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CASE REPORTS

A novel compound heterozygous mutation in *PYGM* gene associated with McArdle's disease

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McArdle's disease is an autosomal recessive glycogenosis due to mutation in the myophosphorylase gene (*PYGM*) resulting in a pure myopathy. The clinical onset typically occurs in childhood with cramps, myalgia, and intolerance to physical exercise, although late onset forms are also reported. We describe a case of a 17-year-old male complaining of cramps and myalgia following brief and intense exercise. The patient reported marked improvement in muscle fatigability few minutes after starting aerobic exercise. When he was a child, he had experienced few episodes of vomiting, nausea, and black colored urine following physical activity. Laboratory testings revealed high creatine kinase serum levels. Genetic testings for metabolic myopathies demonstrated a compound heterozygous for two *PYGM* mutations (p.R570Q and p.K754Nfs*49) allowing the diagnosis of McArdle's disease. To date, 183 mutations in the PYGM gene are listed in Human Gene Mutation Database Professional 2021.2, but this novel compound heterozygosis has never been reported before.

Key words: McArdle's disease, glycogenosis, *PYGM*, hyperCKemia, second wind phenomenon

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Introduction

McArdle's disease, also known as glycogen storage disease (GSD) type V, is an autosomal recessive GSD due to mutations in the gene of myophosphorylase (*PYGM*) (NM_005609), located on chromosome 11q13; this condition leads to myophosphorylase deficiency and the subsequent reduction of glycogen breakdown in voluntary muscles thus blocking glycogenolysis [1]. As a consequence, the low levels of pyruvate and adenosine triphosphate cause, in turn, a fuel shortage in voluntary muscles, as well as the secondary impairment of oxidative phosphorylation [2]. Therefore, McArdle's disease results in a pure myopathy characterized by intolerance to static or dynamic exercise, myalgia, muscle's contractures and high serum creatin kinase levels (hyperCKemia); furthermore, there is a reduced oxygen consumption during exercise and an unbalanced exercise-induced increase in heart rate. Symptoms occur in childhood in most patients, although the diagnosis may be delayed until 30 years of age [1]. To date, 183 mutations affecting *PYGM* gene are listed in Human Gene Mutation Da-

tabase Professional 2021.2 including missense and nonsense mutations, splicing mutations, small insertions and deletions (http://www.hgmd.cf.ac.uk). Herein, we report the case of a young male referred to our Neuromuscular Clinic for intolerance to static exercise and hyperCKemia who was diagnosed with McArdle's disease caused by a novel compound heterozygous mutation in *PYGM* gene.

Case report

In January 2020, a 17-year-old boy presented to our Neurologic Clinic at the University Hospital "Paolo Giaccone", Palermo, Italy, complaining of isolated muscle cramps and myalgia after brief and intense exercise. The past medical history was non-contributory, despite he reported the occurrence of vomiting, cephalalgia and black-colored urine following physical exercise in childhood. His parents were not consanguineous and they did not suffer from any neurological disease. The young boy exhibited an occasional laboratory analysis showing hyperCKemia (2937 U/L [normal value 26-192 U/L]) and elevated myoglobin (174,5 ng/ml [normal value less than 60 ng/ml]) and troponin (122.5 pg/ml [normal value less than 14 pg/ml]) serum levels. Other laboratory parameters (i.e., complete blood count, urinalysis, liver function, creatinine and urea) were within normal limits. The neurological examination showed mild motor weakness at biceps and triceps brachii bilaterally (grade 4 according to Medical Research Council) in absence of muscle wasting. Sensory function, deep tendon reflexes and coordination were normal. As a myopathy was suspected, the patient underwent to needle-electromyography of the proximal and distal muscles of the upper and lower limbs, which showed the presence of small motor unit potentials without spontaneous activity in overall tested muscles (Fig. 1). Subsequently, the patient underwent to monthly serum CK testing with the finding of dramatic hyperCKemia (11.375 U/l) in the days following vigorous physical exercise. However, serum CK in his parents was normal. In further examinations, the patient reported marked improvement in muscle fatigability few minutes after starting aerobic exercise. Hence, genetic testing for metabolic myopathies was performed with a high suspicion of McArdle's disease.

