

Alpha-sarcoglycanopathy presenting as myalgia and hyperCKemia in two adults with a long-term follow-up. Case reports

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Two patients with a paucisymptomatic hyperckemia underwent a skeletal muscle biopsy and massive gene panel to investigate mutations associated with inherited muscle disorders. In the *SGCA* gene, sequence analyses revealed a homozygous c.850C > T/p.Arg284Cys in patient 1 and two heterozygous variants (c.739G > A/p.Val247Met and c.850C > T/p.Arg284Cys) in patient 2. Combination of histology and immunofluorescence studies showed minimal changes for muscular proteins including the α -sarcoglycan. These two cases highlight the advantages of next-generation sequencing in the differential diagnosis of mild myopathic conditions before considering the more invasive muscle biopsy in sarcoglycanopathies.

Key words: hyperCKemia, Next Generation Sequencing, muscle biopsy, *SGCA*

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Conflict of interest

The Authors declare no conflict of interest

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Introduction

Elevated blood creatine kinase (CK) is among the signs most likely to prompt referral of children and adults to neuromuscular specialists in Europe (ean.org/Guideline-Reference-Center.2699.0.html). Current international guidelines define persistent hyperCKemia as the presence of serum values more than 1.5 times the upper limit of normal in at least two independent measurements¹, but this definition does not consider the presence or absence of associated clinical manifestations. Indeed, asymptomatic hyperCKemia can run in families long before its chance detection. On the other hand, recent advances clarifying the genetic etiologies of muscle disorders have been crucial in reducing the number of undefined hyperCKemia cases and expanding the spectrum of manifestations associated with the condition. For example, using a multiple gene panel and next-generation sequencing (NGS) in a small cohort of undiagnosed patients with hyperCKemia, we recently detected a subset of paucisymptomatic individuals harboring biallelic variants in known muscular dystrophy genes².

We herein discuss two patients who showed persistent high serum CK levels and occasional exercise intolerance and myalgia in the absence of other neurological signs over a long-term follow-up. Both cases harbored biallelic variants of predicted pathogenic significance in *SGCA*. Patient

1 is 36-year-old man with an unremarkable prenatal and perinatal history and normal psychomotor development. He was first evaluated, because of persistent high CK levels at rest (ranging from 1700 to 8000 UI/L), at the age of 10 years. At that time his neuromuscular examination was unremarkable. At the age of 20, having more recently developed exercise intolerance and sporadic myoglobinuria after competitive exercise, he experienced two episodes of atrial fibrillation. After remission of his symptoms, he recovered completely and is still able to cycle and run for long distances, albeit with occasional muscle pain. At his latest neurological examination, which was unremarkable, moderate calf hypertrophy was observed.

Patient 2 is a 31-year-old woman with a history, from early childhood, of hyperCKemia (ranging from 500 UI/L to 4500 UI/L), almost invariably accompanied by myalgia and exercise intolerance. These complaints persisted unchanged over time in a context of normal psychomotor development. Her family history was significant for an asymptomatic uncle who had persistent high serum CK levels. The patient has undergone annual specialist evaluations over the past 25 years. Her latest neurological, cardiac and respiratory examinations were normal, but we observed minimal hypertrophy of the calves. A muscle MRI study of lower girdle muscles was unremarkable but we observed fat infiltration in the right gluteus minimus (Fig. 1).

In the course of their lives, both patients have twice undergone muscle biopsy; all these examinations showed only minimal myopathic changes on histological assessment and normal immunofluorescence staining for muscle proteins including α -sarcoglycan (Fig. 2). Using a massive gene panel to investigate genes associated with inherited muscle disorders², we identified a homozygous c.850C > T/p.Arg284Cys mutation in patient 1 and two variants (c.739G > A/p.Val247Met and c.850C > T/p.Arg284Cys) in compound heterozygosity in patient 2 in the *SGCA* gene. Both variants were predictably deleterious, with high CADD scores (<https://cadd.gs.washington>.

edu/); both segregated with the disease status in the respective families (Fig. 3), and met the American College Medical Genetics and Genomics recommended criteria for possible pathogenic variants³.

The mutations detected in this study have already been reported in association with myoglobinuria, high CK levels and limb girdle muscle weakness^{4,5}. Our report adds to the evidence that hyperCKemia can be the presenting feature of a sarcoglycanopathy associated with myoglobinuria, exercise-induced myalgia and/or rhabdomyolysis. Contrary to previous reports, our long follow-up of these patients, characterized by unremarkable neurological examinations and only minimal, pseudometabolic complaints, suggests that a sarcoglycanopathy can go undetected in patients and families. This suggests that caution should be exercised before dismissing cases of asymptomatic hyperCKemia as idiopathic, and that such cases should be monitored closely for potential severe myoglobinuria and rhabdomyolysis following minimal exercise. Our report is also significant as it might draw attention of neuromuscular experts to the value of the NGS approach, which can play a fundamental diagnostic role and may obviate the need to perform muscle biopsies in patients with asymptomatic hyperCKemia⁶⁻⁸. In our patients, the combination of muscle histology and immunofluorescence alone would not have identified the cause of the symptoms. This suggests that a first-tier NGS screening in blood should be favoured, especially in children, before considering the more invasive muscle biopsy option, which could instead be kept as a second-level diagnostic approach to be used in the event of uncertain or negative results. Whether other factors besides the genetic mutation influence phenotypic manifestations in sarcoglycanopathies remains unclear and should be further investigated.

