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**Autosomal dominant osteopetrosis type II resulting from a *de novo* mutation in the *CLCN7* gene: A case report**

Song XL *et al.* *CLCN7* mutation in osteopetrosis

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**Abstract**

**BACKGROUND**

Osteopetrosis is a family of extremely rare diseases caused by failure of osteoclasts and impaired bone resorption. Among them, autosomal dominant osteopetrosis type II (ADO II), related to the chloride channel 7 (*CLCN7*) gene, is the most frequent form of osteopetrosis. In this study, we report a *de novo* mutation of *CLCN7* in a patient without the family history of ADO II.

**CASE SUMMARY**

A 5-year-old Chinese boy with ADO II was found to have a *de novo* mutation in the *CLCN7* gene [c.746C>T (p.P249L)]. Typical clinical manifestations, including thickening of the cortex of spinal bones and long bones, non-traumatic fracture of the femoral neck, and femoral head necrosis, were found in this patient. The patient is the first reported case of ADO II with the missense mutation c.746C>T (p.P249L) of the *CLCN7* gene reported in China. We also review the available literature on ADO II-related *CLCN7* mutations, including baseline patient clinical features, special clinical significance, and common mutations.

## CONCLUSION

Our report will enrich the understanding of mutations in ADO II patients. The possibility of a *de novo* mutation should be considered in individuals who have no family history of osteopetrosis.

**Key Words:** Osteopetrosis; Chloride channel 7 gene; Autosomal dominant osteopetrosis type II ; Whole exome sequencing; Case report

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**Core Tip:** Osteopetrosis is a family of extremely rare diseases caused by failure of osteoclast and impaired bone resorption. The 5-year-old Chinese boy presented here is the first reported case of autosomal dominant osteopetrosis type II (ADO II) with the missense mutation c.746C>T (p.P249L) of the chloride channel 7 (*CLCN7*) gene in China. *CLCN7* mutations can be due to *de novo* variants or due to inherited variants. The possibility of a *de novo* mutation should be considered in individuals who have no osteopetrosis family history. Our study systematically reviews the mutations of *CLCN7* in ADO II, thus expanding the thoughts of diagnosis and treatment of osteopetrosis.

## INTRODUCTION

Osteopetrosis, a genetic disorder caused by osteoclast failure, is an extremely rare bone disease with an incidence of 1 in 250000 births<sup>[1,2]</sup>. According to the classification of the Nosology Group of the International Skeletal Dysplasia Society, osteopetrosis is divided into various types by their inheritance pattern and characteristics with various clinical features<sup>[3]</sup>. Among them, autosomal dominant osteopetrosis type II (ADO II) caused by mutations of the chloride channel 7 (*CLCN7*) gene, also called Albers-Schönberg

disease, is considered the most heterogeneous and frequent form of osteopetrosis<sup>[2,4]</sup>. Despite most ADO patients having no symptoms, the increased density of bones may be discovered by coincidental radiographic examination for other reasons, such as fracture<sup>[5]</sup>. The major clinical features of this type of osteopetrosis include non-traumatic fractures, especially in long bones, abnormal side-to-side curvature of the spine, and osteomyelitis in late childhood or adolescence<sup>[6]</sup>.

Here we report a 5-year-old Chinese boy with ADO II who was found to have a *de novo* mutation in the *CLCN7* gene [c.746C>T (p.P249L)]. The patient showed typical clinical manifestations including a thickened cortex of spinal bones and long bones, non-traumatic fracture of the femoral neck, and femoral head necrosis. We also performed a comprehensive literature review to systematically review the *CLCN7* gene mutation features of ADO II.

## **CASE PRESENTATION**

### ***Chief complaints***

A 5-year-old boy complained of painless claudication for 1 mo.

### ***History of present illness***

The patient started to experience painless claudication without any trauma about 1 mo prior to attending our clinic. He had no symptoms of fever, nausea, or vomiting.

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### ***History of past illness***

The patient had no history of hormone treatment or any chronic disease, such as hepatitis, diabetes, or hypertension. His parents had no history of bone fractures or other special family histories.

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### ***Personal and family history***

The patient had no special personal and family history.

### ***Physical examination***

The joint activity of the right hip was limited, especially rotating action. The length of the two lower limbs was equal. In addition, the liver was slightly enlarged, extending 4.0 cm below the right costal margin. Spleen size was normal. On neurological examination, no specific findings were noted.

