular (aortic root dilation), ocular (lens dislocation), and skeletal (arachnodactyly, long limbs) features.

The radiographic findings consist of generalised osteoporosis, moderate to severe osteopenia with thinning of the cortices and decreased bone density, vertebral compression fractures and long bone fractures. Bowing of legs secondary to osteopenia, Hip dislocations, Biconcave vertebral bodies, Multiple Wormian bones within the lambdoid and sagittal sutures, and thinning of the cranial vault. Craniofacial abnormalities include malar hypoplasia and mandibular prognathism, enlarged funnel-shaped mandibular lingula, extension of mandibular premolar and molar roots below the inferior dental canal, and hypercementosis surrounded by a radiolucent halo of several teeth have been reported. In addition to the known manifestations, GO has a peculiar peg-like extension of the metaphysis into the epiphysis of the long bones. They may represent a primary abnormality of growth in a bone disorder (Giedion 1967) or an acquired abnormality secondary to osteopenia. The peg is a age dependent finding that appears during early childhood, around the age of 4 and 5, and becomes invisible following physeal closure [5].

The skin biopsy – On haematoxylin and eosin, the changes in the dermis and epidermis were unremarkable. The Verhoeff-Van Gieson stain showed the absence of elastic fibres in the papillary dermis, with fragmentation and clumping of elastic fibres in the reticular dermis. On electron microscopy, the dermal collagen appeared normal. Elastic fibres were widely spaced with fenestration and clumping of the microfibrillar component.[1]

Laboratory investigation by Analysis of Glycosylation pattern- Although both Gerodermia osteodysplastica and Wrinkly Skin Syndrome demonstrate connective tissue abnormalities; the underlying glycosylation defects differ mechanistically. In GO, glycosylation abnormalities are secondary to GORAB-related Golgi dysfunction, leading to impaired extracellular matrix protein processing. In contrast, certain forms of WSS exhibit more direct disruptions in protein glycosylation pathways, with biochemical evidence of altered N- and O-linked glycosylation patterns. Serum transferrin isoelectric focusing serves as an initial screening tool for detecting N-linked glycosylation defects, particularly in WSS [3]

In WSS with ATP6V0A2 mutations, a Type II pattern may be seen. In GO, transferrin is usually normal because the glycosylation defect is secondary and subtle.

Genetic Testing (Definitive diagnosis)

In cases of GO, Sequence analysis of the GORAB gene is done. For Ehler danlos syndrome COL5A1, COL5A2, (Classical EDS), COL3A1(Vascular EDS), COL1A1(Arthrochalasia EDS), Cutis laxa syndrome has mutation in several genes including ELN, FBLN5, ATP6V0A2, LTBD4 gene. Marfan syndrome due to mutation in FBN1 gene.

Management Of Geroderma Osteodysplastica (GO)

Geroderma osteodysplastica is a rare connective tissue disorder for which no definitive cure is currently available. Therefore, management is primarily supportive and symptomatic, with the main goal of improving quality of life and functional outcomes. A multidisciplinary approach is essential for optimal care.

