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AUTOSOMAL DOMINANT OSTEOPETROSIS – IDENTIFICATION OF A NEW MUTATION

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ABSTRACT

Background: Osteopetrosis comprises a group of rare skeletal dysplasias characterized by increased bone density and paradoxical bone fragility. Among its forms, autosomal dominant osteopetrosis (ADO) is most frequently associated with mutations in the *CLCN7* gene, encoding a chloride antiporter essential for osteoclast function. *CLCN7*-related ADO results from impaired osteoclast acidification and decreased bone resorption. Although bone mineral accumulation is characteristic, skeletal fragility and complications such as osteomyelitis and cranial nerve compression may occur.

Case report: We report three related individuals who exhibited increased bone density and pathognomonic radiographic appearances of "bone-within-bone" and "sandwich-vertebrae". Genetic testing identified a novel heterozygous *CLCN7* mutation, confirming the diagnosis of ADO. This family's novel mutation expands the known genotypic spectrum of ADO and underscores the value of genetic testing in adult-onset bone dysplasias with atypical presentation.

Conclusion: This case report highlights the diagnostic importance of recognizing characteristic radiographic patterns and confirming them through molecular analysis, emphasizing the need for multidisciplinary follow-up and appropriate genetic counselling.

KEYWORDS

Osteopetrosis, *CLCN7* mutation, autosomal dominant osteopetrosis, bone-within-bone

LEARNING POINTS

- Characteristic radiographic features such as "bone-within-bone" and "sandwich vertebrae" are highly suggestive of autosomal dominant osteopetrosis.
- *CLCN7* pathogenic variants account for most cases of autosomal dominant osteopetrosis and justify early genetic testing.
- This case highlights a novel *CLCN7* mutation, reinforcing the genetic heterogeneity of osteopetrosis and the value of family screening.

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INTRODUCTION

Osteopetrosis comprises a heterogeneous group of rare skeletal dysplasias characterized by increased bone density and paradoxical bone fragility, most often due to genetic defects affecting osteoclast function[1]. Among the genes implicated, *CLCN7* encodes a chloride antiporter highly expressed in osteoclast membranes, essential for acid secretion during bone resorption[2,3]. Mutations in *CLCN7* give rise to a clinical spectrum ranging from the infantile malignant autosomal recessive form to the more benign autosomal dominant osteopetrosis (ADO, Albers–Schönberg disease)[1,4].

In ADO, defective osteoclastic resorption leads to progressive bone mineral accumulation, producing distinctive radiographic features such as the "bone-within-bone" pattern and "sandwich vertebrae" appearance[5,6]. Despite the increased bone mass, patients are prone to fractures, osteomyelitis, and—less frequently—cranial nerve compression resulting in visual or hearing impairment[1,7].

CLCN7-related ADO is rare, with an estimated prevalence of about 1 in 20,000 individuals and highly variable expressivity, even within families[6,8]. To date, more than 30 pathogenic variants have been described[4]. Here we report three members of the same family presenting with radiographic features pathognomonic of ADO, in whom a novel *CLCN7* mutation was identified.

CASE DESCRIPTION

A previously healthy 29-year-old man was referred to Internal Medicine because of mechanical lower back pain lasting 4 months. He had no fever, dermatological changes, or other systemic symptoms. Family medical history was

