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Genetic and Clinical Study on a Family with Becker's Muscular Dystrophy Combined with Phenotype of Severe Cardiac Involvement

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Abstract

Background: Becker Muscular Dystrophy (BMD) is a milder form of Duchenne Muscular Dystrophy (DMD). Different types of mutations have been reported in patients with DMD and BMD. In the present study, we identify the dystrophin gene mutation and explore the management of BMD combined with severe cardiac involvement.

Methods: We screened a patient with severe congestive heart failure who was clinically diagnosed with BMD for mutations in the dystrophin gene. We also screened for these mutations in his family members and in 100 controls.

Results: The proband, a 45-yr-old man, was diagnosed with BMD by the identification of a novel mutation c.4998_5000Del GCA, p.1667del) in the exon 35 of the dystrophin gene. Six females and three males in this family carried the same mutation in the dystrophin gene. The proband underwent heart transplantation due to severe heart failure and recovered well after surgery.

Conclusion: We have detected a novel mutation that causes BMD. This confirms the diagnosis and helps to guide effective therapy for this patient and his affected relatives. Cardiac transplantation is an effective treatment for the patient with BMD combined with phenotype of severe heart failure.

Keywords: Becker's muscular dystrophy; Genetic analysis; Severe cardiac phenotype; Cardiac transplantation

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Introduction

Duchenne's Muscular Dystrophy (DMD) and the milder variant, Becker's Muscular Dystrophy (BMD) represent X-linked genetic diseases related to mutations in the dystrophin gene which is located on chromosome Xp21.1 [1]. In BMD, the deletion mutations usually do not cause a shift in the reading frame; this tends to produce a functional but truncated version of the dystrophin protein. DMD is characterized by progressive, generalized weakness and wasting of muscle. Almost all DMD patients will develop cardiomyopathy [2]. BMD patients can usually walk and have a near normal life span and there is a 70% chance of them developing cardiac problems [3]. Cardiac involvement in BMD may be totally absent throughout life, may remain subclinical throughout life or for long periods, or may become symptomatic. However, once the heart damage caused by BMD develops into heart failure, the condition is progressively worsened, and the conservative drug treatment effect is extremely poor, and the treatment is more difficult. In this study, genetic diagnosis, treatment (heart transplantation) and follow-up of a BMD family with cardiac involvement will be reported.

Methods

Index case

The proband (Subject III-27), a 45-yr-old man, consulted our hospital complaining of exertional dyspnea. He was diagnosed at 43 years of age as a BMD patient in local hospital with an increased serum Creatine Kinase (CK) level at rest (1267 IU/l, n.v. 0–200), and in subsequent serial determinations. He complained of limb weakness, myalgia. On neurological examination, he showed bilateral calf hypertrophy, difficulty in hopping and mild weakness in the proximal limb

muscles. Electrocardiographic (ECG) and Echocardiographic (UCG) results were normal. He underwent 2 years of un-supervised resisted strength training and aerobic training programs including walking-hiking, running-jogging, cycling, aerobic dance or swimming in order to improve physical capacity and quality of life. During the training period, the patients improved in walking function, muscle strength, endurance, level of activity, and fatigue.

On admission, blood pressure was 110/70 mmHg, and the pulse rate was 70 beats/min. A third cardiac sound was audible. Hepatomegaly with slight tenderness was also noted. Muscle strength in the extremities was decreased, with predilection in the proximal area. The thighs were atrophic and calves were hypertrophic. Deep tendon reflexes were normal. There was no sensory disturbance, pathologic reflex.

