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The Radiological Findings in an Infant Suffering from Osteopetrosis Due to a Novel Variant in the *CLCN7* Gene

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Dear Editor,

Osteopetrosis, also known as marble bone disease, is a rare inherited skeletal disorder primarily defined by abnormally increased bone density. Its estimated incidence ranges between 1 in 100,000 and 1 in 500,000 live births.1 Based on the mode of inheritance, the condition is classified into three major types: the benign autosomal dominant osteopetrosis (ADO), the severe autosomal recessive osteopetrosis (ARO), and a less common X-linked variant. ADO is observed in approximately 1 in 20,000 births, while ARO appears in about 1 in 250,000. The autosomal dominant form is typically diagnosed in adulthood and often presents with mild or no symptoms, whereas the recessive infantile form can be life-threatening if not treated promptly[1]. Radiologically, the disease is marked by generalized or localized bone sclerosis, increased bone mass, and a tendency for pathological fractures. Osteopetrosis encompasses a spectrum of clinically and genetically heterogeneous conditions, all linked by a common pathophysiology: impaired bone resorption due to defective osteoclast development or function.

According to the Nosology Group of the International Society of Skeletal Dysplasia, disorders characterized by increased bone density are categorized based on clinical presentation, patterns of inheritance, and their molecular and pathogenic underpinnings[2]. In most cases, the management of osteopetrosis remains supportive, addressing symptoms rather than the root cause. Hematopoietic stem cell transplantation may be considered in selected severe cases, particularly in ARO. However, due to the disease's variable and often non-specific clinical manifestations, misdiagnosis is not uncommon. As a result,

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comprehensive genetic testing and molecular analysis play a crucial role in establishing an accurate diagnosis and may also pave the way for emerging therapeutic approaches, including gene-based interventions[3].

Osteopetrosis results from a disruption in osteoclast differentiation or function, with pathogenic variants in at least 10 genes identified as the underlying cause. These variants account for approximately 80% of cases.1 Genetic variants in the *TCIRG1* and *CLCN7* genes are identified in nearly 70% of ARO individuals. Among these, *CLCN7* variants account for approximately 75% of ADO cases, 10-15% of ARO cases, and are implicated in all currently recognized cases of the intermediate form of the disease. Pathogenic alterations in *CLCN7* impair the osteoclasts' ability to acidify their extracellular environment, thereby hindering effective resorption of the inorganic bone matrix. This functional disruption contributes to the diverse clinical manifestations observed in affected patients[4].

The *CLCN7* gene, part of the CLC gene family in mammals, encodes a chloride channel protein that plays a crucial role in osteoclast function. In osteoclasts, the CLCN7 protein is localized to the membranes involved in the late stages of the endosomal-lysosomal pathway, specifically at the fringe margin, where it contributes to the acidification of resorption lacunae.4 Previous studies elucidated the physiological role of the CLCN7 protein, demonstrating that pathogenic variants in this gene cause severe osteopetrosis in animal models. Accordingly, this protein is regarded as key in the process of acidifying resorption lacunae within the extracellular matrix. The function of these lacunae is to facilitate the process of osteoclast-mediated bone resorption, which is integral to the regulation of bone mass. In summary, the *CLCN7* gene assumes a pivotal role in bone remodeling, and its pathogenic variants are likely to result in fragile, excessively dense bones. In osteopetrosis, increased bone density paradoxically makes fractures more likely, commonly affecting the proximal sections of the femur and tibia[4].