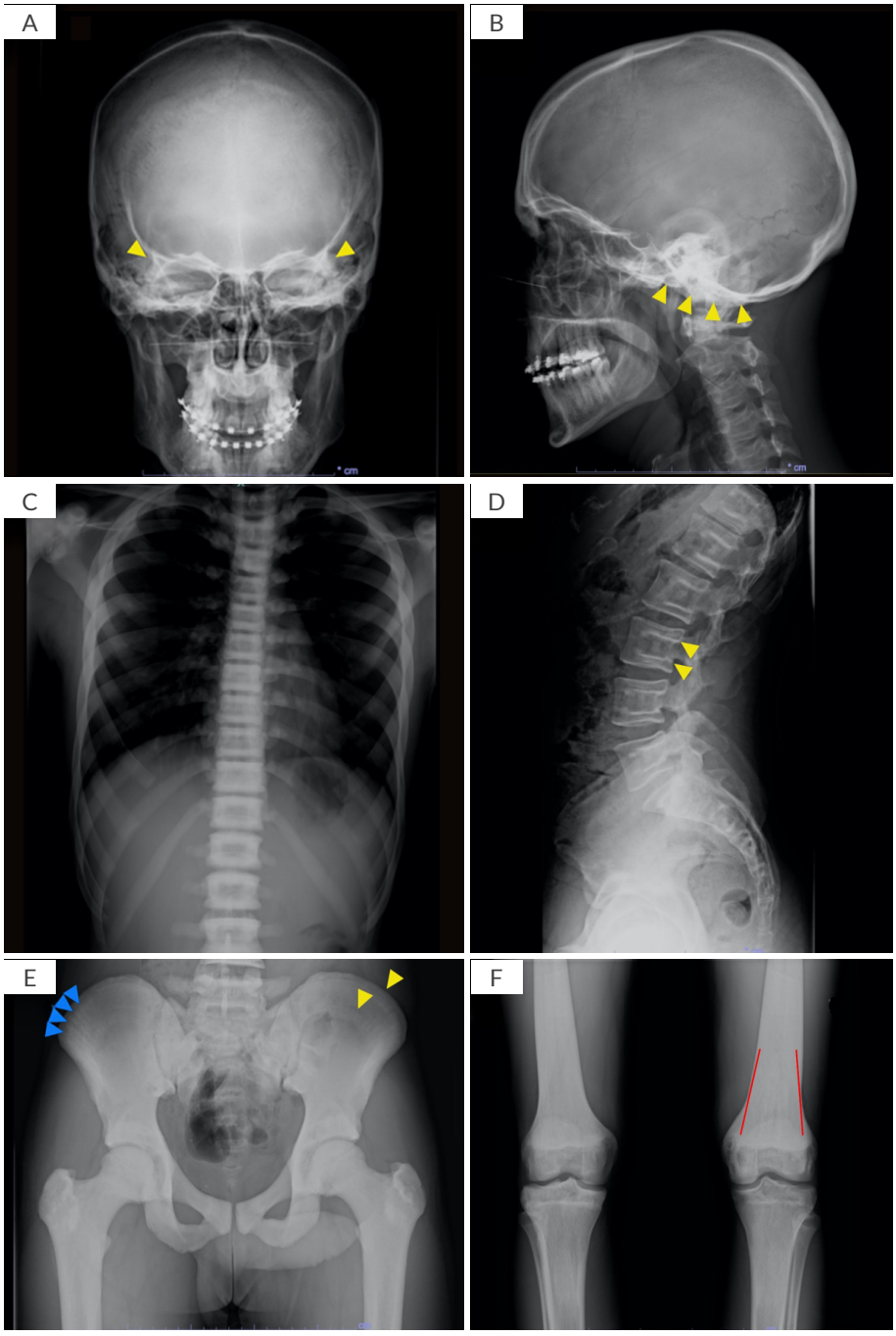


Figure 1. Plain radiographs of our patient showing increased bone density in the superior orbital arcades (A, yellow arrowheads) and in the base of the skull (B, yellow arrowheads), characteristic bone-within-bone images of the vertebral bodies (C), with typical thickening of the endplate of vertebrae (yellow arrowheads) giving it a "sandwich" appearance (D). Bone-within-bone images were also evident in several bones, particularly in the iliac bones (E, yellow arrowheads), and alternating radiolucent and radiodense metaphyseal lines (E, blue arrowheads). Also typical were "Erlenmeyer flask" type deformities of the tubular bones like the femur (F, red lines).

unremarkable. However, the patient's clinical presentation and imaging findings raised suspicion of a hereditary skeletal dysplasia.

Plain radiographs showed characteristic features of ADO, including generalized bone sclerosis, thickened bones, and diffuse increase in bone density, more evident at the skull base and superior orbital arches. Additional findings included "bone-within-bone" images in the tarsal bones, phalanges, vertebral bodies, and iliac bones, as well as endplate thickening of vertebrae producing the typical "sandwich vertebrae" appearance *(Fig. 1)*.

Genetic testing identified a previously undescribed heterozygous mutation in the *CLCN7* gene — [c.2252-11_2260del (p.?)-intron 23], corresponding to a 21-base pair deletion between positions 2252-11 and 2260, predicted to cause skipping of exon 24. This variant, not reported in the literature to date, was considered pathogenic based on its likely structural impact on the encoded chloride antiporter and was classified as causative of ADO.

Recommended surveillance for ADO includes complete blood count monitoring for cytopenias, annual ophthalmologic and audiologic evaluations, and biannual dental assessments. Our patient had normal hematologic, ophthalmologic, audiologic, and dental findings. Serum calcium and parathyroid hormone levels were within normal range.

