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Surprising genotype expressed as a common limb-girdle muscular dystrophy

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ABSTRACT

Limb-girdle muscular dystrophies (LGMDs) comprise a phenotypical spectrum of muscular dystrophies with a high degree of genotypical variability. We describe the case of a 56-year-old male with a history and clinical picture suggestive for LGMD with skeletal and cardiologic involvement.
Histopathological examination shows a severe dystrophic picture and genetics testing revealed a unique never reported genotype association: a homozygous variant in the DES gene, associated with myofibrillar myopaty type 1 and LGMD2R, as well as a heterozygous variant in the CRYAB gene, associated with myofibrillar myopathy type 2, both of which could be responsible for the clinical picture.

Keywords: limb-girdle muscular dystrophy, LGMD2R, myofibrillar myopathy (MMF), CRYAB

INTRODUCTION

Limb girdle muscular dystrophies (LGMDs) represent a phenotypical spectre of hereditary myopathies with predominantly progressive proximal muscle weakness but with heterogeneous age of presentation and great variability in their clinical course which can range from severe to very mild forms, often affecting the heart and respiratory muscles (1). Based on their inheritance pattern they are classified into autosomal dominant (LGMD1) and autosomal recessive (LGMD2), having an appended letter representing the order of discovery for each chromosomal locus (2,3). Next generation sequencing approaches have led to an increase in the number of LGMD genes from sixteen loci thirteen years ago (4) to thirty-one in the present, eight being autosomal dominant (LGMD1A-H) and twenty-three autosomal recessive (LGMD2A-W) (1).

In contrast, myofibrillar myopathies (MFM) are part of the LGMD spectrum but are defined by their common histopathological features and otherwise show a greater phenotypical variability with either skeletal, cardiac or mixed muscle abnormalities, the former also ranging from predominantly proximal muscle involvement to more distal forms. There are six known genes associated with MFM (DES, ABC, MYOT, LDB3, FLNC and BAG3) responsible mainly for abnormalities leading to mutant protein aggregation and their decreased elimination (5).

CASE PRESENTATION

We present the case of a 56-year-old male whose first clinical symptoms started about 15 years ago with proximal muscle weakness of the upper limbs followed by slow progression to the proximal low-

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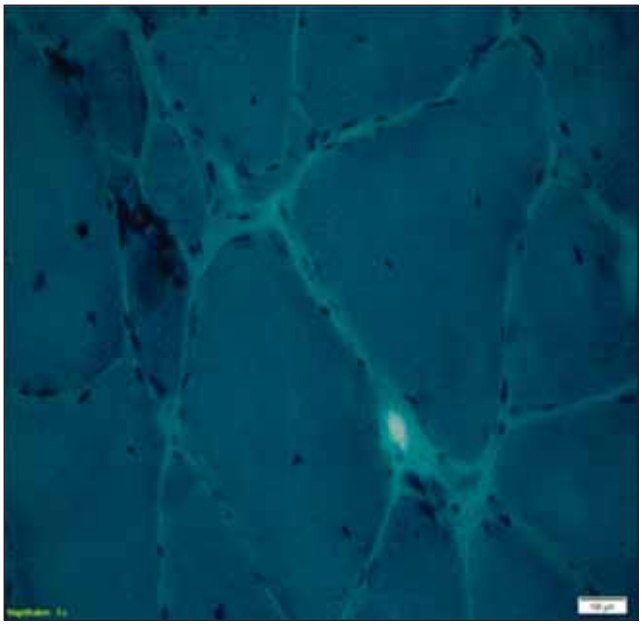
er limb musculature. Subsequently he developed gait abnormalities and difficulty at climbing stairs and rising from a squatting position or chair. His first visit to a physician was for symptoms of palpitations and dyspnea when he was diagnosed with dilated cardiomyopathy and atrial fibrillation. Family history is unremarkable, with no indications of similar diseases. He is an only child born of non-consanguineous parents and has no abnormalities concerning his birth history or developmental milestones.

Physical examination showed a waddling gait, with the impossibility of walking on toes and a positive Gowers' sign. He had proximal atrophy of all limbs, pseudohypertrophy of the calves and a symmetrical weakness of the upper limbs (shoulders – 3/5 MRC; elbow – 4/5 MRC; hand – 4/5 MRC) and lower limbs (hip joint - 3/5 MRC; knee – 3/5 MRC; ankle – 4/5 MRC). Deep tendon reflexes were globally diminished and fasciculations were absent. There was no involvement of extraocular, pharyngeal, neck flexors or facial muscles.

Routine laboratory testing showed only elevated creatinine phosphokinase (669 UI/L; reference range: 38-174 UI/L) and NT-proBNP (776 pg/mL; reference range: 0-125 pg/mL). Electrocardiography revealed atrial fibrillation and right bundle branch block, while the echocardiograpic examination showed changes suggestive for dilated cardiomyopathy with significant systolic dysfunction (left ventricular ejection fraction of 40%). Spirometry demonstrated a moderate restrictive ventilatory defect.

