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CASE REPORT

Homozygous deletion, c. 1114-1116del, in exon 8 of the *CRPPA* gene causes congenital muscular dystrophy in Chinese family: A case report

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Abstract

BACKGROUND

Congenital muscular dystrophy (CMD) is a clinically and genetically heterogeneous group of inherited muscle disorders. Mutations in the *CRPPA* gene (encoding CDPLribitol pyrophosphorylase A) are recognized as causative factors of dystroglycanopathies, a subtype of CMD with defects in glycosylation.

CASE SUMMARY

The present study examined a Chinese family, whose proband presented mainly with muscle weakness in both lower limbs but without brain and eye symptoms. In this family, a homozygous deletion, c. 1114-1116del (p.V372del), was identified in exon 8 of *CRPPA* in the proband, while a heterozygous deletion was identified in the proband's father and mother, who lacked symptoms. A mild dystroglycanopathy of CMD was diagnosed.

CONCLUSION

The findings of this study expanded the clinical and mutational spectrum of patients with CMD associated with *CRPPA* mutations.

Key Words: Congenital muscular dystrophy; *CRPPA*; Mutation; Dystroglycanopathy; Case report

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Core Tip: A homozygous deletion, c. 1114-1116del (p.V372del), was identified in the exon 8 of the *CRPPA* gene in a Chinese family, which was diagnosed as congenital muscular dystrophy. Mutations in the *CRPPA* gene are recognized as causative factors of dystroglycanopathies, a subtype of congenital muscular dystrophy with defects in glycosylation. Findings in this study expanded the clinical and mutational spectrum of congenital muscular dystrophy patients with the *CRPPA* gene.

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INTRODUCTION

Congenital muscular dystrophy (CMD) is a clinically and genetically heterogeneous group of inherited muscle disorders, with muscle weakness often apparent at birth or in infancy. CMD is subtyped mainly by the causative pathogenic variants of multiple genes[1]. Currently, there are no complete or satisfactory classification systems. Classification by phenotype has shortcomings because the same phenotype can be caused by pathogenic variants in different genes, while one gene can result in a spectrum of clinical phenotypes. CMD is often subtyped according to the gene and its encoded protein in which the pathogenic variants occur, for example, defects in structural proteins (Laminin alpha-2 deficiency; collagen VI-deficient CMD), defects in glycosylation (dystroglycanopathies), defects of endoplasmic reticulum proteins (*SEPN1*-related CMD), and defects of nuclear envelope proteins (*LMNA*-related CMD) [2,3]. More than 19 gene mutations in *POMT1*, *LARGE1*, *POMT2*, *FKRP*, *POMGNT1*, *FKTN*, and Isoprenoid synthase domain-containing (*ISPD*, also called *CRPPA*) genes have been identified in dystroglycanopathies[4,5].

The *CRPPA* gene encodes CDP-L-ribitol pyrophosphorylase A, a protein involved in glycosylation. CRPPA helps to produce ribitol 5-phosphate, which is an important component of α-dystroglycan. The α-dystroglycan protein helps to anchor the cytoskeleton to the lattice of proteins and other molecules in the extracellular matrix. In skeletal muscles, glycosylated α-dystroglycan helps to stabilize and protect muscle fibers[6]. *CRPPA* mutations can cause deficiency of functional α-dystroglycan and damaged muscle fibers, which affects the development, structure, and function of skeletal muscles[7]. Besides causing dystroglycanopathies, *CRPPA* mutations have been identified in Walker–Warburg syndrome, muscle-eye-brain disease, and limbgirdle muscular dystrophy[5,8].

Most of the reported CMDs are inherited in an autosomal recessive manner and often affect one individual in non-consanguineous, small families. In contrast, most individuals with *LMNA*-related CMD and collagen VI-deficient CMD have a de novo pathogenic variant following an autosomal dominant manner. In the present study, we examined a family with CMD inherited in an autosomal recessive manner and identified a deletion, c. 1114-1116del, in the *CRPPA* gene as the cause.

CASE PRESENTATION

Chief complaints

A 26-year-old male presented with a 20-year history of elevated creatine kinase levels, and he had been diagnosed with fatigue in both lower limbs 4 years ago.