The proband and his parents signed the informed consent forms for diagnostic workup and genetic analysis. The documents were those currently in use at "P Giaccone" University Hospital, Palermo, Italy and at Association Oasi Maria SS, Troina, Enna, Italy. Genetic testing was performed via Next Generation Sequencing (NGS), which included a complete genetic panel for metabolic myopathies. The presence of pathogenetic or potentially pathogenetic variants was confirmed by Sanger

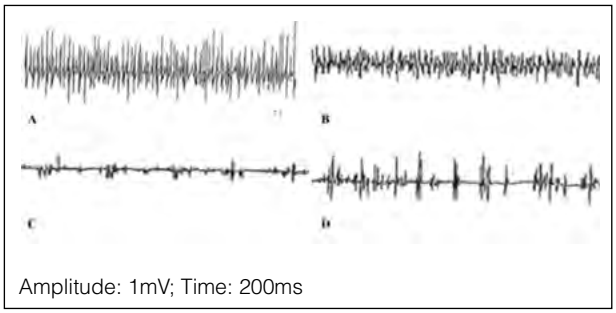

Figure 1. Needle-electromyography during maximal muscular contraction shows early motor unit recruitment as well as the presence of both small and high-amplitude motor units potentials at right biceps brachii (A); small and polyphasic motor unit potentials are showed at right deltoideus (B), right gastrocnemius (C) and right tibialis anterior (D)

sequencing. Variant analysis was performed employing bioinformatic prediction tools (i.e., Mutation Taster, Sift, Polyphen, ClinVar) and the pathogenicity classification was conducted according to the American guidelines College of Medical Genetics and Genomics (ACMG). NGS revealed the missense mutation c.1709G > A (p.R570Q) and the frameshift mutation c.2262delA (p.K754Nfs*49) in a novel compound heterozygous of the *PYGM* gene, confirming the diagnosis of McArdle's disease (Fig. 2).

The patient routinely underwent to urinalysis and laboratory testings (i.e., CK, urea, creatinine). He was recommended to avoid toxic drugs such as statin and isometric exercise in favor to mild aerobic exercise. Also, carbohydrates assumption before physical activity was recommended. At the scheduled follow-up visits after six, twelve and eighteen months from the diagnosis, the neurological examination was normal without disease progression although serum CK was persistently elevated (i.e., 2555 U/l, 2204 U/l and 3055 U/l respectively).

Discussion

We described a case of McArdle's disease caused by a novel compound heterozygous mutation in the *PYGM* gene consisting of the missense mutation p.Arg570Gln (p.R570Q;c.1709G > A) and the frameshift mutation p.Lys754AsnfsTer49 (p.K754NfsX49; c.2262delA), in the exons 14 and 18, respectively (Fig. 2). The familiar segregation analysis showed the presence of p.R579Q and p.K754NfsX49 mutations in the mother and in the father of the proband, respectively (Fig. 3). Both these mutations are known as pathogenetic, although their compound heterozygous has never been reported to date. The p.R570Q mutation was found to be in compound

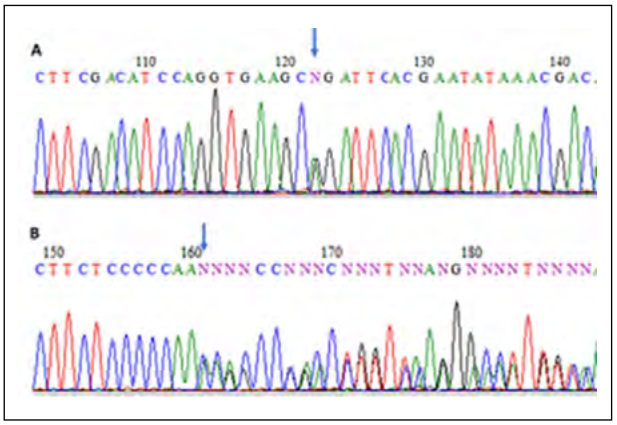

Figure 2. Electropherogram of the exon 14 region encompassing the c.1709A > G mutation (p.R570Q) in *PYGM* gene (A); Electropherogram showing the A deletion at nt2262 in the exon 18 resulting in a frameshift and a premature termination of the protein 47 amino acids downstream of the mutation (B).