### ***Laboratory examinations***

There was no remarkable abnormality in serum biochemistry, other than elevated concentrations of creatine kinase, lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) (Supplementary Table 1).

### ***Imaging examinations***

<sup>1</sup> X-rays in a local clinic revealed a generalized increase in bone density. Pelvis X-rays, computed tomography, and magnetic resonance imaging scans revealed that thickening of the cortex and narrowing of the medullary cavity were found in the pelvis and bilateral femora, consistent with osteopetrosis. In addition, suspected bilateral femoral head necrosis and an old fracture of the right femoral neck were also found (Figure 1A-C). A chest X-ray showed increased bone density in the thoracic vertebrae, lumbar vertebrae, bilateral ribs, and bilateral humeri, with no obvious abnormalities in the lungs, heart, or septum (Figure 1D).

### **<sup>9</sup> FINAL DIAGNOSIS**

The final diagnosis of the presented case was ADO II.

### **TREATMENT**

After admission, the patient was treated by percutaneous traction and fixation of both lower limbs for 1 mo, and then discharged from our hospital.

### **OUTCOME AND FOLLOW-UP**

No significant change was found in the pelvic X-ray at 1 mo after discharge. At the 2-year follow-up, a pelvic X-ray showed that the patient had recovered from a fracture of the right femoral neck, but widespread sclerosis of the right femur, thickened cortex, narrowed medullary cavity, and short femoral neck were still present, consistent with osteopetrosis (Figure 1G). Further follow-up is needed for a long-term prognosis.

## **DISCUSSION**

Osteopetrosis is a disorder with symptoms including failure of osteoclasts and impaired bone resorption. The disorder is caused by mutations in at least 10 genes in humans<sup>[1,7]</sup>. The patient described in this report is the first case of ADO II with the missense mutation c.746C>T (p.P249L) of the *CLCN7* gene reported in China. The genotype of the parents was wild-type, indicating that a *de novo* mutation was highly likely to affect protein function in this 5-year-old boy. The *CLCN7* gene encodes chloride channel 7 (CLC-7), which plays a central role in the normal function of osteoclasts, and takes part in bone remodeling to ensure strong and healthy bones<sup>[8]</sup>. Mutations in the *CLCN7* gene lead to the abnormal function of osteoclast-mediated extracellular acidification and disturb dissolution of the bone inorganic matrix, thus resulting in ADO II<sup>[1,9]</sup>. Among them, more than 70 different mutations in *CLCN7* have been reported to be associated with ADO II<sup>[10]</sup>.

*CLCN7* is also regarded as the genetic basis of ADO II<sup>[1]</sup>. The symptoms and signs of osteopetrosis range widely in severity. In addition to the manifestations of ADO II, the boy reported in our study showed increased bone density, pathological fractures of bilateral femora, and modeling defects at the metaphyses, but no symptoms of osteomyelitis, diffuse or focal sclerosis, or dental abnormalities (including tooth eruption defects and dental caries). Besides, there was no hematological failure or cranial nerve compression in this boy.

We also conducted a literature search of PubMed, MedlinePlus, Embase, and Ovid databases from January 2004 to February 2021 using the following search terms: “*CLCN7* gene” and “osteopetrosis” and “autosomal dominant osteopetrosis type II”

without language restrictions. Finally, 21 published studies were identified as meeting the search criteria (Supplementary Figure 1). A summary of previous reported cases of ADO II patients as well as our case is provided in Table 1. In addition, several series of family studies are included<sup>[11-24]</sup>. Based on our summary of the literature, we found more female patients (53% of total) than males. There have been increasingly more studies on the gene mutations in ADO II since the year 2012. To date, nearly 40 mutations in *CLCN7* have been identified linked to ADO II. As the gene expression profiles and characteristics of mutations are related to ethnic background, there have been more reports of *CLCN7* mutations causing cases of ADO II in the Asian population than in Western countries over the last decades. These results help provide some clue to the analysis of the phenotype-genotype relationship.

Another reported *de novo* mutation, c.2144A>G (p.Tyr715Cys) change in *CLCN7*, appeared to be a gain-of-function variant<sup>[25]</sup>. In that case, both patients manifested developmental delay, organomegaly, and hypopigmentation resulting from lysosomal hyperacidity, abnormal storage, and enlarged intracellular vacuoles, but the patients were osteopetrosis-free. Functional study showed that p.Tyr715Cys was a gain-of-function *CLCN7* variant. In our case, the patient manifested osteopetrosis which indicated the inactivating effect of the c.746C>T (p.P249L). However, further study is still needed to prove the loss-of-function mechanism caused by the mutation.

