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# Osteogenesis Imperfecta in a Family with a Novel Variant in the *COL1A1* gene and Gonadal Mosaicism: a Clinical Case

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## ABSTRACT

Osteogenesis imperfecta (OI) is a clinically heterogeneous genetic disorder whose primary clinical manifestations include susceptibility to recurrent pathological fractures and progressive skeletal deformities. In clinical practice, cases are observed where the proband's parents show no overt signs of the disease despite having multiple affected children. This may suggest gonadal mosaicism – a condition in which the causative variant is present only in a subset of parent's germ cells.

Gonadal mosaicism remains an understudied inheritance mechanism in monogenic diseases, complicating genetic counseling and reproductive risk assessment. In OI, this phenomenon may account for sporadic cases or recurrent births of affected children to clinically healthy parents.

This article presents a case report of a family in which the proband and his younger sister were diagnosed with *COL1A1*-associated OI, while the parents and other children showed no disease manifestations. Based on clinical and genetic data, the likelihood of gonadal mosaicism in one parent is discussed, along with considerations for differential diagnosis, patient management strategies, and family genetic counseling.

This case highlights the importance of molecular genetic testing not only for the probands but also for their parents to clarify the inheritance mechanism and predict the risks of disease recurrence in the family.

**Keywords:** osteogenesis imperfecta; gonadal mosaicism; *COL1A1*

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# Несовершенный остеогенез в семье с новым вариантом в гене *COL1A1* и гонадным мозаицизмом: описание клинического случая

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**РЕЗЮМЕ**

Несовершенный остеогенез (НО) – генетически гетерогенное заболевание, основными клиническими проявлениями которого являются склонность к рецидивирующим патологическим переломам и прогрессирующая деформация скелета. В клинической практике встречаются случаи, когда у родителей пробанда отсутствуют явные признаки заболевания, несмотря на наличие нескольких пораженных детей, что может указывать на гонадный мозаицизм – состояние, при котором каузативный вариант присутствует только в части половых клеток родителя.

Гонадный мозаицизм остается недостаточно изученным механизмом наследования моногенных заболеваний, что создает сложности в генетическом консультировании и оценке репродуктивных рисков. В случае НО этот феномен может объяснять спорадические случаи или рекуррентные рождения больных детей у клинически здоровых родителей.

В статье представлен клинический случай семьи, в которой у пробанда и его младшей сестры диагностирован *COL1A1*-ассоциированный НО, тогда как родители и другие дети не имеют признаков заболевания. На основании клинических и генетических данных обсуждается вероятность гонадного мозаицизма у одного из родителей, а также рассматриваются вопросы дифференциальной диагностики, тактики ведения пациентов и медико-генетического консультирования семьи.

Это наблюдение подчеркивает важность молекулярно-генетического тестирования не только пробанда, но и его родителей для уточнения механизма наследования и прогнозирования рисков повторных случаев заболевания в семье.

**Ключевые слова:** несовершенный остеогенез, гонадный мозаицизм, *COL1A1*

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## INTRODUCTION

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a connective tissue disorder characterized by bone fragility and susceptibility to fractures. Individuals with OI typically present with low bone mass, susceptibility to long bone fractures, vertebral compression, various bone deformities, scoliosis, and growth deficiency. OI can also lead to a range of extra-skeletal manifestations, including blue sclerae, hearing loss, dentinogenesis imperfecta, basilar invagination, and cardiovascular and pulmonary abnormalities [1].

The estimated prevalence of OI is approximately 0.4–1.1 per 10,000 individuals based on population survey data and patient registries [2-4].

Approximately 90% of cases are caused by heterozygous pathogenic variants in the *COL1A1* and *COL1A2* genes, which encode type I collagen (α1 and α2 chains, respectively) [1, 5]. The remaining 10% of OI cases are caused by pathogenic variants in "non-collagen" OI genes with autosomal recessive (*P3H1, CRTAP, SPARC, TENT5A, KDELR2, BMP1, TMEM38B, CREB3L1, SERPINH1, PHLDB1, WNT1, SP7, PPIB, MESD, SERPINF1, FKBP10, CCDC134*), X-linked recessive (*MBTPS2*), and autosomal dominant (*IFITM5*) inheritance patterns (according to the OMIM® database) [6].