Echocardiogram revealed markedly increased Left Ventricular End-Diastolic Volume (LVEDV=239 ml/m^2 with n.v. 55–73 ml/m^2) with severe reduction of left ventricular ejection fraction (LVEF=25.7% with n.v. 50%–60%). Right Ventricular End-Diastolic Volume (RVEDV) was not increased (55 ml/m^2 with n.v. 38–58 ml/m^2) with a normal ejection fraction (64% n.v. 52%–68%). No dilation of left atrium was observed (55 ml/m^2 with n.v., 60 ml/m^2). Doppler and color echocardiography showed relevant mitral regurgitation. ECG abnormalities previously described to be typical in patients with BMD [4] including a R:S-ratio ≥ 1.0 in lead V1, a deep Q-wave in leads I, II, aVF, V5-V6 and a incomplete right bundle branch block. He showed an increased CK level at rest (1232 IU/l, n.v. 0–200), BNP serum values were elevated (701.6 fmol/ml, n.v. <400. Cardiovascular Magnetic Resonance (CMR) and Positron Emission Tomography (PET) were conducted, and the results were shown in Figure1a, 1b. Biopsies of the skeletal muscle (quadriceps femoris) and cardiac muscles were examined Figure 2a, 2b. Skeletal muscle specimens showed dystrophic changes such as large variation in fiber size and a small number of necrotic fibers. The patient underwent Orthotopic cardiac transplantation using the Bicaval technique on January 10th, 2011.

Study of the family

A pedigree was constructed for the family (Figure 3). The family in this study inhabits Liaoning province. Because of a strong family history, the son of the proband's mother's sister (63 years of age, Subject IV-4), showing muscle weakness, and had been diagnosed with BMD at another hospital, establishing that the mutation was transmitted from the maternal lineage. A total of 38 available at-risk subjects (excluding the index case) had genetic testing, and these subjects also had physical examination and cardiac evaluation. The medical charts were reviewed to obtain clinical data by using a standardized data collection sheet. Variables recorded include sex, age, age at onset, smoking, height, weight, muscle weakness, physical exercise, calf hypertrophy, disability, serum CPK, dystrophic change in muscle biopsy, and the results of ECG, UCG and CMR.

DNA sequencing

Genetic analysis was performed in the proband; his at-risk relatives after informed consent had been obtained. We also recruited 100 normal controls after informed consent had been obtained to determine whether the variations were common genetic polymorphisms. Genomic DNA was extracted from blood leucocytes according to a standard procedure. For mutation screening, all coding exons of the dystrophin gene were amplified by the Polymerase Chain Reaction (PCR) using a set of 79 primer pairs. The primers were designed as previously described [5]. PCR products were purified using PCR purification (Qiagen, Hilden, Germany). All samples were sequenced using the ABI-Prism 377 (PE Biosystems, Foster City, CA).

The study was approved by the Ethics Committee of Fuwai Hospital, Peking Union Medical College, Beijing, China. All participants provided written informed consent.

Results

Genetic analysis

Molecular analyses of the DNA of the proband revealed the presence of a frame shift mutation (c.4998_5000Del GCA, p.1667del) in the exon 35 of the dystrophin gene. Six females and three males in this family carried the same mutation in the dystrophin gene.

This mutation in the proband (III-21) was also found in a son of the proband's ant, and his two nephews, IV-9 and IV-10, in Figure 4. No other variant of the dystrophin gene was detected. The 100 controls have not detected the mutation, indicating that this is a novel mutation and not a common genetic polymorphism.

Clinic phenotype

The females were all mutation carriers without abnormal clinic phenotype. The son of the proband's ant (63 years of age, Subject

