

# Central Core Disease - A Disease That Is Easily Misdiagnosed as Duchenne Muscular Dystrophy

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**Abstract:** As a kind of congenital myopathy (CM), central core disease (CCD) is mainly characterized by low muscle tension, slow progressive or static proximal limb weakness. CM can be characterized by no symptoms to be unable to walk independently in the clinic, pathological changes can be manifested as only significant type 1 muscle fiber dominant type to typical central axial space structure, and there are also many genetic ways. Duchenne muscular dystrophy (DMD) is a common congenital myopathy, which is mainly manifested in the typical pathological changes of early progressive myasthenia and muscular dystrophy. Both CCD and DMD show similar clinical symptoms and their serum creatine kinase can be increased, which is often difficult to distinguish them through clinical characterization and laboratory examination. In this study, we report the clinical and genetic characteristics of two patients with progressive muscle weakness with elevated creatine kinase. They are the product of a first-cousin marriage and seek medical treatment due to asymptotic walking difficulties, muscle atrophy, joint contracture, scoliosis, and elevated creatine kinase levels. It was previously suspected as Duchenne muscular dystrophy. After that, the patient's DNA was sequenced by whole-exome sequencing (WES), and all coding regions were investigated. It was found that a new heterozygous missense mutation c.5092g > A in the RYR1 gene. Similar mutations have not been reported in the literature before. Bioinformatics software predicts that they have the possibility of pathogenesis, which is highly correlated with CCD. The purpose of this case is to report a new heterozygous mutation of the RYR1 gene, summarize the similarities and differences of clinical manifestations, genetic characteristics, and pathological changes of CCD and DMD, and provide a new idea for its differential diagnosis.

**Keywords:** Central Core Disease, Duchenne Muscular Dystrophy, RYR1, Differential Diagnosis

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## 1. Introduction

Congenital myopathy (CM) is a group of genetic hereditary myopathy, the clinical manifestations are varying degrees of muscle weakness and or hypotonia, and specific muscle fiber structure abnormalities are the pathological characteristics. The diagnosis of congenital myopathy is mainly based on characteristic clinical manifestations and pathological changes.

Central core disease (CCD) is a kind of congenital myopathy (CM), which is mainly characterized by low muscle tension and slow or non-progressive proximal limb weakness [1-2]. CCD can be divided into three types (light, severe and classic) according to the severity of clinical manifestations. The onset period of each type is often different.

Mild patients often come on after adulthood, with no obvious symptoms, or even no found symptoms, and only the hollow structure of the muscle fiber axis appears in muscle biopsy. In severe cases, symptoms often appear during the fetal period, fetal movement weakens during pregnancy, and even fetal death. After birth, the fetus is difficult to feed and has poor physical quality, which can be manifested as poor sucking, incomplete respiratory function, and backward motor development compared with children of the same age. Classic patients can show low muscle tone in infancy, that is, soft infants. In early childhood, it can be characterized by slow motor development, muscle weakness, late walking, poor running and jumping ability compared with peers, easy to fall, laborious climbing and descending stairs, etc. [3]

The serum creatine kinase (CK) activity of CCD is usually

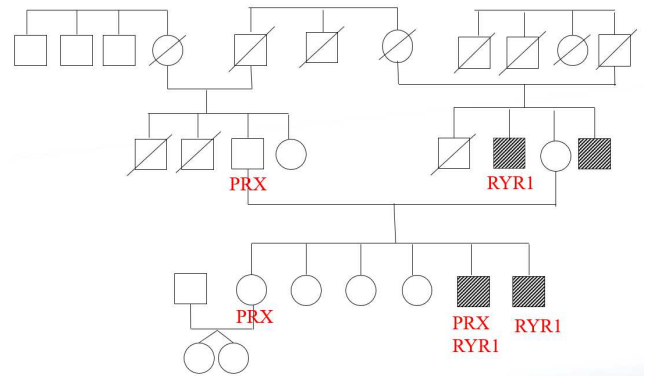
normal, but in some cases, it can be increased to 6 to 14 times the normal value [4]. Due to the lack of mitochondria, in mitochondrial oxidase staining, the biopsy of CCD patients often shows the axial space structure with central or eccentric muscle fibers, single or multiple, and clear peripheral boundary [5].