Due to the low incidence of osteopetrosis, it is often overlooked in daily clinical diagnosis. Most ADO II patients are diagnosed based on the typical clinical manifestations and presence of special radiological appearance, including thickening of the cortex and narrowing of the medullary cavity of vertebrae, ribs, and humerus<sup>[1,5,26]</sup>, especially the presence of “sandwich vertebrae” and the “bone-within-bone” appearance of the iliac spine<sup>[26]</sup>. Almost 80% of osteopetrosis patients experience fractures, while 30% have hip osteoarthritis. However, ADO II patients might attend hospital just because of low back pain without any familial penetrance of the disease. Some special characteristics have been reported previously, including severe anemia, mild malocclusion with hypodontia, enamel dysplasia, right femur osteomyelitis,



proximal renal tubular acidosis, renal stones, epilepsy, and blindness<sup>[18]</sup>. Biochemical markers have been considered for the diagnosis of osteopetroses, such as elevated creatine kinase MB isoenzyme (CK-MB), LDH, and AST<sup>[27,28]</sup>. However, considering the genetic heterogeneity of ADO II, next-generation sequencing (NGS) technology should be preferred during diagnostic examination.

By now, genetic testing has become widely used in the screening, diagnosis, and prognosis prediction of various diseases. In combination with clinical information, high-throughput DNA analysis according to whole-exome sequencing using NGS methods have been used to identify Mendelian disorders related to diseases and even to guide drug therapy<sup>[29]</sup>. In this case, even without the family history of ADO II, the possibility of a *de novo* mutation in the *CLCN7* gene and subsequent ADO II cannot be ruled out. In addition to the conventional neurological, imaging, and biochemical examinations, whole-exome sequencing is critical for final diagnosis.

## **CONCLUSION**

In summary, we describe the case of a 5-year-old Chinese boy with ADO II with a *de novo* mutation in the *CLCN7* gene [c.746C>T (p.P249L)] and review the literature of *CLCN7* gene related osteopetrosis cases reported before. To our knowledge, this is the first study that systematically reviews the mutations of *CLCN7* in ADO II, which not only enriches the understanding of the pathogenesis of osteopetrosis but also expands the ideas on its diagnosis and treatment.



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| <b>2</b> | Elena-Raluca Nicoli, Mary R. Weston, Mary Hackbarth, Alissa Becerril et al. "Lysosomal Storage and Albinism Due to Effects of a De Novo CLCN7 Variant on Lysosomal Acidification", The American Journal of Human Genetics, 2019<br><small>Crossref</small>   | 17 words — 1% |
| <hr/>    |  |               |
| <b>3</b> | Yang Xue, Weiguang Wang, Tianqiu Mao, Xiaohong Duan. "Report of two Chinese patients suffering from CLCN7-related osteopetrosis and root dysplasia", Journal of Cranio-Maxillofacial Surgery, 2012<br><small>Crossref</small>  | 17 words — 1% |
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| <b>6</b> | Hiroshi Kajiya. "Characteristics of ClC7 Cl <sup>-</sup> channels and their inhibition in mutant (G215R) associated with autosomal dominant osteopetrosis type II in native osteoclasts and hClcn7 gene-expressing cells", Pflügers Archiv - European Journal of Physiology, 06/19/2009<br><small>Crossref</small> | 11 words — 1% |
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7 Ming-Liang Sui, Chang-Jiang Wu, Ya-Di Yang, Da-Mei Xia, Tian-Jie Xu, Wei-Bing Tang. "Extensive myocardial calcification in critically ill patients receiving extracorporeal membrane oxygenation: A case report", World Journal of Clinical Cases, 2022 11 words — 1%

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8 Del Fattore, A.. "Genetics, pathogenesis and complications of osteopetrosis", Bone, 200801 10 words — 1%

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9 Yi Zhao, Xiao-Qiang Xue, Di Xia, Wei-Feng Xu, Guang-Hua Liu, Yi Xie, Zhi-Gang Ji. "Pneumothorax during retroperitoneal laparoscopic partial nephrectomy in a lupus nephritis patient: A case report", World Journal of Clinical Cases, 2022 10 words — 1%

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