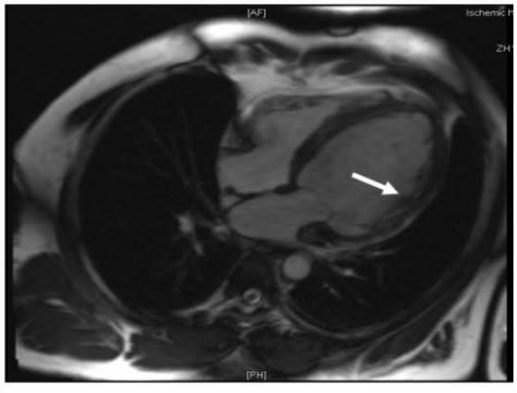

Figure 1a

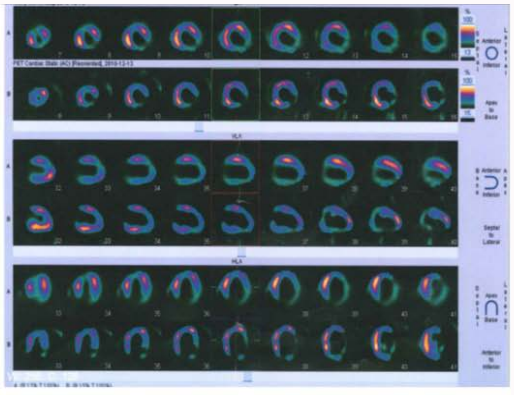

Figure 1b

Figure 1: a) Cardiac magnetic resonance imaging. A: The 4-chamber view displays myocardial wall abnormalities with areas of wall thinning and irregular border of the endocardial wall (arrow). b) PET viability images show marked perfusion/metabolism damage or mismatch in the inferior and lateral walls.

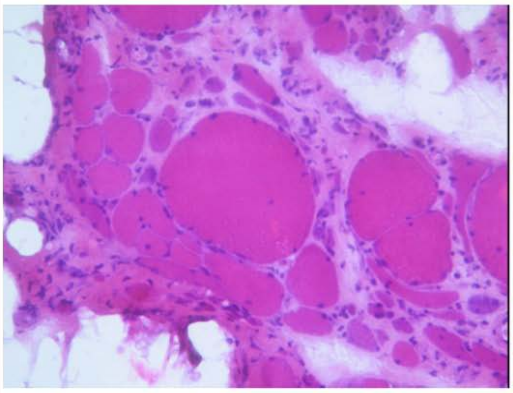

Figure 2a

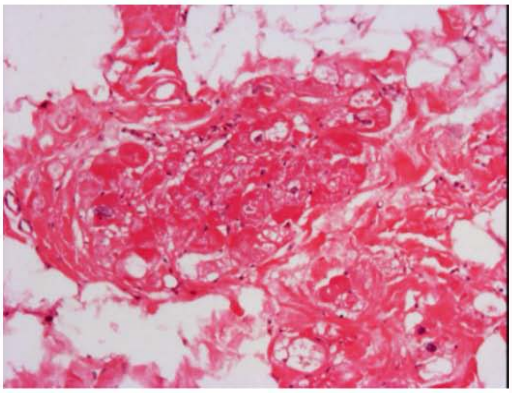

Figure 2b

Figure 2: Clinical muscle biopsy of the quadriceps muscle (a) and myocardium in the proband (b). Muscle general histopathology: Variation in size, internal nuclei, necrosis and regeneration, endomysial fibrosis, fat replacement.