History of present illness

The patient visited the local hospital due to poor performance in his physical education class and was found to have an increase in creatine kinase levels (12270 U/L) 20 years ago when he was 6-years-old). At that time, there were no obvious symptoms of physical weakness in ordinary life, only the poor performance in physical education. No deletion of the *DMD* gene (encoding dystrophin) was detected

using 25 pairs of primers. The patient accepted treatment with Chinese herbal medicine; however, the level of creatine kinase did not decrease significantly. Four years ago (at 22-years-old), the patient began to experience weakness in both lower extremities, manifested as strenuous standing up from a squatting position and strenuous stepping up the stairs, which gradually worsened to the point that standing up from squatting required hand support on the knees.

History of past illness

The patient was healthy before.

Personal and family history

The patient denied consanguineous marriage and any special medical history and personal history. The parents had no symptoms of muscle weakness and had a normal creatine kinase level.

Physical examination

Physical examinations showed a 4/5 muscle strength when lying down while holding the head up; 5/5 muscle strength for the double upper extremity deltoid muscles, triceps, flexor and extensor carpal muscles, and short flexor extensor; 4/5 muscle strength for the biceps; 3/5 muscle strength for the double lower limb iliac muscles, gluteus maximus, and quadriceps; 1/5 muscle strength for the thigh adductor; 4/5 muscle strength for the gluteal middle muscle and hamstring muscle; and 5/5 muscle strength for tibialis anterior muscle and gastrocnemius muscle. The muscle tone was normal, and the upper tendon reflex and ankle reflex were normal. However, there was no reflex of both knees. Bilateral Babinski sign was negative.

Laboratory examinations

Enzyme tests showed creatine kinase of 11082 U/L and creatine kinase myocardial band of 126 U/L.

Imaging examinations

A routine electrocardiogram showed sinus arrhythmia and left ventricular high voltage. Pulmonary function test showed nonspecific ventilation dysfunction. Chest computed tomography showed left interlobar pleura and local pleura nodular thickening, suggesting an inflammation. Heart Doppler ultrasound and liver, gallbladder, pancreas, spleen, and urinary tract ultrasound showed no obvious abnormalities. Neuromyography showed no obvious abnormalities in motor nerve and sensory nerve conduction velocity. Quantitative electromyography measurement showed some myogenic changes in the right medial femoral muscle, gastrocnemius muscle, and tibialis anterior muscle. Magnetic resonance imaging of the right calf showed that the gastrocnemius muscle and soleus muscle were experiencing atrophy to different degrees, mainly in the medial head of the gastrocnemius muscle (Figure 1).

Mutation analysis

The proband and his parents were enrolled after providing informed written consent. Genomic DNA was extracted from white blood cells using a Genomic DNA extraction kit (Qiagen, Hilden, Germany). All exons of the *CRPPA* gene were sequenced using whole exome sequencing (Yulong Biomedical Group, Shanghai, China).

A homozygous deletion, c. 1114-1116del (p.V372del), was identified in exon 8 of the *CRPPA* gene (NM_001101426.3) in the proband (Figure 2B), while a heterozygous deletion was identified in the proband's father and mother (Figure 2C and 2D). This variant was not included in the 1000 Genomes Project database or the ESP6500 data set of the National Heart, Lung, and Blood Institute exome sequencing project.

FINAL DIAGNOSIS

A mild dystroglycanopathy of CMD was diagnosed.

TREATMENT

The patient was treated with vitamin B2 (5 mg three times a day) and coenzyme Q10 (10 mg three times a day).

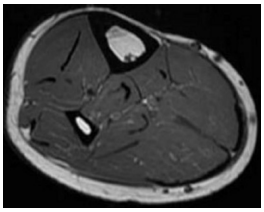

Figure 1 Magnetic resonance imaging of the right calf. The gastrocnemius muscle and soleus muscle showed mild atrophy, mainly in the medial head of the gastrocnemius muscle.

