



## Case report

Late-onset limb-girdle muscular dystrophy caused by *GMPPB* mutationsHasan Balcin <sup>a,\*</sup>, Johanna Palmio <sup>b</sup>, Sini Penttilä <sup>b</sup>, Inger Nennesmo <sup>c</sup>, Mikaela Lindfors <sup>b</sup>,  
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## Abstract

Mutations in *GMPPB* gene have been reported in patients with early-onset disease ranging from severe congenital muscular dystrophies to limb-girdle muscular dystrophy (LGMD) with mental retardation. More recently mutations in *GMPPB* have been identified with congenital myasthenic syndromes as well as milder phenotypes. We report two unrelated cases with LGMD that underwent clinical, histopathological and genetic studies. In both cases, we found identical compound heterozygous *GMPPB* mutations c.79G>C p.D27H and c.859C>T p.R287W, leading to a glycosylation defect of alpha-dystroglycan. The onset of muscle weakness was 30–40 years and the progression rate mild to moderate. Case 2 became wheelchair-bound at the age of 60. No cognitive or behavioral symptoms were noted. These cases provide further evidence that *GMPPB* mutations can also cause late-onset recessive LGMD with milder phenotypes than previously reported, and thus should be considered in the differential diagnosis of patients with adult-onset muscular dystrophies.

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## 1. Introduction

Dystroglycanopathy is a collective term for a heterogeneous group of muscular dystrophies caused by aberrant glycosylation of alpha-dystroglycan ( $\alpha$ -DG), a sarcolemmal structural membrane protein, and leading to a loss of its laminin-binding activity [1–3]. Dystroglycanopathies have a wide clinical spectrum from severe forms of congenital muscular dystrophies (CMD) with brain and eye abnormalities, to milder phenotypes such as limb-girdle muscular dystrophy type 2I (LGMD2I). To date, mutations in 18 genes have been associated with glycosylation defect of  $\alpha$ -DG and all of them but DAG1-related mutations are known to cause secondary dystroglycanopathies [4,5].

*GMPPB* gene encoding guanosine diphosphate mannose pyrophosphorylase B protein plays an important role in the

glycosylation of proteins and lipids [6], including alpha-dystroglycan. Mutations in *GMPPB* cause hypoglycosylated  $\alpha$ -DG with phenotypes ranging from CMD with brain and eye abnormalities to severe intellectual disability and epilepsy to a case resembling LGMD with only mild cognitive disability [4,7–9]. The first reported cases had an early childhood-onset and typically severe disease with central nervous system (CNS) involvement. Later *GMPPB*-mutated adult- or adolescence-onset LGMD with or without intellectual disability was described [10–12]. More recently congenital myasthenic syndromes have been associated with *GMPPB* mutations as well [13,14]. In this report, we present two additional unrelated patients with milder adult-onset LGMD without CNS involvement caused by *GMPPB* mutations.

## 2. Case reports

## 2.1. Case 1

A 40-year-old woman of Swedish-Belgian descent, born to non-consanguineous parents, with normal motor milestones

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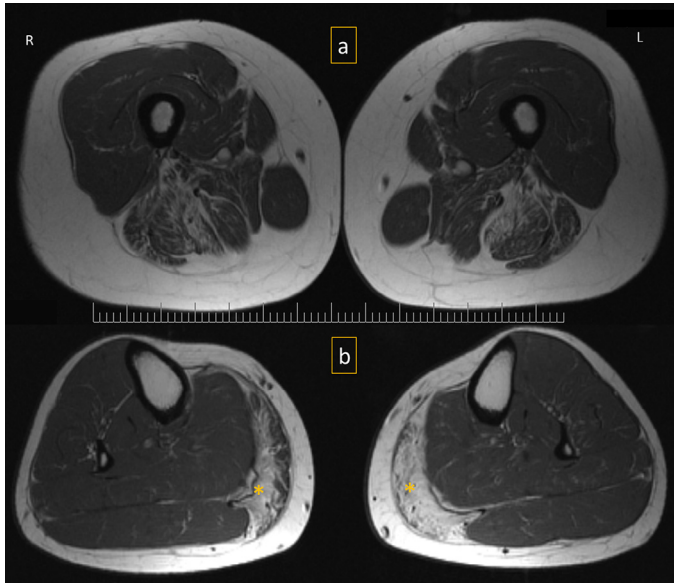


Fig. 1. Muscle imaging findings. Muscle MRI (Case 1), axial T1-weighted images, 1.5 Tesla, illustrating lower limbs, showing fat and connective tissue replacement in the posterior compartment of the thigh (a), especially of the hamstring muscles and of the medial gastrocnemius (\*) muscle bilaterally in the lower leg (b).