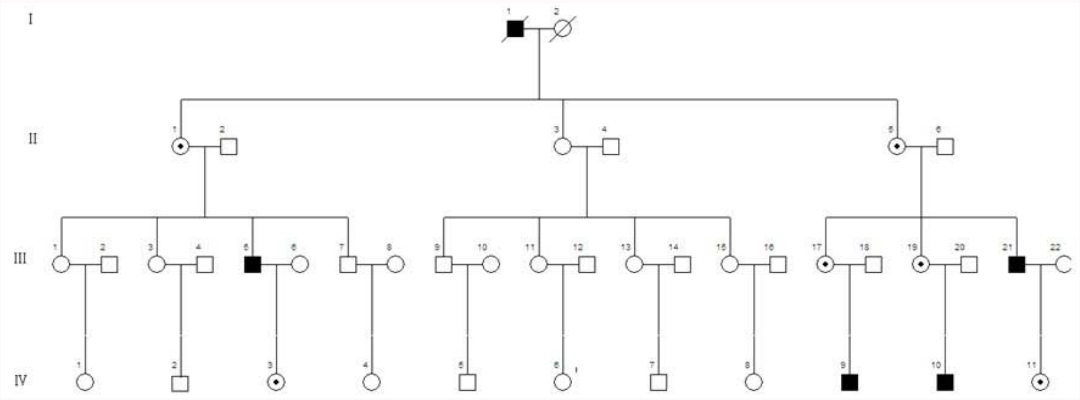

Figure 3: Pedigree of the affected family. ☐◯, Unaffected male, female; affected male;■ ⊙ , carrier female ; ■ ∅ dead male, female.

Table 1: Skeletal muscle involvement in affected members.

Pedigree no.	age	Age at onset	Physical exercise	Muscle weakness	Calf hypertrophy	disability	Serum CPK	Dystrophic change in muscle biopsy
III-5	63	28	-	+	+	+	1382	+
III-21	45	43	+	+	+	-	2267	+
IV-9	21	18	-	+	+	-	1266	Not done
IV-10	20	17	+	+	+	-	854	Not done

Table 2: Cardiac involvement in affected members.

Pedigree no.	clinical	ECG	UCG	CMR
III-5	normal	normal	normal	normal
III-21	Ventricular extrasystole Heart failure Cardiomegaly	Ventricular extrasystole Non-specific T wave changes	Cardiomegaly	Cardiomegaly
IV-9	normal	normal	normal	normal
IV-10	Cardiomegaly	Non-specific T wave changes	Cardiomegaly	Cardiomegaly

III-5), showing muscle weakness, and had been diagnosed with BMD at another hospital. Weakness of the quadriceps femoris was the only manifestation for a long time. As the severe morphological abnormalities and high serum creatine kinase values, restraint from physical exercise and a sedentary lifestyle was recommended. No cardiac abnormalities were found.

Two nephews of the proband (IV-9 and IV-10) were proved to have the same deletion mutation at exon 35 of the dystrophin gene as the proband. Both of them demonstrated elevated normal serum muscular enzyme activities and showing muscle weakness, and had been diagnosed with BMD after the screening of dystrophin gene.

IV-9 was a 20-year-old male patient. During the 3 years before he was diagnosed with BMD, he took up physical training to oppose the muscle weakness. He trained his legs and arms with bicycle training equipment 30 min every day without getting too tired. Additionally, he played basket-ball two times a week. The echocardiogram of IV-9 showed that left ventricular diastolic dimension was 71 mm and systolic dimension 69 mm. These results suggested the presence of