This study reveals an unobserved variant within the *CLCN7* gene in a patient with osteopetrosis and presents evidence for its plausible pathogenicity. A 14-day-old male infant was admitted to our hospital due to respiratory distress and low platelet count. The patient was born at 37 weeks of gestation, weighing 2,780 grams, through a normal spontaneous vaginal delivery during the first pregnancy. Upon examination, it was noted that the patient's lower extremity was immobilized in a plaster cast due to a fracture. Family history revealed consanguinity between the parents. On admission, the patient's general condition was moderately compromised, and a cast was noted on the lower extremity. Physical examination also revealed hepatomegaly and splenomegaly, with both organs palpable 5 cm below the costal margin. Laboratory results showed the following: leukocytes 10,610/mm³, hemoglobin 14.1 g/dL, platelets 45,000/mm³, alanine aminotransferase (SGPT) 40 U/L, aspartate aminotransferase (SGOT) 162 U/L, total bilirubin 1.08 mg/dL, inorganic phosphorus 1.50 mg/dL, direct bilirubin 0.46 mg/dL, glucose 88 mg/dL, albumin 4.3 g/dL, calcium 9.9 mg/dL, sodium 138 mEq/L, uric acid 3.4 mg/dL, urea 11 mg/dL, and alkaline phosphatase 987 U/L. Calcium levels were within normal limits, while phosphorus levels were low. Both alkaline phosphatase and parathyroid hormone levels were elevated. Vitamin D levels were low, and radiographs confirmed the diagnosis of osteopetrosis and rickets. Vitamin D supplementation was initiated, and subsequent radiologic imaging revealed enlargement of the distal metaphyses of the ulna and radius on hand and wrist radiographs (**Figure 1A**).

Coronal temporal computed tomography (CT) showed decreased aeration in the mastoid portions of the bilateral temporal bones and sclerosis in the bony structures of the inner ear (**Figure 1B**). The axial CT section showed sclerosis and cortical thickening in the bilateral orbital bones, the sphenoid bone, and the bones forming the maxillary sinus (**Figure 1C**). Within 15 days, the homozygous NM_001287.6: c.957G>A p.Trp319Ter variant was discovered in the *CLCN7* gene

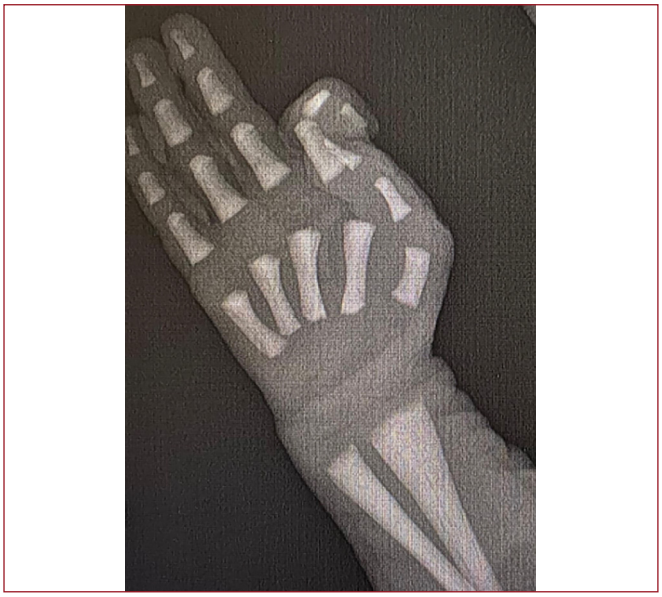

Figure 1A. Widened distal ulna and radius on X-ray due to vitamin D deficiency

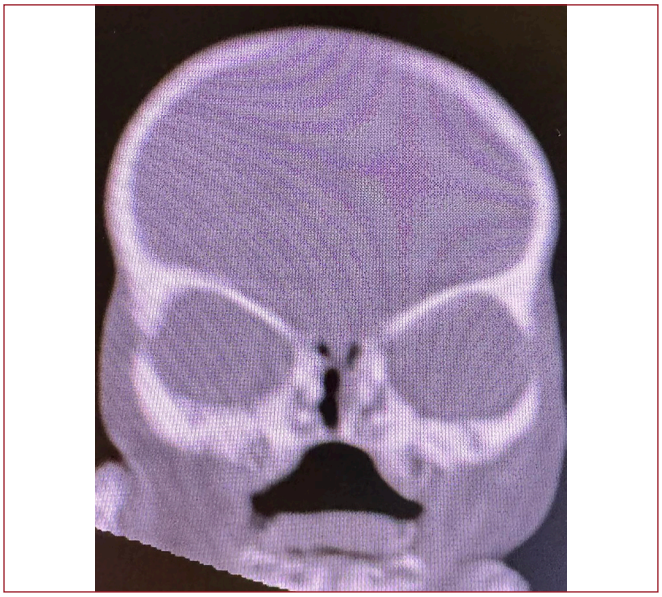

Figure 1B. Coronal CT shows bilateral mastoid hypoaeration and inner ear bony sclerosis