According to previous literature reports, more than 93% of CCDs are caused by type 1 ryanodine receptor (RYR1) gene mutation [6]. RYR1 is a ligand-gated release channel of calcium ions stored in the terminal pool and plays a key role in excitation contraction (e-c) coupling by regulating the level of intracellular calcium ions. The genotype-phenotype correlation associated with RYR1 gene mutation is complex. The CCD phenotype is closely related to the C-terminal (MHS / CCD region 3, amino acids 4550 – 4940) mutation of dominant RYR1 [4].

Duchenne muscular dystrophy (DMD) is a common congenital myopathy in the clinic, mainly characterized by early progressive myasthenia [7]. Serum creatine kinase (CK) in patients with DMD increased significantly in the early stage of the disease, often tens to hundreds of times higher than the normal value. In the last stage of the disease, because a large number of muscle fibers have been necrotic, the increase of muscle enzyme is not as significant as that in the early stage [8-9]. DMD is caused by the mutation of the dystrophin gene (DMD, site Xp21.2) on the X chromosome [10], and its characteristic pathological changes are mainly the pathological changes of muscular dystrophy and the deletion of dystrophin on the muscle fiber membrane [11].

Patients with CCD or DMD show a progressive walking difficulty, muscle weakness, and elevated creatine kinase, which makes the differential diagnosis of these two diseases

more challenging. In this study, we reported the clinical and genetic characteristics of two patients with progressive muscle weakness with elevated creatine kinase, and summarized the similarities and differences of clinical manifestations, genetic characteristics, and pathological changes of CCD and DMD, to provide a new idea for their differential diagnosis.



**Figure 1.** Family pedigree and gene screening results of patients.

PRX: a heterozygous nonsense mutation c.2035c > t in PRX gene (nm\_181882.2). It is considered that the patient's father and his second sister are carriers of PRX gene c.2035c > T and have no disease, so it is not considered that they are the pathogenic genes of patients 1 and 2. RYR1: heterozygous missense mutation c.5092g > A in RYR1 gene (nm\_000540.2). Combined with the fact that two uncles (dead) of the patient had similar symptoms, their mother is the carrier of the missense mutation. It is considered that this mutation was the pathogenic gene of patients 1 and 2.

**Table 1.** Clinical data.

	physical examination	Supplementary Examination	Personal and family history
Patient 1	Both upper limbs muscles with MMT of grade 4; Both lower limbs muscles with MMT of grade3 -; Berg Balance Scale: 7 points; Holden Walking Ability Evaluation: grade 0; VAS score: 3 points; The modified Barthel Index: 20 points; Dysmetria on heel-to-shin testing; Romberg Sign: difficult to complete; Muscle tension, joint activity, and limb sensation were normal. Cranial nerve examination showed no abnormality, and pathological signs were not drawn out.	2012 (10 years old): aspartate aminotransferase: 243u / L; lactate dehydrogenase: 996u / L; creatinine kinase: 1707u / L, creatine kinase isoenzyme: 441u / L; There was no abnormality in cardiac color Doppler ultrasound, ECG and Chest X-ray; No deletion mutation or repeat mutation of the DMD gene exon was detected in the MLPA gene of Pseudohypertrophic muscular dystrophy (DMD / BMD).	1. The motor development before onset was the same as that of normal children; 2. Parents are cousins to each other; 3. Two uncles (dead) had similar symptoms (Figure 1).
Patient 2	both upper limbs muscles with MMT of grade 4; the proximal end of both lower limbs muscles with MMT of grade3 +, and the distal muscles with MMT of grade3; Berg Balance Scale: 46 points; Holden Walking Ability Evaluation: grade V; VAS score: 0; The modified Barthel Index: 80 points; Dysmetria on heel-to-shin testing; Romberg Sign: difficult to complete; Muscle tension, joint activity, and limb sensation were normal. Cranial nerve examination showed no abnormality, and pathological signs were not drawn out.	Biochemical results in 2016 (11 years old): Aspartate aminotransferase: 180u / L; Lactate dehydrogenase: 634u / L; Creatine kinase: 5359 U / L; Creatine kinase isozyme: 194 U / L; α-Hydroxybutyrate dehydrogenase: 520u / L.	