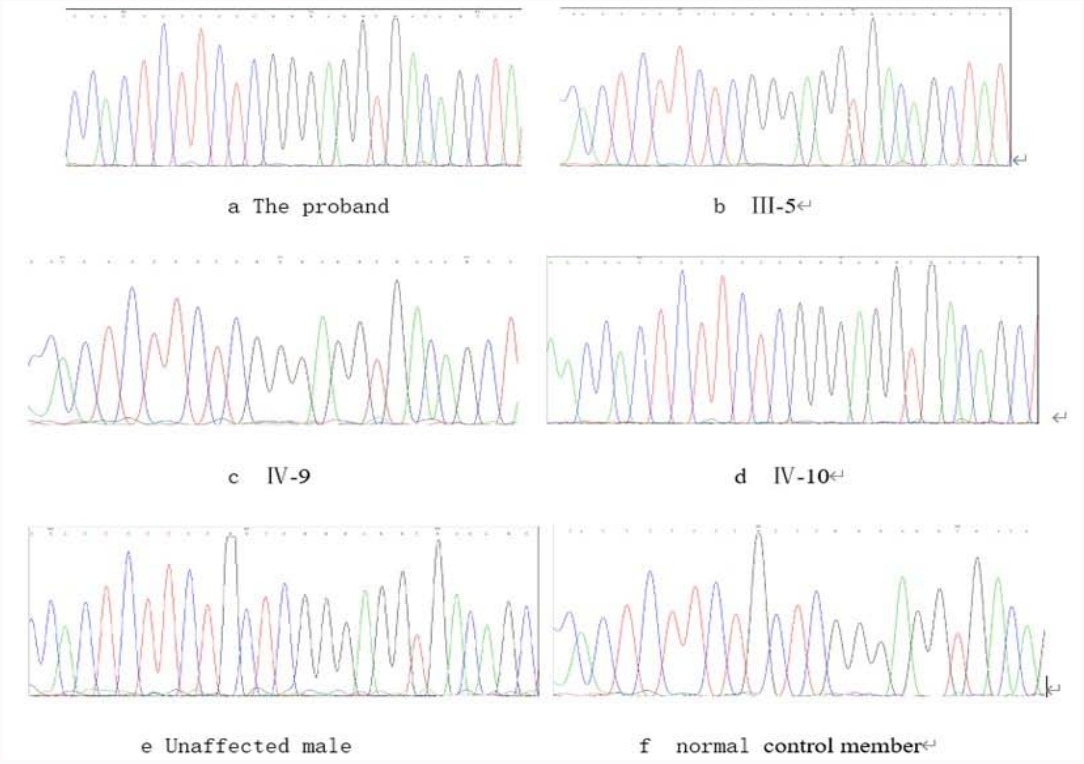

Figure 4: Results of mutation screening of in dystrophin gene exon 35.
a-d) A novel frame shift mutation (c.4998_5000Del GCA, p.1667del) was discovered in the proband, III-5, IV-9, IV-10. e,f) The corresponding normal sequence in the unaffected family members and the 100 unrelated control samples displayed by an arrow.

the cardiac involvement.

IV-10 was also a 19-year-old male patient and was diagnosed with BMD. He seldom takes part in any physical training and lived a sedentary lifestyle. Cardiac evaluation with Cardiac MRI (CMRI) showed no abnormalities.

The data on skeletal muscle and cardiac involvement are summarized in Table 1, 2.

Treatment and Long-term outcomes

The proband's heart was obviously enlarged with severe cardiac insufficiency and progressively worsening of the condition, medical treatment was ineffective, and cardiac transplantation was approved after discussion by the ethics committee. The patient recovered well and routinely took anti-graft rejection drugs after surgery. He can work and live normally.

The ECG examinations were normal at 1 month, 3 months, half a year, 1 year, 3 years 5 years and 9 years after operation. The echocardiogram showed that the left and right ventricle diameters of the transplanted heart were approximately normal, and the Ejection Fraction (EF) was 70% to 76%.

Although family members III-5, IV-9, IV-10 are with different degrees of cardiac involvement, but the heart function is grade II, conservative treatment with drugs, strict monitoring of heart function, and muscular dystrophy were given standard treatment after neurological consultation. The patient's condition progresses slowly and normal daily work can be carried out.

Discussion

In this study, we report a family with different phenotypic expression of BMD ranging from severe peripheral myopathy to severe congestive heart failure. Molecular analysis revealed the absence of deletion within the DMD gene. Since the same DMD gene allele was found in our patients' mother and the elder healthy brother, a frame shift mutation (c.4998_5000Del GCA, p.1667del) in the exon 35 of the dystrophin gene is responsible for the onset of the disease.