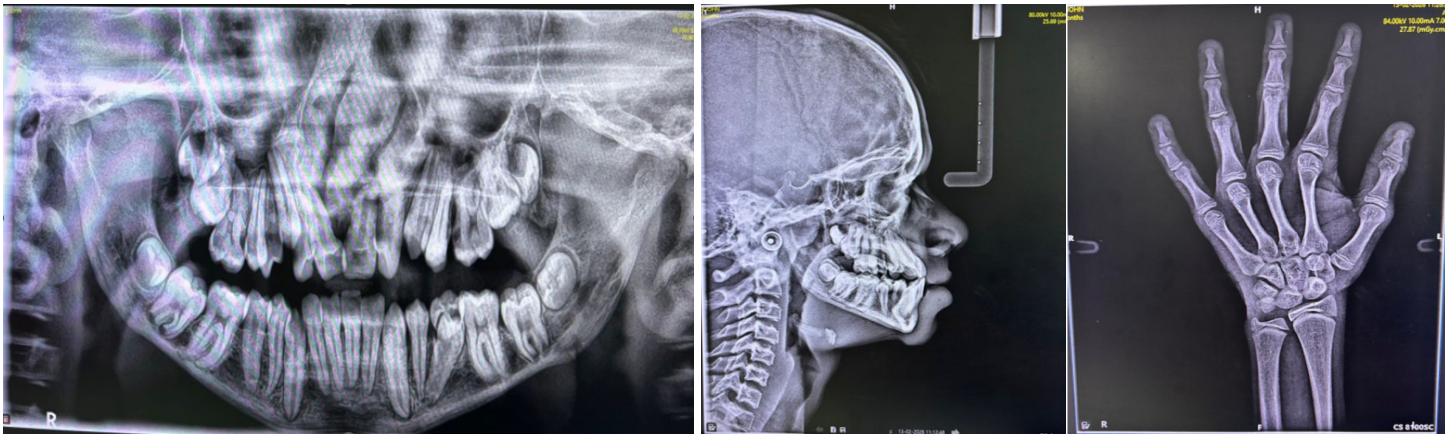
1. Bone Health Management

The most critical aspect of management is addressing severe osteoporosis to reduce the risk of fractures.

• Bisphosphonates are commonly used to improve bone mineral density (BMD) and decrease fracture risk

• Vitamin D supplementation is recommended to support bone health

2. Orthopedic Management



Radiological Investigation

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Patient Details

Name	: GIRISHWARAN	Sex / Age	: Male / 14 Years	Case ID	: 50829603386
Ref By	: DR.ANANTHI NAGAJOTHI	PT. ID	:	Test Name	: Institute Orion
Bill. Loc.	: NCGM-GOVT CASH				

Sample Details

Registration Date & Time	: 2025-08-06 05:14:43 PM	Sample Type	: Whole Blood EDTA	Sample Date & Time	: 2025-08-06 05:14:00 PM
Ref ID 1.	: -	Report Date & Time	: 2025-08-30 02:42:43 PM		

Clinical History

Consanguinity status: Present. Salient features: Syndromic short stature, high arched palate, sunken eyes, sandals gap, skin wrinkling, clinodactyly, joint laxity (hyper extensible joints), thumb and wrist sign - present, hypomobile joints, diffuse osteopenia, multiple vertebral body compression (with < 50% reduction in vertebral body height noted in thoracic vertebrae) pattern. Possible Ehlers Danlos syndrome. Investigations: X-Ray (Bone age): Olecranon process (bone age- 11 years)

Test Results and Interpretation

HOMOZYGOUS PATHOGENIC VARIANT IN GORAB GENE CONSISTENT WITH PHENOTYPE DETECTED. MOLECULAR DIAGNOSIS CONFIRMED.

NO SIGNIFICANT VARIANT RELATED TO EHLERS DANLOS SYNDROME DETECTED.

Summary Of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature	Zygosity	Classification	OMIM Phenotype	Inheritance
GORAB (NM_152281.3)	Exon 2	c.190C>T p.Gln64Ter [97x /97x]	Homozygous	Pathogenic	Geroderma osteodysplasticum	Autosomal recessive

Variant Details

GORAB

Variant Nomenclature	c.190C>T (p.Gln64Ter)
Genomic Nomenclature	chr1:g.170508479C>T