Note: MMT: Manual Muscle Testing; VAS: Visual Analogue Scale/Score.

## 2. Case Presentation

Patient 1, a 13-year-old male, went to the rehabilitation physiotherapy department for the first time in 2016 because of "progressive walking difficulty and poor sitting and standing position transfer for 3 years". His motor symptoms began at the age of 10, ranging from slight gait abnormalities to lower limb weakness, frequent falls, and he was unable to complete the transfer between bed and wheelchair, between wheelchair and toilet, and between sitting and standing positions alone. The results of the external examination showed that the serum creatine kinase was elevated, and the possibility of Duchenne muscular dystrophy (DMD) was considered. Patient 2 (younger brother), 11 years old, male, was treated with patient 1 because of "progressive walking difficulty for more than 1 year". The onset time and disease progression were the same as patient 1. The clinical manifestation of patient 2 was mild at the time of treatment. The transfer between bed and wheelchair, between wheelchair and toilet, and between sitting position and standing position can be completed independently at the time of treatment. Table 1 also shows other data. For prenatal consultation, the second sister of patient 1 went to the rehabilitation physiotherapy department in 2019. After signing the informed consent, 3ml of peripheral blood of patients 1 and 2 and their families (two sisters and their parents) were collected for whole exon trio family samples. RYR1 gene (nm\_000540.2) was detected in patients 1 and 2 and their mothers, Heterozygous missense mutation c.5092g > A was detected (Figure 1), and no similar mutation was reported in the literature. Bioinformatics software predicted that it had the possibility of pathogenesis, which was highly correlated with CCD.

## 3. Discussion

### 3.1. Clinical Manifestation

Both CCD and DMD exhibit muscle weakness, leading to symptoms such as scoliosis, abnormal gait, and joint contractures. CCD shows static or slow muscle weakness, mainly involving the proximal limbs. The symptoms of the lower limbs are more serious than those of the upper limbs, mainly involving the pelvic belt muscles and trunk muscles [3]. Most patients can walk independently, and the overall prognosis is good. CCD patients are often complicated with orthopedic complications, such as congenital dislocation of the hip joint, posterior process of the spine, joint contracture, and arcuate foot [12]. Some patients are accompanied by facial muscle weakness, and a few will have focal weight loss [13], but there are few cardiac and intellectual involvement [4]. The serum creatine kinase (CK) activity of CCD is usually normal, but in rare cases, it can be increased to 6 to 14 times the normal value [4]. Serum creatine kinase (an important indicator of DMD) is often significantly higher than normal by tens to hundreds of times. The two patients in this report started at about 10 years old, manifested as

weakness of both lower limbs and abnormal gait, and finally developed into the inability to walk independently, muscle atrophy, scoliosis, etc. Combined with the increase of serum creatine kinase and creatine kinase isozyme, they were suspected to be Duchenne muscular dystrophy (DMD). However, DMD patients are more than 3-5 years old, show progressive muscle weakness, lose walking ability more than 12 years old, and respiratory, orthopedic, and cardiac complications will also occur at the same time or later [10]. Neurocognitive impairment is also common [6, 14]. In this case, two patients had a late-onset and slow progress of muscle weakness. Both of them had no symptoms of the respiratory system and cardiac system, and their neurocognitive function was intact, which was not completely consistent with the performance of DMD.