Type I collagen is the primary protein component of the extracellular matrix in bones, skin, and tendons and is predominantly secreted by osteoblasts, dermal fibroblasts, and tenocytes. The triple helix of type I collagen consists of two α1 chains and one α2 chain, which plays a crucial role in the stability of the entire collagen molecular structure. Generally, variants in the *COL1A1* gene result in a more severe clinical phenotype than those in the *COL1A2* gene. This can be explained by the molecular stoichiometry of type I collagen, which implies the presence of a mutant chain in 75% and 50% of collagen triple helices due to defects in the α1 and α2 chains, respectively [5, 7].

According to observations by S.M. Pyott et al., in 32% of families with asymptomatic parents and a first child with OI, the disease recurred in subsequent children [8]. The recurrence of OI in siblings is attributed to an autosomal recessive inheritance pattern or parental gonadal mosaicism, which is estimated to account for 5–8% of all OI cases [9–12].

Mosaicism is a genetic phenomenon in which an individual has two or more cell populations with distinct genotypes. In the context of OI, this means the causative variant is present only in a specific proportion of the cell pool. Gonadal mosaicism is of particular clinical interest – a specific form of mosaicism where the genetic abnormality is confined to a subset of germ cells (gametes), while somatic cells remain genetically normal. This circumstance is of fundamental importance for genetic counseling, as a clinically healthy parent with gonadal mosaicism can transmit the pathogenic variant to their offspring, explaining the occurrence of sporadic OI cases in families with no relevant medical history. The risk of transmitting the variant varies depending on the proportion of affected gametes in the gonads, creating significant challenges for assessing reproductive risks. The mechanism underlying mosaicism involves postzygotic sequence variants occurring during early embryonic development, highlighting the necessity of using modern molecular genetic diagnostic methods to accurately determine the nature and prevalence of mosaicism in each specific case.

## CASE REPORT

Proband: A 7-year-old male. Family history: the parents are of mixed ethnic background (mother IS Tatar, father IS Kazakh). He has an elder brother and two elder sisters (all clinically healthy), as well as a younger sister (2.5 years old) who has bluish sclerae and experienced a lower leg fracture before the age of 1. The mother's obstetric – gynecological history includes 8 pregnancies (5 deliveries, 3 abortions). The current pregnancy of the mother (resulting in the proband) was her seventh, complicated by anemia and toxemia. Perinatal history: the proband was delivered at term during the mother's fourth spontaneous vaginal delivery. His birth weight was 3,450 g, birth length was 52 cm, and the Apgar score was 8/8. A cephalohematoma was noted at birth. Developmental history: the proband's motor, mental, and speech development were age-appropriate.

Presenting complaints: multiple fractures (6 episodes) and impaired vision. History of fractures: at 11 months: fracture of the left tibia; at 1 year and 4 months: fracture of the right tibia; at 2 years: consolidated fracture of both bones of the right lower leg; at 3 years and 5 years: repeated fractures of the right lower leg; at 5 years and 8 months: closed displaced fracture of both bones of the left lower leg. At the age of 6 years and 1 month, the diagnosis of osteogenesis imperfecta was first established clinically, and therapy with bisphosphonates was initiated.

## INSTRUMENTAL AND LABORATORY FINDINGS

Bone densitometry (in the context of bisphosphonate therapy) revealed reduced bone mineral density (BMD) in the lumbar spine (L1–L4) with a Z-score of –2.1. Total body BMD was not reduced (Z-score –0.3).

Blood biochemistry: a single episode of low ionized calcium level at 1.02 mmol / l (reference range 1.13–1.32 mmol / l) and vitamin D deficiency at 24.6 ng / ml. Other parameters of calcium – phosphate metabolism (alkaline phosphatase, total calcium, inorganic phosphorus, parathyroid hormone) were within normal limits.

Radiography of the lower leg bones: the bones showed a moderate valgus deformity; rarefaction of

the bone structure with horizontal sclerotic bands in the metaphyses was observed.

Pure tone audiometry: no hearing pathology was detected.

## PHENOTYPIC FEATURES

Anthropometric data: head circumference – 51 cm (–0.85 SD), height – 116 cm (–0.89 SD), weight – 20 kg (BMI –0.52 SD). Facial phenotype: synophrys, blue – grey sclerae, long eyelashes, flattened nasal bridge. Other characteristics: significant joint hypermobility, widely spaced nipples (nipple hypertelorism), pes planovalgus (flat feet), and impaired/abnormal posture.