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Patient Name: GIRISHWARAN

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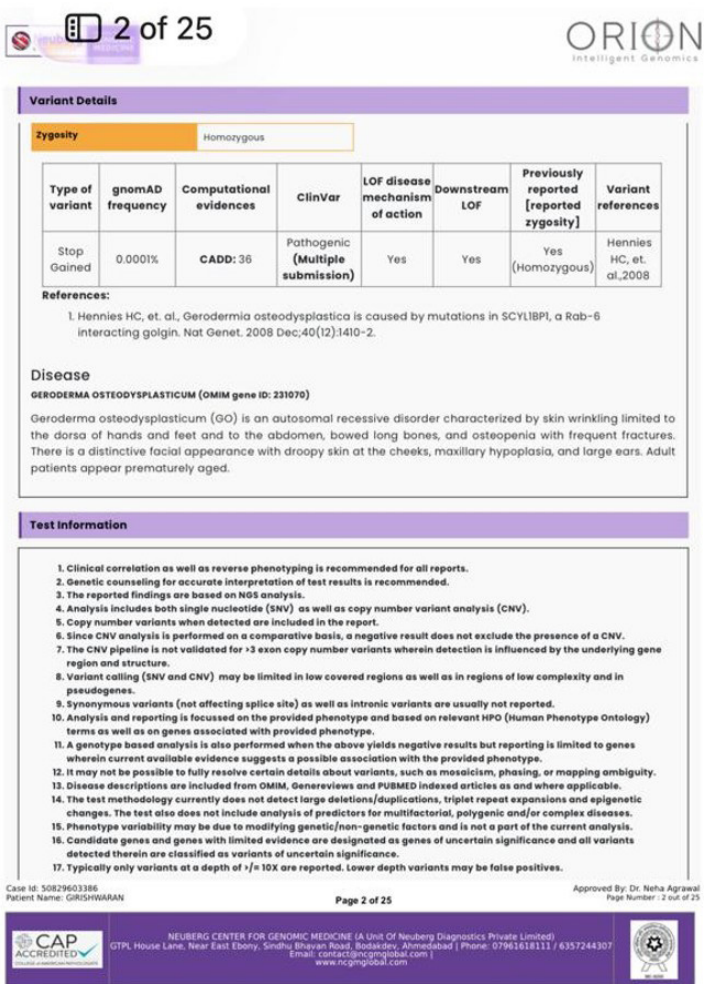

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Variant Details

Zygosity	Homozygous

Type of variant	gnomAD frequency	Computational evidences	ClinVar	LOF disease mechanism of action	Downstream LOF	Previously reported [reported zygosity]	Variant references
Stop Gained	0.0001%	CADD: 36	Pathogenic (Multiple submission)	Yes	Yes	Yes (Homozygous)	Hennies HC, et. al.,2008

References:

1. Hennies HC, et. al., Gerodermia osteodysplastica is caused by mutations in SCYL1BP1, a Rab-6 interacting golgin. Nat Genet. 2008 Dec;40(12):1410-2.

Disease

GERODERMA OSTEODYSPLASTICUM (OMIM gene ID: 231070)

Geroderma osteodysplasticum (GO) is an autosomal recessive disorder characterized by skin wrinkling limited to the dorsa of hands and feet and to the abdomen, bowed long bones, and osteopenia with frequent fractures. There is a distinctive facial appearance with droopy skin at the cheeks, maxillary hypoplasia, and large ears. Adult patients appear prematurely aged.