For patients with BMD, disease severity can vary for the same mutations, sometimes even within the same family and there is also variation in the extent in which the heart is affected. Because BMD is characterized by weak muscles, the clinical aspects of the cardiac defects are often masked by the muscle weakness, which may cause increased physical activity to improve muscle strength and often leave the dystrophic heart untreated. The heart is potentially at greater risk than the skeletal muscle. Firstly, in both skeletal and cardiac muscle, the function of dystrophin is to protect against contraction-induced damage. In skeletal muscle, there exists a resident stem cell population, the satellite cells, which can repair the damaged fibers even though the repair is still with dystrophin deficient cells. However, there are no stem cells in the heart to regenerate the damaged cardiomyocytes so damaged cardiomyocytes will tend to die and be replaced by fibrotic tissue earlier than skeletal muscle [6]. Secondly, cardiac muscle will repeatedly contract around 86,400 times per day, even more contract times when the patients take excise, whereas skeletal muscle contract much less than the cardiac muscle. These continual contractions result in constant fluxes in the intracellular calcium levels associated with each excitation contraction cycle, which undoubtedly accelerates the deterioration process within the cardiomyocytes compared to skeletal myofibres. Thirdly, the release of intracellular calcium and actually initiating contraction of the heart, leading to extra contractions of the BMD hearts. These extra contractions directly cause more damage to

the cardiomyocytes. There is therefore a vicious cycle initiated by the loss of dystrophin plus the cardiomyocyte is particularly susceptible to damage and there is no regenerative capacity in the heart to replace the lost cardiomyocytes all of which leads to the development of the cardiomyopathy.

The diagnosis of BMD combined with heart damage is mainly based on clinical symptoms, electromyography, muscle biopsy and genetic diagnosis, color Doppler ultrasound and electrocardiogram. In recent years, it has been reported in the literature that CMRI is used to evaluate the disease status of patients with muscular dystrophy cardiomyopathy and can judge the scope and degree of the myocardium lesion, confirmation of cardiomyocyte fat lesions, with high specificity and sensitivity, and no radiation, high resolution, non-invasiveness. And CMRI image quality is less affected by body habitus, and multiple studies have revealed that CMRI is superior to echocardiography for diagnosing DMD-related ventricular dysfunction [7]. It can be of important diagnostic value in the early diagnosis and prognosis judgment of BMD heart disease [8].

Cardiomyopathy is a principal source of morbidity and mortality. With the goal of slowing the onset and progression of heart failure complications, cardiac care is focused on surveillance and management. Important emerging therapies include new heart failure medications, mechanical circulatory support with ventricular assist devices, heart transplantation, and internal cardiac defibrillators. Conceptually, replacing the mutated gene with a normal one would cure the disease. However, this task has encountered significant challenges due to the enormous size of the gene and the distribution of muscle throughout the body [9]. The recognized effective treatment plan is the use of glucocorticoid therapy. At present, the treatment of DMD/BMD patients with a clear genetic diagnosis are actively exploring [10,11], such as the use of recombinant related viral vector-mediated dystrophin small gene SMCKA3999 is a promising method for the treatment of DMD [12]. New strategies for therapy are aimed at restoring muscle Dystrophin by exon skipping and nonsense mutation suppression [13-16]; patients with nonsense mutations in the DMD gene can inhibit the formation of stop codons in advance, thereby synthesizing the complete dystrophin protein [17]. When a BMD patient is associated with heart damage, early symptomatic treatment is mainly given to nutrient myocardium, dilation of blood vessels, diuresis, etc. ACE inhibitors, angiotensin receptor blockers, beta-blockers and/or aldosterone antagonists tended to improve or preserve left ventricular systolic function and delay the progression of BMD-associated cardiomyopathy [18-20].

Heart transplantation is the standard of treatment for patients with refractory end-stage heart failure [21]. However, controversy exists regarding cardiac transplantation in patients with irreversible dysfunction of other organ systems. Our study showed that heart transplant may be a viable option for BMD patients with severe left ventricular dilation and valvular regurgitation at the late time of cardiomyopathy.

Conclusion

We have detected a novel mutation that causes BMD. This confirms the diagnosis and helps to guide effective therapy and prevent morbid outcomes for this patient and his affected relatives. Cardiac transplantation may be an effective treatment for the patient with BMD combined with phenotype of severe heart failure.

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