FIGURE 1. *Muscle fragment fixed in paraffin, hematoxylin-eosin staining*



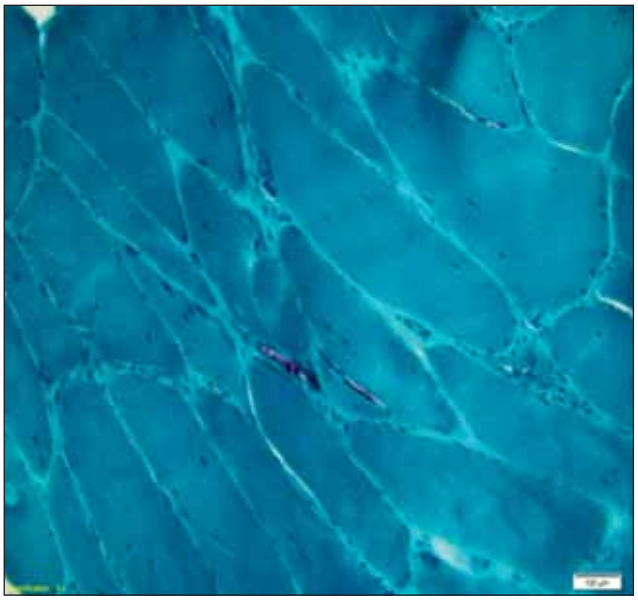


FIGURE 2, FIGURE 3. *Cryosections of muscle tissue, Gomori trichrome staining*

Nerve conduction studies were normal and needle electromyography performed in the right upper limb and left lower limb had a myopathic pattern.

Muscle biopsy from the right deltoid muscle showed a great variability in fibre size with both atrophic and markedly atrophic fibres and fatty infiltration (Fig. 1) as well as some hypertrophic ones. There is also fiber spliting, relatively rare fibers with multiple internal nuclei and some that show small areas of reduced oxidative enzyme activity. Gomori trichrome-stained sections exhibit intracitoplasmatic inclusions (Fig. 2) and rimmed

vacuoles (Fig. 3) suggestive of MFM. Immunohistochemistry demonstrated normal expression of dystrophin 1, 2 and 3, utrophin, alpha-, beta- and gamma-sarcoglycan and beta-dystroglycan but reduced dysferlin.

The patient benefited from genetic testing (next generation sequencing) through the "MYO-SEQ" project at The John Walton Muscular Dystrophy Research Centre, Newcastle University, UK. Based on the mode of inheritance and the clinical details provided, 169 genes were tested and two mutations that could potentially be responsible for the clinical picture were identified: a homozygous variant in the desmin (DES) gene (c.1245-3T>G) associated with MFM type 1 and LGMD2R and a heterozygous variant in the CRYAB gene (c.166C>T; p.Arg56Trp) associated with MFM type 2.

LGMD2R is an autosomal recessive form of limb-girdle muscular dystrophy associated with mutations in the DES gene which encodes for desmin, a muscle-specific member of the intermediate filament protein family that is present in skeletal, cardiac and smooth muscle cells (1,5). Patients with this mutation have progressive proximal muscle weakness and non-specific atrophy of both upper and lower limbs and they can also associate dilated cardiomyopathy and type 1 MFM (1) – as it appears to be the case with our patient. MFM type 1 with DES mutation has a clinical pattern that usually associates skeletal and cardiac muscle involvement with a median age of onset of 37 years (5). Most patients present with distal weakness, though some cases show initial proximal deficits which prompt to a possible limb-girdle muscular dystrophy (5). Prognosis is mainly determined by the severity of the cardiac involvement which can take the form of dilated, hypertrophic or restrictive cardiomyopathy as well as dysrhythmias or conduction defects leading to implantation of pacemakers, defibrillators or even heart transplantation (5). Respiratory involvement is also common.

The CRYAB gene encodes for alpha-B crystalin a small heat-shock protein found in cardiac and skeletal muscles that plays an important role as a chaperone for actin and desmin filaments, tubulin subunits of microtubules and other proteins (6). Mutations in the CRYAB gene lead to MFM type 2 (7). The clinical pattern usually consists of a predominantly distal muscle weakness of the lower limbs and a mostly proximal involvement of the upper limbs with typical onset between 30 and 40 years (8). Some patients have hypertrophic cardiomyopathy with rhythm abnormalities (8). While only partially superposing on our patient's clinical picture it should be considered that very few cases of this type of MFM have been reported.

CONCLUSION

We describe the association of mutations in two different genes, one potentially responsible for LGMD2R and/or MFM type 1, and another for MFM type 2. Both of them could be responsible for the patient's clinical presentation either alone or in association, the former having a much greater probability of phenotypical expression. We found no report in the literature of both mutations in a person with this clinical phenotype.

Even though there is an important skeletal muscle involvement with great impact on the patient's quality of life, prognostic factors mostly involve the accompanying cardiologic complications.

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REFERENCES

1. **Nigro V., M. Savarese.** Genetic basis of limb-girdle muscular dystrophies: the 2014 update. *Acta Myol,* 2014. 33(1): p. 1-12.
2. **Bushby K.M.** Diagnostic criteria for the limb-girdle muscular dystrophies: report of the ENMC Consortium on Limb-Girdle Dystrophies. *Neuromuscul Disord,* 1995. 5(1): p. 71-4.
3. **Bushby K.M., J.S. Beckmann.** The limb-girdle muscular dystrophies – proposal for a new nomenclature. *Neuromuscul Disord,* 1995. 5(4): p. 337-43.
4. **Nigro V., Piluso G.** Next generation sequencing (NGS) strategies for the genetic testing of myopathies. *Acta Myol,* 2012. 31(3): p. 196-200.
5. **Behin A. et al.** Myofibrillar myopathies: State of the art, present and future challenges. *Rev Neurol* (Paris), 2015. 171(10): p. 715-29.
6. **Graw J.** Genetics of crystallins: cataract and beyond. *Exp Eye Res,* 2009. 88(2): p. 173-89.
7. **Vicart P. et al.** A missense mutation in the alphaB-crystallin chaperone gene causes a desmin-related myopathy. *Nat Genet,* 1998. 20(1): p. 92-5.
8. **Fardeau M. et al.** Familial myopathy with desmin storage seen as a granulo-filamentar, electron-dense material with mutation of the alphaB-cristallin gene. *Rev Neurol* (Paris), 2000. 156(5): p. 497-504.