

## Case Report

# Clinical and Genetic Studies of Limb Girdle Muscular Dystrophy: Reports of Two Cases

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### Abstract

*Limb girdle muscular dystrophy (LGMD) presents with weakness and wasting of muscles, initially appear at proximal group of pelvic and shoulder girdles and inherited by an autosomal recessive disorder mainly and rarely autosomal dominant trait. We report two young girls of limb girdle muscular dystrophy (LGMD), who presented with gradual onset of weakness in proximal muscle of all four limbs. There was positive family history in one girl. Neurological examination revealed pseudo hypertrophy of both calves, hypotonia in all four limbs, muscle power diminished, more on proximally. All deep tendon reflexes were diminished with planters bilateral flexors. Gower sign was positive and winging of scapula was also present. Electromyography (EMG) showed myopathic pattern. Both had elevated creatinine phosphokinase levels and finally genetic study confirmed the diagnosis.*

**Key words:** Limb Girdle Muscular Dystrophy; Genetic; Clinical

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## Introduction

Limb-Girdle Muscular Dystrophy (LGMD) is heterogeneous group of disorders. Individuals with LGMD generally show weakness and wasting restricted to the limb musculature, proximal greater than distal, and muscle degeneration/regeneration on muscle biopsy.<sup>1</sup> LGMD can be classified as autosomal dominant (LGMD1) with an adult age of onset or recessive (LGMD2). LGMD1 is not common, which

is less than 10% of all LGMDs whereas LGMD2 are more frequent (1:15000).<sup>1</sup> NGS (Next generation sequencing) panels facilitate diagnosis, identify and help genotype phenotype correlations.

## Case 1

A 9-year-old girl presented with proximal weakness in both upper limbs and lower limbs for 2 years,

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which was insidious and gradually progressive. She had difficulty in climbing stairs, running, getting up from squatting position, and raising arms above the head. There was no history of distal muscle weakness, twitching of the muscles, pain in the limbs, breathlessness, cranial nerve involvement or sensory symptoms and bladder and bowel disturbances. She is the second child born of consanguineous marriage. Birth history and developmental milestones were normal. Family history revealed that her younger sister who is 4-year-old, has been suffering from similar weakness in lower limbs for last 6 months and is now frequently falling during walking. General physical examination was normal. Neurological examination showed normal mental functions including speech and cranial nerves function. She had pseudo-hypertrophy of both calves, hypotonia in all four limbs. Power was 3/5 at both shoulders, 4/5 at both elbows, 5/5 at both wrists, 3/5 at both hip joints, 3/5 at both knees, 5/5 at both ankles. Gower's sign was positive. Winging of the scapula was present. All deep tendon reflexes were diminished and bilateral planter flexors response was present. Sensory system was normal. She had waddling gait. There were no cerebellar signs, spine was normal. Other systemic examinations were normal. Haemogram, thyroid function, and renal function tests were normal. Urine routine test was normal. Creatine phosphokinase was 11320 U/L (ref 26–308 U/L), Aldolase was 87.7 U/L (ref up to 13.5 U/L), LDH was 866 U/L (ref 208–378 U/L), AST 282 U/L (ref <35 U/L), ALT 229 U/L (ref ≤35 U/L), ECG normal, echocardiography revealed sub-pulmonic VSD with L-R shunt. Nerve conduction studies were normal. EMG performed in right upper and lower limb showed myopathic pattern.

Muscle biopsy from right quadriceps showed muscle fibers of various sizes, fiber necrosis and fiber regeneration. There was crowding of the nuclei in the center, along with lymphocyte, histiocyte and eosinophil infiltration, mild stromal fat infiltration and fibrosis was seen, which are consistent with muscular dystrophy. Whole exome sequencing for muscular dystrophy revealed a homozygous pathogenic mutation at gene SGCA (ENST00000262018.3) on exome 5 and reported as LGMD3 (on OMIM)

with variants (c515T>A) of unknown significance. Based on the history, proximal muscle weakness, creatine phosphokinase and other muscle enzyme level, muscle biopsy, EMG and finally on genetic study diagnosis of LGMD was made. She was finally treated with oral steroid (deflazacort), vitamin D and calcium supplement, co-enzyme Q along with other supportive measures including occupational therapy and physiotherapy.