### 3.2. Genetic Inheritance

CCD is caused by the mutation of the ryanodine receptor (RYR1) gene on chromosome 19. Most of them are autosomal dominant inheritance, but there are also a few reports of sex chromosome and autosomal recessive inheritance [4]. RYR1 encodes a calcium ligand-gated release channel in the terminal pool. Mutation-induced conformational changes of RYR1 protein are considered to change the excitability of muscle cells [15]. DMD is caused by a mutation in the dystrophin gene located on the X chromosome. Nearly 80% of DMD patients have a deletion (about 60% - 65%) or duplication (5% - 15%) of dystrophin gene exon due to large gene rearrangement, and approximately 20% of patients have point mutations caused by single base changes or small mutations caused by the insertion or deletion of one or more nucleotides. These mutations lead to the lack of sub osteoprotegerin crucial to the stability of muscle structure, resulting in progressive muscle degeneration [10]. RYR1 gene exists in two patients and their mothers in this report (nm\_000540.2) heterozygous missense mutation c.5092g > A, no DMD gene mutation was detected, which was inconsistent with the diagnosis of DMD and CCD.

### 3.3. Pathological Features

The typical change of muscle biopsy in CCD patients is that there is a single axial space structure in the central area of muscle fibers under histochemical staining, or multiple central axial spaces or eccentric axial spaces. Occasionally, it can only show significant dominant or uniform type 1 muscle fibers and poor maintenance of type 1 muscle fibers [4]. Muscle biopsy in patients with DMD mainly showed the typical pathological changes of muscular dystrophies, such as different muscle fiber sizes, active muscle fiber necrosis and regeneration, connective tissue hyperplasia, and so on. In addition, if the muscle anti-dystrophin-n, -R, -C monoclonal antibody immunohistochemical staining indicates that the anti dystrophin is completely absent in the muscle fiber membrane, DMD can be diagnosed [7, 11]. It

should be noted that the degree of histopathological changes may vary with sampling site, patient age, and course of the disease. In 2017, Minting Lin reported that a CCD patient underwent muscle biopsy at the age of 16 without typical central axial space structure and was diagnosed as "facial shoulder brachial muscular dystrophy (FSHD)". However, when the muscle biopsy was performed again at the age of 31, there was a typical central axial space structure on type I muscle fibers, suggesting that the pathological changes of CCD muscle may change with the progress of the disease [16]. In addition, the typical pathological changes of CCD and the central axial space structure can also be observed in other clinical environments such as tenotomy, denervation ("target fiber") [17], or malignant high fever susceptible individuals without other congenital myopathy characteristics [18]. Therefore, the muscle biopsy results of suspected CCD patients should be treated dialectically in combination with the course of the disease and clinical manifestations.

#### 4. Conclusions and Expectations

Patients with CCD and DMD can have similar clinical symptoms and elevated serum creatine kinase, which is difficult to be distinguished by clinical characterization and laboratory examination. However, CCD, as a benign congenital disease, progresses slowly, and there are few diseases of the respiratory system, cardiovascular system, and neurocognition. In addition, the pathological changes and pathogenic genes of CCD and DMD are also different. It should be noted that the pathological changes of CCD may vary according to the sampling site, patient age, course of the disease, and sampling technology. In addition, the characteristic pathological changes do not correspond to CCD one by one. Therefore, in clinical work, it is necessary to strengthen the understanding of CCD and a series of congenital myopathy, and comprehensively analyze the clinical manifestations, serum related muscle enzyme examination indexes, second-generation sequencing results, and pathological examination, to avoid relying too much on a certain result and leading to misdiagnosis.

Because some individuals with suggestive clinical features and the same genetic background do not necessarily show characteristic histopathological features, the differential diagnosis between CM is more difficult. It may be an important direction for the diagnosis and differential diagnosis of CM in the future to routinely sequence the whole exon genes of the whole family, establish a complete gene and disease phenotype corresponding library, and explore the relationship between protein structure abnormalities and function caused by a gene mutation.

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