Clinical course: following the initiation of bisphosphonate therapy, no new fractures have been recorded. A positive trend was observed, evidenced by improved bone mineral density on follow-up densitometry of the lumbar spine after one year, with an increase in the Z-score (L1–L4) to –1.5. The total body Z-score was –0.2.

To verify the clinical diagnosis, quad whole-genome sequencing with the analysis of the Arthrogryposes panel was performed for the proband, his younger sister, and both parents. Sequencing was conducted in collaboration with Biotechnology Campus LLC as part of the 100,000 + Me national genetic initiative.

DNA analysis (isolated from peripheral blood lymphocytes) of the patient and family members was performed on a DNBSEQ-T7 genetic analyzer by the paired-end (PE150) method. Sample preparation was performed by the PCR-free method with enzymatic fragmentation (MGI).

A previously unreported heterozygous variant of uncertain significance was identified in exon 39 of the *COL1A1* gene (chr17:50189527del). This variant led to a frameshift (NM_000088.4: c.2679del, p.(Pro895LeufsTer213)). The identified variant was not present in the control population of the Genome Aggregation Database (gnomAD v3.1.2). Heterozygous variants in the *COL1A1* gene were described in patients with type II OI (OMIM: 166210), Caffey disease (OMIM: 114000), Ehlers – Danlos syndrome, type 1 arthrochalasia (OMIM: 130060), type I OI (OMIM: 166200), {Bone mineral density variation QTL, osteoporosis} (OMIM: 166710), combined OI and Ehlers – Danlos syndrome 1 (OMIM: 619115), type IV OI (OMIM: 166220), and type III OI (OMIM: 259420). The depth of coverage at the variant position was 37x. Based on the totality of this evidence, the variant was classified as likely pathogenic according to the Guidelines for the Interpretation of Human DNA Sequence Data Obtained by Massively Parallel Sequencing (MPS) Methods [13].

The same variant was also identified in a heterozygous state in the proband's younger sister but was not detected in either parent. These findings suggest parental gonadal mosaicism. Investigation of paternal semen samples is currently planned to test for the presence of the identified variant.

## CONCLUSION

The analysis of this clinical case of OI, associated with a novel *COL1A1* variant and suspected gonadal mosaicism, highlights the diagnostic challenges and complexities in genetic counseling for this condition. The identification of a likely pathogenic variant in the proband and his sister, despite the absence of clinical manifestations in the parents, underscores the necessity for comprehensive genetic testing of all family members, including screening for mosaic forms, which are reported in 5–8% of OI cases [9, 10].

The presumption of gonadal mosaicism significantly alters the assessment of reproductive risks. The empirical average recurrence risk for a family with a child affected by an autosomal dominant disease exceeds the general population risk and is estimated at 1–3%. However, in individual cases, the actual risk of disease recurrence is influenced by the proportion of affected gametes, posing significant challenges for genetic counseling [14]. An important aspect is the application of high-coverage next-generation sequencing (NGS) methods to detect low-level mosaicism. Paternal gonadal mosaicism can be identified through molecular genetic analysis of spermatozoa [15]. A distinct challenge remains the detection of maternal gonadal mosaicism due to the inability to routinely study oocytes. For couples with a high risk of gonadal mosaicism (e.g., those with multiple affected children), the use of *in vitro* fertilization with preimplantation genetic testing for monogenic disorders (PGT-M) or invasive prenatal diagnosis are potential options.

This observation emphasizes the importance of developing standardized approaches to diagnosing mosaic forms of OI, including the application of advanced sequencing techniques, and the need to establish patient registries for such cases to better understand the clinical significance of varying levels of mosaicism. The obtained results broaden the understanding of the genetic heterogeneity of OI and highlight the critical role of interdisciplinary collaboration in managing these patients. This is essential for refining diagnostic

algorithms, optimizing therapeutic strategies, and improving the quality of genetic counseling for families with suspected mosaic forms of the disease.

Prospects for future research include investigating the correlation between the level of mosaicism and clinical manifestations, developing new pathogenetic treatments, and refining management protocols for patients with rare forms of OI.

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