## Case 2

An 11-year-old girl presented with proximal weakness in both upper limbs and lower limbs since five years of age, which was insidious and gradually progressive. She had difficulty in climbing stairs, running, getting up from squatting position, and raising arms above the head. There was thinning of shoulders, arms and thighs. She was the third child born of consanguineous marriage. Birth history was uneventful and developmental milestones were normal. General physical examination was normal. Neurological examination showed normal mental functions including speech and cranial nerves were normal. She had atrophy of both shoulders with wasting of both deltoids, thinning of thighs and pseudohypertrophy of both calves, hypotonic in all four limbs. Power was 3/5 at both shoulders, 5/5 at wrists, 3/5 at both hip joints, 5/5 at both ankles. Gower's sign was positive. Winging of the scapula was present. All deep tendon reflexes were diminished and superficial reflexes were present with planter bilateral flexors. Sensory system was normal. She had waddling gait. There were no cerebellar signs and spine was normal. Respiratory and cardiovascular systems and abdomen were unremarkable. Investigations showed haemogram, liver function and renal function tests were normal. Creatine phosphokinase was 1290 IU/L (ref <170 IU/L). Urine routine test was normal. ECG, chest X-ray, echocardiography were normal. Nerve conduction studies were normal. EMG performed in right upper and lower limbs showed myopathic pattern. Whole exome sequencing for muscular dystrophy revealed a heterozygous pathogenic mutation at SGCB (ENST00000181431.5) on exome 5 and reported as LGMD4 (on OMIM) with

variants (c638 T>C) of unknown significance. Based on the history, proximal muscle weakness, creatine phosphokinase levels, EMG and finally on genetic study diagnosis of LGMD was made. She was also treated with oral steroid (prednisolone), vitamin D and calcium supplement along with other supportive measures including occupational therapy and mild physiotherapy.

## Discussion

Limb-girdle muscular dystrophies (LGMD) are a group of muscular dystrophies that were previously identified in patients by 'diagnosis by exclusion'. Estimates for prevalence of all forms of LGMD range from one in 14,500 to one in 123,000.<sup>2</sup> Males and females are both affected equally with onset from late in the first decade to the fourth decade.<sup>3</sup>

The term LGMD1 (1A–G) includes groups of LGMD showing dominant inheritance whereas LGMD2 (2A–W) refers to types with autosomal recessive inheritance. Pathogenic variants at more than 50 loci have been reported, making accurate diagnosis a challenge.<sup>4</sup> Individuals with LGMD generally show weakness and wasting involving mainly proximal (the shoulder, pelvic girdle, upper thighs, and upper arms) limb musculature compared to distal parts (lower legs and feet, lower arms and hands). Onset, progression, and distribution of the weakness and wasting may vary considerably among individuals and genetic subtypes.

LGMDs are typically limited to skeletal muscle with relative sparing of the bulbar muscles. Presentation varies depending on the genetic subtype. Both our patients are autosomal recessive type of LGMD who had proximal muscle weakness, pseudohypertrophy of the calves and raised creatine phosphokinase. The gold standard to secure diagnosis is the demonstration of causative mutations in the relevant gene. Because of the large number of loci involved, it is generally necessary to direct mutation detection to specific loci.<sup>3</sup>

Sarcoglycanopathy (LGMD2C-F) is the most common subtype among children. Symptoms may present in early life typically 4–7 years old and presentation may occur up to the second decade.<sup>5</sup> Respiratory failure and cardiomyopathy may commonly occur. Serum CK level is generally very high and the diagnosis

is typically established by a lack or reduction of sarcoglycan expression on biopsies and finally by genetic testing. In both of our patients onset of weakness was at 7 and 5 years of age respectively and both had high serum CK level. Our patient 1 having mutation on SGCA, reported as LGMD3 and patient 2 having mutation on SGCB gene, reported as LGMD4, both encodes for sarcoglycan protein and function is to connect the sarcolemma to the extracellular matrix, stabilization of the dystroglycan complex.<sup>6</sup>

