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ABOUT COVER

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CASE REPORT

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

Xiu-Li Song, Li-Yuan Peng, Dao-Wen Wang, Hong Wang

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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

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.

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INTRODUCTION

Osteopetrosis, a genetic disorder caused by osteoclast failure, is an extremely rare bone disease with an incidence of 1 in 250000 births[1,2]. 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[3]. 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[2,4]. 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[5]. 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[6].

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.

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.

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

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).

FINAL DIAGNOSIS

The final diagnosis of the presented case was ADO II (Figure 1E and F).

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[1,7]. 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[8]. 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[1,9]. Among them, more than 70 different mutations in *CLCN7* have been reported to be associated with ADO II[10].

CLCN7 is also regarded as the genetic basis of ADO II[1]. 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[11-24]. 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[25]. In that case, both patients manifested developmental delay, organomegaly, and hypopigmentation resulting from lysosomal hyperacidity, abnormal storage, and enlarged

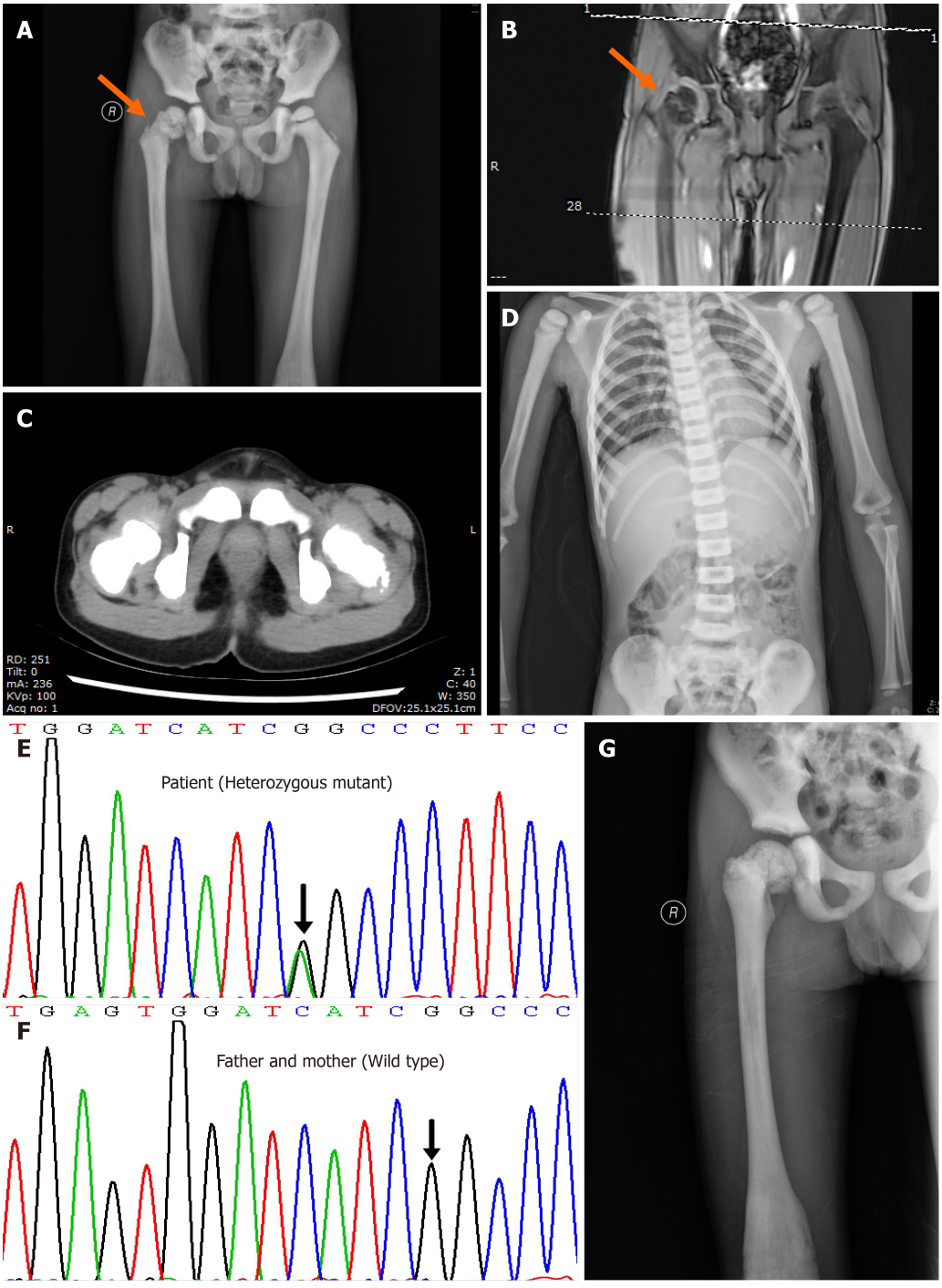

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Figure 1 Diagnostic process. A-C: Pelvis X-ray (A), magnetic resonance imaging (B), and computed tomography (C) showed thickening of the cortex and narrowing of the medullary cavity in the pelvis and bilateral femurs. The neck of the right femoral head was irregular in shape and showed some free small bone shadow, suggesting the possibility of right femoral head and neck fracture (orange arrows); D and G: X-rays of the chest and right femur showed extensive bone density in the thoracic vertebrae, lumbar vertebrae, bilateral ribs, and bilateral humerus. There were no obvious abnormalities in the lungs, heart, or septum; E and F: Sanger sequencing to verify the heterozygous mutation of the *CLCN7* gene (c.746C>T)