There is currently no disease-specific therapy for ADO; management is mainly symptomatic. Fractures may heal poorly because of decreased bone vascularity, and surgical procedures carry a high risk of implant failure, refracture, defective remodelling, and osteomyelitis. Orthopaedic surgery should therefore be reserved for unavoidable indications. In severe cases, bone marrow failure can lead to anaemia and transfusion dependence.

In our patient, only pain management was required since no major complications were present. As the proportion of *CLCN7*-related osteopetrosis caused by de novo variants are unknown, parental evaluation is recommended in apparently sporadic cases[4]. Molecular testing of the patient's mother and cousin revealed the same mutation, and both showed characteristic radiographic findings consistent with ADO *(Fig. 2)*. All affected individuals were advised to avoid activities with a high risk of fracture. None had experienced fractures or functional limitations at the time of reporting. The two younger patients received genetic counselling regarding the 50% inheritance risk. Among the younger family member tested to date, no carriers of the mutation have been identified.

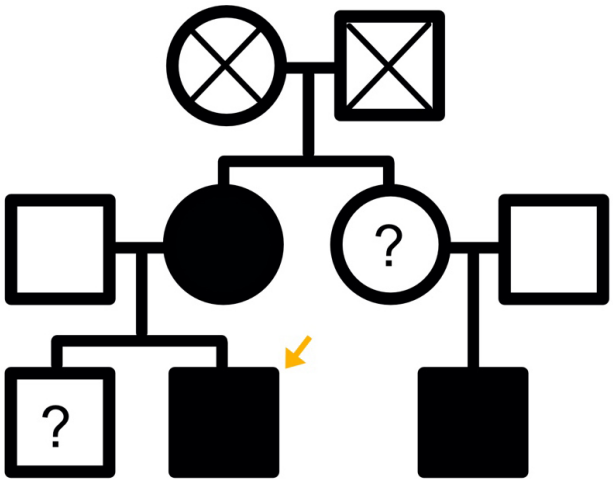


Figure 2. Genogram showing our patient (yellow arrow), and his family members, some of them affected with the mutation (black), namely his mother and cousin. His young brother has history of at least two fractures of different bones of the foot, but no genetic testing yet. His aunt is asymptomatic and also was not tested for the mutation. Both his grandparents have already passed away.

DISCUSSION

Traditionally, the diagnosis of osteopetrosis relied on radiographic features alone, but advances in molecular genetics have greatly improved the accuracy of disease classification and subtype identification. Autosomal dominant osteopetrosis (ADO) results from defective osteoclastic function, most frequently due to missense mutations in *CLCN7*, which account for approximately 70% of cases[4]. The absence of *CLCN7* variants in the remaining patients suggests that additional genes contribute to the pathogenesis of ADO. Furthermore, about one third of individuals carrying a *CLCN7* mutation show no clinical or radiographic evidence of disease, reflecting incomplete penetrance[4]. Once a familial *CLCN7* pathogenic variant is identified, prenatal and preimplantation genetic testing become feasible options for at-risk families.

Recent reviews have highlighted the considerable clinical variability of ADO and the absence of disease-modifying therapies[9]. The management of adults with ADO should ideally involve a multidisciplinary team including internists, orthopaedic surgeons, dentists, haematologists, and genetic counsellors. As no specific or curative therapy currently exists, treatment remains supportive and focused on preventing and managing complications[1,4]. Further research is needed to define evidence-based management strategies and to assess novel therapeutic approaches such as allele-specific gene silencing.

Our patient presented only with mechanical lower back pain, consistent with previous reports describing chronic bone pain in up to 86% of ADO cases[10]. The aetiology of this pain remains uncertain; proposed mechanisms include trabecular microfractures due to abnormal bone matrix, impaired vascularization, and possible dysregulation of peripheral nociceptive pathways[6].

The identification of a novel *CLCN7* mutation in this family expands the known genotypic spectrum of ADO and highlights the diagnostic value of integrating radiological findings with molecular testing. All three affected individuals exhibited classic radiographic features of ADO without fractures or other complications at present.

We describe a novel *CLCN7* mutation responsible for autosomal dominant osteopetrosis in three related

individuals. The findings reinforce the diagnostic importance of recognizing characteristic radiographic patterns and confirming them through molecular analysis. Early identification allows appropriate monitoring, family screening, and genetic counselling, even in asymptomatic carriers.

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