Test Information

1. Clinical correlation as well as reverse phenotyping is recommended for all reports.
2. Genetic counseling for accurate interpretation of test results is recommended.
3. The reported findings are based on NGS analysis.
4. Analysis includes both single nucleotide (SNV) as well as copy number variant analysis (CNV).
5. Copy number variants when detected are included in the report.
6. Since CNV analysis is performed on a comparative basis, a negative result does not exclude the presence of a CNV.
7. The CNV pipeline is not validated for >3 exon copy number variants wherein detection is influenced by the underlying gene region and structure.
8. Variant calling (SNV and CNV) may be limited in low covered regions as well as in regions of low complexity and in pseudogenes.
9. Synonymous variants (not affecting splice site) as well as intronic variants are usually not reported.
10. Analysis and reporting is focussed on the provided phenotype and based on relevant HPO (Human Phenotype Ontology) terms as well as on genes associated with provided phenotype.
11. A genotype based analysis is also performed when the above yields negative results but reporting is limited to genes wherein current available evidence suggests a possible association with the provided phenotype.
12. It may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity.
13. Disease descriptions are included from OMIM, Genereviews and PUBMED indexed articles as and where applicable.
14. The test methodology currently does not detect large deletions/duplications, triplet repeat expansions and epigenetic changes. The test also does not include analysis of predictors for multifactorial, polygenic and/or complex diseases.
15. Phenotype variability may be due to modifying genetic/non-genetic factors and is not a part of the current analysis.
16. Candidate genes and genes with limited evidence are designated as genes of uncertain significance and all variants detected therein are classified as variants of uncertain significance.
17. Typically only variants at a depth of >/= 10X are reported. Lower depth variants may be false positives.

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Genetic Report

Orthopedic intervention is often required to manage skeletal complications.

• Surgical correction of hip dislocations

• Stabilization of long bones using intramedullary rodding

• Management of recurrent fractures and bone deformities

3. Physical and Occupational Therapy

Rehabilitation therapies play an important role in improving mobility and function.

• Physical therapy helps manage joint laxity and enhance muscle strength

• Occupational therapy assists in improving daily functional activities

4. Supportive Care

Ongoing monitoring and supportive management are essential.

• Regular assessment of skeletal growth and development

• Dental and maxillofacial care for underdeveloped maxillary and malar structures

Dental Management

Dental management of Geroderma Osteodysplastica is primarily preventive and supportive, with the aim of maintaining oral health and minimizing complications related to bone fragility. Emphasis is placed on strict oral hygiene, regular dental check-ups, and fluoride therapy to prevent caries.

Craniofacial abnormalities such as maxillary and malar hypoplasia and mandibular prognathism may require orthodontic assessment and, in severe cases, carefully planned orthognathic surgery, considering the poor bone quality. Prosthodontic rehabilitation is often achieved using removable prostheses, while dental implants are used with caution due to the risk of failure. During dental procedures, gentle handling is essential to avoid pathological fractures, especially during extractions. Coordination with medical management is important, particularly in patients receiving bisphosphonates, due to the risk of medication-related osteonecrosis of the jaw. A multidisciplinary approach involving dental and medical specialists, along with patient education on oral hygiene and trauma prevention, is essential for optimal long-term care

Prognosis

Despite the presence of features resembling premature aging, life expectancy is generally normal. Additionally, the frequency of bone fractures may decrease with age, leading to some improvement in clinical outcomes over time.

Conclusion

Geroderma osteodysplastica is a rare autosomal recessive connective tissue disorder characterized by lax and wrinkled skin, joint hypermobility, and significant skeletal involvement, particularly osteopenia and vertebral compression fractures. Due to overlapping clinical features with other connective tissue disorders such as Ehlers–Danlos syndrome and Wrinkly Skin Syndrome, clinical diagnosis alone may be challenging. In the present case, the patient initially presented with features suggestive of a connective tissue disorder, including progeroid facial appearance, hyperextensible skin, generalised joint hypermobility, and vertebral osteopenia. However, a definitive diagnosis was established through genetic testing, which revealed a mutation in the GORAB gene, confirming Geroderma osteodysplastica. This case highlights the importance of careful clinical evaluation, radiographic assessment, and molecular genetic analysis for accurate diagnosis. Early recognition is essential for appropriate multidisciplinary management, prevention of skeletal complications, and providing proper genetic counselling, especially in individuals born to consanguineous parents.

Declaration of Patient Consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial Support And Sponsorship: Nil.

Conflicts of Interest: There are no conflicts of interest.

Citation: Dr. Gayathri Sundar, Geroderma Osteodysplastica. Jour of Clin Cas Rep, Med Imag and Heal Sci 14 (4)-2026.