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[1,5,26], especially the presence of "sandwich vertebrae" and the "bone-within-bone" appearance of the iliac spine[26]. Almost 80% of osteopetrosis patients experience fractures, while 30%

Table 1 Characteristics of osteopetrosis patients with chloride channel 7 mutation from reported cases

Ref.	Year	Country	Sex	Age (yr)	SNP property	Function change	Nucleotide change	Symptoms
Letizia *et al*[11]	2004	Italy	M	16	Exon 25 missense	A262D (p.Ala262Asp)	788 C>A	Lumbar spine and pelvis pain; right ear deafness
Zhang *et al*[12]	2009	China	F	32	Exon 24 nonsense	R767W (p.Arg767Trp)	2337C>T	Back pain
			M	17	Exon 25 frameshift	E798 FS (p.Glu798FS)	60_61–/G	Back pain
Xue *et al* [13]	2012	China	M	28	Exon16 missense	P470 L (p.Pro470Leu)	1409 C>T	Recurrent swelling in the right face; fractures of the legs; unerupted teeth with root dysplasia
			M	38	Exon 10 missense	R286 W (p.Arg286Trp)	856C>T	Osteomyelitis; nonunion of a femur fracture; unerupted teeth with root dysplasia
Rashid *et al*[14]	2013	Iraqi-Kurdish	F	12	Exon 15 missense	R409 W (p.Arg409Trp)	1225C>T	Anemia; diffuse cutaneous ecchymosis with gum bleeding; recurrent epistaxis; chest infections; right-sided conductive deafness; back pain
			M	16	Exon 15 nonsense	R409W (p.Arg409Trp)	c.1225C>T	Decline in visual acuity
Zheng *et al*[15]	2014	China	M	51	Exon 7 missense	G215 R (p.Gly215Arg)	643 G>A	Femur fracture
			M	12	Exon 10 missense	A299V (p.Ala299Val)	896C>T	Pain in the left foot
			F	75	Exon 11 missense	W319R (p.Trp319Arg)	955T>A	Clavicle fracture; knee osteoarthritis; anemia
Ozkan *et al*[16]	2015	Turkey	F	46	Na	NA	NA	Back pain
Chen *et al*[17]	2016	China	M	43	Exon 20 missense	P619 L (p.Pro619Leu)	c.1856C>T	Discomfort in lower extremities
Piret *et al*[18]	2016	United Kingdom	F	49	Exon 20 missense	G215 R (p.Gly215Arg)	c.643G>A	Fractures (tibia, ankle)
Zheng *et al*[19]	2016	China	M	5	Exon 4 missense	Tyr99 Cys (p.Y99C)	c.296 A>G	Fracture of the right clavicle
			F	35	Exon 10 missense	V289L (p.Val289Leu)	c.865G>C	NA
			F	8-month-old	Exon 17 missense	A542V (p.Ala542Val)	c.1625C>T	Flexion and abduction of the left hip was restricted
			F	27	Exon 24 nonsense	R767W (p.Arg767Trp)	c.2299C>T	Neck discomfort
Zhang *et al*[20]	2017	China	M	2	Exon 9 missense	G240E (p.Gly240Glu)	c.791G>A	Completely blind in his right eye
			F	5	Exon 11 missense	F318S (p.Phe318Ser)	c.953T>C	Pneumonia
			F	62	Exon 24 nonsense	S753W (p.Ser753Trp)	c.2258C>G	Back pain
Kim *et al*[21]	2018	Korea	F	68	Exon 4 missense	Y99C (p.Tyr99Cys)	c.296A>G	Pain in hip joint; unable to walk independently
Kang *et al*[22]	2019	Korea	M	18	Exon 9 missense	P249 L (p.Pro249Leu)	c.746C>T	Pain in the right shin
Li *et al* [23]	2019	China	F	15	Exon 9 missense	R286W (p.Arg286Trp)	c.856C>T	Back pain
			F	42	Exon 22 missense	Y746D (p.Try746Asp)	c.2236T>G	Anemia
			M	10	Exon 3 missense	Y99C (p.Tyr99Cys)	c.296A>G	Recurrent influenza; fractures in the left tibia
			F	32	Exon 10	E313K	c.937G>A	Blind; fractures; tinnitus; splenomegaly

					missense	(p.Glu313Lys)		
			M	24	Exon 24 missense	G793R (p.Gly793Arg)	c.2377G>C	Discomfort in the abdomen; fractures; cementoma; anemia; thrombocytopenia
			F	37	Exon 16 missense; Exon 7 insertion	P470L (p.Pro470Leu); p.Lys217X	c.1409C>T; c.647_648 dupTG	Growth retardation; cysts; recurrent infections of the right knee joint; arthralgia, ankylosis, deformity of the right knee with claudication; amblyopia of the left eye; amblyacousia of the left ear, dental problems, fracture, anemia
Peng *et al*[24]	2020	China	F	22	Intron 1 missense	M560V (p.Met560Val)	c.1678A > G	Bone pain; fracture in the hip

SNP: Single nucleotide polymorphism; M: Male; F: Female; NA: Not available.

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[18]. Biochemical markers have been considered for the diagnosis of osteopetroses, such as elevated creatine kinase MB isoenzyme (CK-MB), LDH, and AST[27,28]. 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[29]. 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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FOOTNOTES

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