and without prior medical history. At the age of 15, the patient noticed poor performance in school sports without obvious weakness or exercise intolerance. Due to persistent elevation of liver enzymes at the age of 17, she underwent liver biopsy with a diagnosis of unspecified hepatitis. Aged 20, she had trouble climbing stairs and rising from the floor. On clinical examination, aged 37, she had waddling gait with a prominent Trendelenburg sign on the left side, left-sided scapular winging, mild calf hypertrophy, increased lumbar lordosis, and shortness of breath in the supine position without signs of nocturnal hypoventilation. Muscle testing (MRC) revealed: elbow flexion/extension and shoulder abduction 4/5, knee extension/flexion 3+/5, hip flexion/extension and abduction 2/5, neck-extension 4/5, neck-flexion 3+/5. Distal muscle strength was normal. CK values were 3–5 times of the upper limit of normal values (ULN) and liver enzymes, alanine aminotransferase and aspartate aminotransferase, varied between 1.5 and 5 times of ULN during the last decade. Echocardiography and 24 h-Holter-EKG were normal. Spirometry on two occasions showed slightly reduced forced vital capacity (78–84% predicted). EMG showed a myopathic pattern in the proximal muscles without spontaneous activity. By the age of 39, muscle weakness had progressed to involve the neck muscles, and the patient uses calipers indoor and electric scooter outdoor. Muscle MRI showed fatty degenerative changes in lumbar paravertebral, gluteus minimus, adductor longus, medial gastrocnemius and less pronounced in gluteus medius, semitendinosus, biceps femoris long head and adductor magnus muscles, without presence of notable edema (Fig. 1). No cognitive, behavioral, sensory, bulbar or cardiac symptoms have been reported by the patient. Brain MRI was normal.

## 2.2. Case 2

A 69-year-old Finnish woman, born to non-consanguineous parents, had unremarkable childhood and adolescence, and negative family history. She noticed first signs of muscle symptoms in her 30s, and progressive muscle weakness after the age of 40 with difficulties in climbing stairs, lifting objects and in ordinary walking but continued working until age 53. On initial examination, proximal weakness was evident and more pronounced in the lower limbs, gait was waddling but distal muscle strength preserved. The calves were pseudohypertrophic. The progression of the disease was moderate but steady; she started to use sticks at age 53 and motorized/electrical wheelchair at age 60. At the last examination (age 67) there was no active movement in the pelvic muscles or in ankle dorsal and plantar flexion. Knee extension and flexion was 2–2.5/5. Elbow and finger extension and flexion was 4/5, but arm abduction less than 90 degrees. There was no facial, bulbar or neck muscle weakness, no contractures or scapular winging. EMG showed myopathic changes and widespread spontaneous activity. CK values were constantly elevated up to 10 times ULN and liver enzyme alanine aminotransferase was elevated twofold. Echocardiogram and spirometry tests showed normal results. Cognitive or behavioral disturbances have not been noticed.

## 2.3. Muscle biopsy findings

### 2.3.1. Case 1

Biopsy from the deltoid muscle and vastus lateralis showed fiber-size variation, and fibers containing increased amount of internalized nuclei in both muscles. Necrotic fibers were present in the deltoid muscle (Fig. 2A). Immunohistochemical evaluation of dystrophin (DYS 1–3), beta-dystroglycan, spectrin, alpha-, beta-, gamma- and delta-sarcoglycan, myotilin (all from Novocastra NCL), merosin (Chemicon) and caveolin-3 (Santa Cruz Biotechnology) showed normal expression. Additional immunohistochemistry of  $\alpha$ -DG was performed on four occasions and each time revealed irregular patchy expression (Fig. 2B, C). Western blot analysis (WB) was conducted for calpain-3 and dysferlin (both from Novocastra NCL) with normal results. WB for  $\alpha$ -DG (Santa Cruz Biotechnology, (IIH6)) showed a markedly reduced immunostaining (Fig. 2D). The finding indicated a glycosylation defect of  $\alpha$ -DG.

### 2.3.2. Case 2

Three muscle biopsies from both distal and proximal muscles indicated general dystrophic changes: atrophic fibers, necrosis, fibrosis, and excess of fat. Immunohistochemistry performed 20 years earlier using DYS 2 antibody (Novocastra NCL) showed uneven staining and also WB showed reduced amount of DYS 2 leading to initial diagnosis of manifesting female carrier of dystrophinopathy.

## 2.4. Molecular genetic studies

Initial genetic analyses, such as *FKRP*, *CAPN3*, *DMD* and *DYSF*, showed normal results. Targeted next generation sequencing was performed as previously described [15] using version 2 of the MYOcap gene panel that is targeted to the exons

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