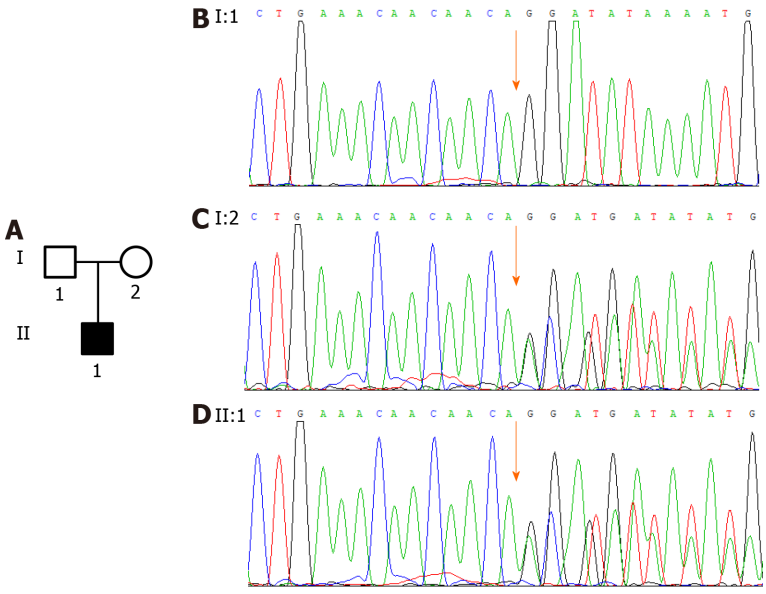

Figure 2 Congenital muscular dystrophy family. A: A pedigree with the *CRPPA* variant; B: The variant identified in the proband's father; C: The variant identified in the proband's mother; D: The variant identified in the proband. Arrows mean the site of the variant.

OUTCOME AND FOLLOW-UP

During a follow-up period of 3 mo, the symptoms remained the same.

DISCUSSION

The pedigree presented in this study suggested a recessively inherited muscle disorder with progressive muscle weakness. Although there were no obvious symptoms of physical weakness in ordinary life in the proband at 6-years-old, his creatine kinase level was elevated and his performance in physical education was poor. This suggested mild muscle damage. Thus, the proband was diagnosed with congenital muscular dystrophy.

Muscular dystrophy is a disorder often caused by mutations in genes involved in muscle structure and function, which leads to muscle weakness and progressive disability[9]. Patients with muscular dystrophy often have an elevated level of creatine kinase caused by muscle damage[10]. Mostly, muscular dystrophy runs in families and can be a recessive, dominant, or X-linked inherited disorder[9]. In this study, gene mutation detection found a homozygous mutation, c. 1114-1116del, in *CRPPA* in the proband; however, his mother and father have a heterozygous deletion. The heterozygous mutation did not cause obvious muscle weakness in the patient's parents, suggesting that only the homozygous mutation is pathogenic. We therefore propose that CMD caused by mutation of c. 1114-1116del of the *CRPPA* gene operates in a recessively inherited manner in this family.

Dystroglycanopathies are a group of CMDs caused by defects in glycosylation and are extremely variable in phenotypic severity. Severe dystroglycanopathies can result in structural brain, eye, and muscle abnormalities, while less severe forms of the disease group often have an adult onset without brain or eye abnormalities[11]. In this

study, the symptoms of physical weakness occurred in the proband at 22-years-old, and no brain or eye abnormalities were found. This suggested mild dystroglycanopathy. Thus, CMD with c. 1114-1116del in the *CRPPA* gene progressed slowly. The proband was diagnosed with a mild dystroglycanopathy of CMD.

To date, mutations in 18 genes, including those encoding proteins involved in αdystroglycan glycosylation (*FKTN*, *FKRP*, *ISPD*, and *TMEM5*) have been identified in patients with the dystroglycanopathy subtype of CMD, and all these mutations demonstrate autosomal recessive inheritance[12]. The *CRPPA* gene has over ten other names, including ISPD[5]. *ISPD* mutations were identified in several dystroglycanopathy variants including CMD, Walker–Warburg syndrome, limbgirdle muscular dystrophy, and cobblestone lissencephaly[13]. In our pedigree, no mutation of the *DMD* gene was detected. *DMD* is the largest known human gene that is involved in the production of dystrophin, which functions in muscle movement. In contrast, the *CRPPA* gene produces a protein that regulates α-dystroglycan in glycosylation, which subsequently stabilizes and protects muscle fibers.

CONCLUSION

In conclusion, this study reported a pedigree in which the proband had mild dystroglycanopathy of CMD caused by a homozygous mutation, c. 1114-1116del, of the *CRPPA* gene.

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