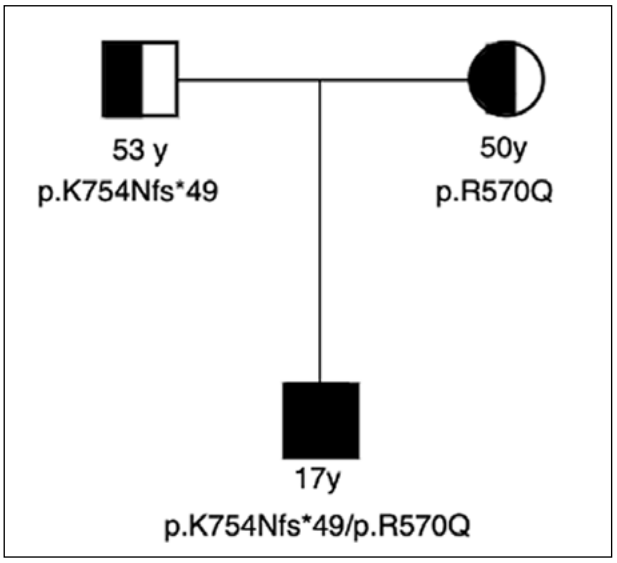

Figure 3. Familiar segregation analysis. The parents of the proband are healthy carriers for mutations; the proband was found to be compound heterozygous for p.R570Q and p.K754NfsX49 mutations in *PYGM* gene.

heterozygosis with the p.R50X in a Portuguese patient[3]. Moreover, the p.K754NfsX49 mutations was found to be homozygous or in compound heterozygous together with the p.R50X mutation [4]. The genotypes p.R50X/p.R50X and p.R50X/p.W798R account for about the 50% of *PYGM* genotypes undelying McArdle's disease; indeed, the p.R50X nonsense mutation in the exon 1 of *PYGM* gene, is the most frequent mutation in Caucasian and Brazilian patients, whereas it has not been found in Japan, where the most frequent is the p.F710del mutation [5]. The clinical heterogeneity (e.g., age at symptoms onset, disease severity, neurological impairment) and an unclear genotype-phenotype relationship make challenging the diagnosis of McArdle's disease. The complete absence of *PYGM* enzymatic activity and the absence of its gene-transcript in overall *PYGM* mutations have been reported as underlying factors of the lacking genotype-phenotype relationship [6]. However, Vissing et al. reported a little genotype-phenotype correlation in McArdle's disease, because of two patients affected by milder phenotype of McArdle's disease were found to be compound heterozygous for deep intronic mutations and other alleles with a subsequent residual *PYGM* enzymatic activity [7]. However, although we did not test the *PYGM* enzymatic activity, our case resembles a typical case of McArdle's disease. In this scenario, it is reasonable to collect a detailed medical history focusing on exercise intolerance, both static and dynamic as well as on vomiting episodes, cephalalgia and black colored urine following physical activity. Moreover, the "spontaneous second wind phenomenon" and the "glucose-induced second wind phenomenon" are highly specific and sensitive for McArdle's disease; the former refers to the marked improvement in muscle fatigability between 8 and 10 minutes after starting exercise, whereas the latter indicates the rapid improvement in exercise-tolerance after intravenous glucose infusion [8]. The biochemical mechanisms underlying the "glucose-induced second wind phenomenon" are strictly connected with the recommendation to assume carbohydrates before exercise. Moreover, the persistently elevated serum CK levels with episodic peaks following short-intensity exercise, as well as a normal level of serum lactate after forearm exercise, support the clinical suspicion of McArdle's disease even with a normal neurological examination [9]. Finally, the muscle biopsies of the vastus lateralis or the biceps brachialis might show subsarcolemmal or intermyofibrillar glycogen deposits driving toward the diagnosis of McArdle's disease [10]. However, given the availability of NGS with a genetic panel for metabolic myopathy and the stringent pandemic restrictions, genetic testing was the first choice for the diagnosis. Future studies are needed to better clarify the genotype-phenotype relationship in McArdle's disease.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Authors' contributions

SI, AL and VDS diagnosed and followed up the patient. EB performed the genetic analyses. SI drafted the manuscript. SI, AL, VDS and FB designed the report and made the final revision. All authors reviewed and approved the final version of the manuscript.

Ethical consideration

The manuscript in part or in full has not been submitted or published anywhere. All procedures were in accordance with the standards of the bioethical committee and the Declaration of Helsinki.

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