Both LGMD3 and LGMD4 are autosomal recessive condition and caused by homozygous or compound heterozygous mutation in the alfa-sarcoglycan gene (SGCA) and beta-sarcoglycan gene (SGCB) on chromosome 17q21 and 4q12 respectively. At the 229<sup>th</sup> ENMC international workshop LGMD2D was renamed LGMDR3 and LGMD2E was renamed LGMDR4.<sup>7</sup> Several mutations (null and missense) were found in the adhalin gene in 10 affected families of LGMD2D (LGMDR3) from Europe and North Africa. Disease severity varied in age of onset and rate of progression, and patients with null mutations were the most severely affected.<sup>8</sup>

A homozygous 400-kb microdeletion of chromosome 4q11–q12 was found in 6 members of a consanguineous East Anatolian family with a severe form of LGMD2E (LGMDR4) with joint hyper laxity and contractures.<sup>9</sup> Patients presented with proximal symmetric weakness and atrophy of the limb and trunk muscles. The average age at onset was 7.6 years (range 4 to 12), and loss of walking occurred between 12 and 38 years. Calf hypertrophy was also observed.<sup>10</sup> Both LGMD3 and LGMD4 show marked interfamilial variability and genotypic-phenotypic heterogeneity.

Genetic study is not only important for confirmation of diagnosis and genetic counseling is also needed in the management purpose, as treatment strategies differ in different forms of LGMD. In dysferlinopathies, deflazacort is not an effective therapy since steroid treatment should not be administered in patients with dysferlinopathy.<sup>11</sup>

No specific disease-altering treatment currently exists. Update of therapeutic trials in humans includes gene therapy (rAAV), rituximab (IV), dantrolene,

deflazacort, prednisone, vitamin D3, creatine MH, CoQ10, and lisinopril.<sup>11-17</sup> Although enzyme replacement therapy is an available treatment option in patients with LGMD2V (acid maltase deficiency). Corticosteroids have been reported helpful in maintaining muscle function in LGMD2I. However, novel therapies and treatment approaches are being explored in disorders where inflammatory pathways may play a role (e.g., dysferlinopathies).<sup>18</sup> The use of monoclonal antibodies like rituximab to block B cell activation or the use of intravenous immunoglobulin to prevent complement attack complex activations are important modalities.<sup>19</sup> Molecular therapeutic approaches have demonstrated promising new treatment potentials in LGMD in the forms of exon skipping and gene therapy.<sup>20</sup>

Physical therapy and occupational therapy should be encouraged for most patients to prevent the formation of contractures and to maximize limb use. Symptomatic treatment with either baclofen, tizanidine, or gabapentin may be provided for muscle cramp.<sup>18</sup>

In patients with cardiac involvement (i.e., LGMD types 1A, 1B, 1C, 2C, 2D, and 2E), serial ECG and echocardiograms are mandatory for monitoring cardiac status. Cardiologic follow-up is crucial for management of cardiomyopathy and placement of intracardiac pacemaker or defibrillators should be done when indicated.<sup>18</sup> None of our patients had cardiac involvement.

Respiratory involvement is common in most LGMD types, especially in patients with severe peripheral weakness (including Pompe disease). Pulmonary function tests are useful in identification of respiratory weakness. Noninvasive or invasive methods of ventilation are helpful in this clinical setting.<sup>18</sup>

All of the LGMD syndromes cause progressive weakness, but the rates of progression vary considerably. Certain LGMD syndromes have cardiac involvement, and affected patients are prone to cardiac conduction system defects, which may lead to sudden death. Rarely, respiratory insufficiency may occur, but usually in severely affected patients and in late stages of the disease. Later onset disease predicts a better prognosis.<sup>18</sup>

Sarcoglycanopathies are transmitted in an autosomal recessive manner. It is important to offer genetic counseling regarding potential risks to offspring and reproductive options to young adults who are affected, are carriers, or are at risk of being carriers. Once the pathogenic variant(s) have been identified in an affected family member, prenatal diagnosis for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.<sup>1</sup>

## Conclusion

We are reporting two cases of LGMD here. Both the cases presented in pediatric age, had typical clinical features and suggestive biochemical profiles and genetically proven.

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