CT: Computed tomography

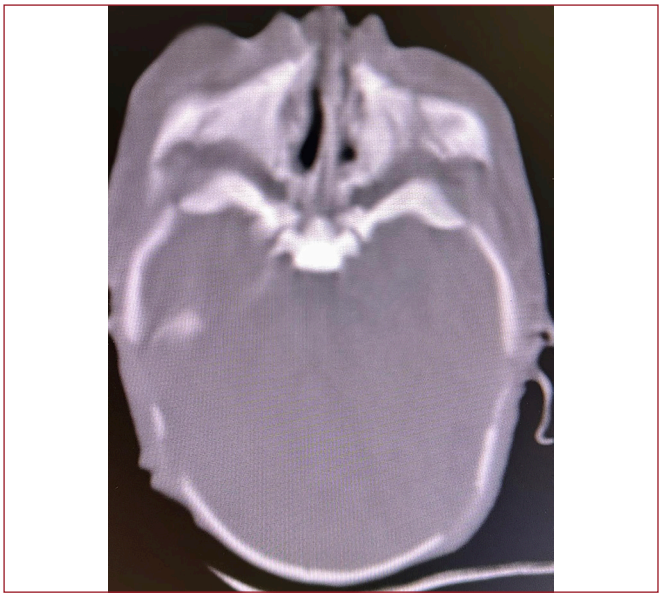

Figure 1C. Axial CT demonstrates cortical thickening and sclerosis of the orbital walls, sphenoid, and maxillary sinus bones
CT: Computed tomography

by rapid whole-exome sequencing. This nonsense variant, previously unreported in both the literature and healthy population databases (gnomAD aggregated allele frequency: not available), was classified as likely pathogenic according to American College of Medical Genetics and Genomics (ACMG) criteria because it is a rare (PM2) truncating variant expected to result in nonsense-mediated decay of the mRNA produced by the *CLCN7* gene (PVS1)[5]. The results were confirmed by targeted variant analysis based on next-generation sequencing, and the variant was found to be heterozygous in both parents. The patient and his family were informed, and an urgent bone marrow transplant was scheduled.

CLCN7-related osteopetrosis is inherited in an autosomal recessive or autosomal dominant manner[6]. As previously mentioned, ARO-as seen in our patient-has an early onset and a malignant course. Additionally, *CLCN7*-related ARO is typically caused by biallelic loss-of-function variants in the gene. Although the identified homozygous nonsense variant has not been previously reported in the literature, its molecular mechanism and consistency with the clinical phenotype support a clear interpretation of its association with ARO.

In this research, we discovered a previously unreported variant in the *CLCN7* gene in a patient with osteopetrosis, suggesting its potential impact. Although various indirect lines of evidence point to the deleterious nature of the newly identified *CLCN7* variant, it has been classified as "likely pathogenic" according to the ACMG guidelines[5]. In conclusion, we have identified a novel likely pathogenic variant in the *CLCN7* gene, explaining its association with ARO through detailed clinical findings.

Footnotes

Author Contributions: Çapkan DÜ: Radiological Practices, Concept, Design, Data Collection or Processing, Literature Search, Analysis or Interpretation, Writing; Demir B: Medical Practices, Concept; Baş H: Genetic Practices, Concept, Literature Search, Writing; Tatlı M: Medical Practices, Concept; Doğan M: Medical Practices, Concept; Ünal E: Medical Practices, Concept, Design, Data Collection or Processing, Literature Search, Analysis or Interpretation, Writing.

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