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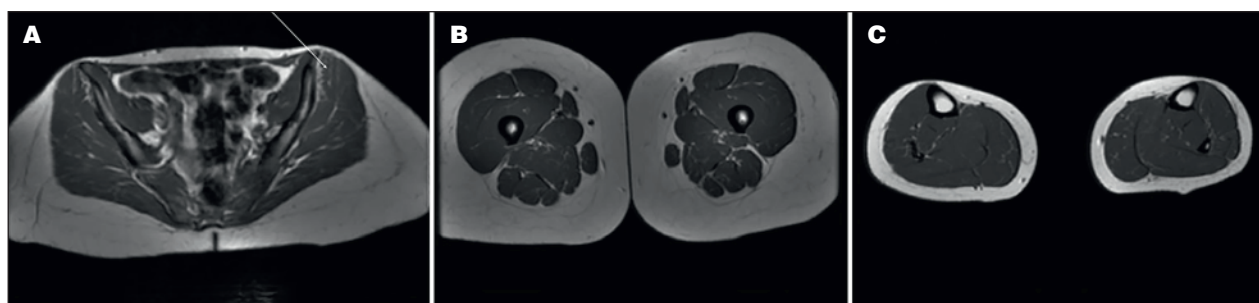


Figure 1. Muscle MRI findings in patient 2 at pelvi (A), thigh (B) and calf level were obtained using conventional T1-weighted spin-echo transverse images. No muscles fat infiltration were evident in all muscles except in the right gluteus minimus.

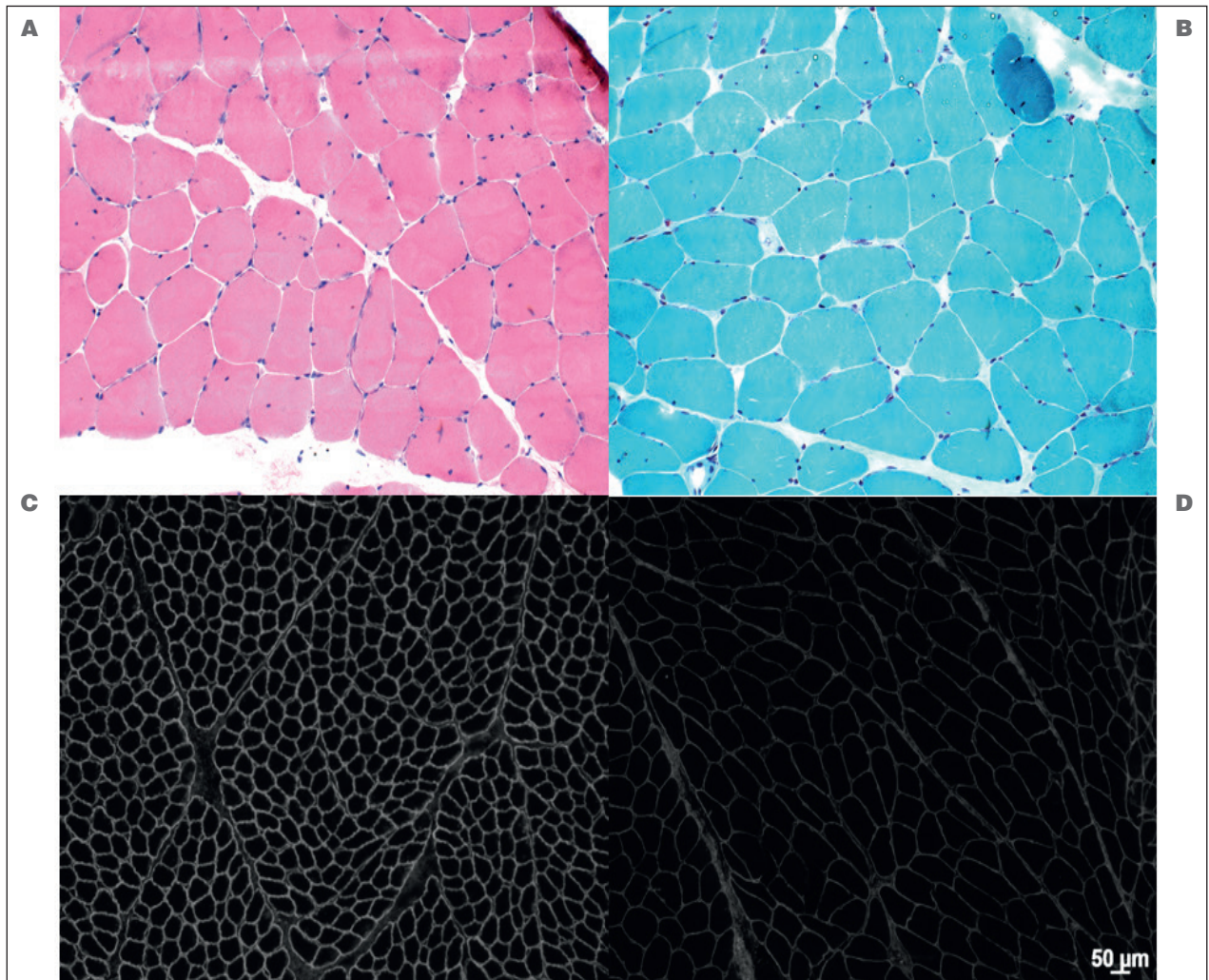


Figure 2. Myopathological changes in patient 2. Hematoxylin and eosin (A) and Gomori trichrome (B) staining demonstrating slight variation in fiber size and some central nuclei. Immunofluorescence labeling of α -sarcoglycan showing decreased expression in patient 2 (D) compared with an age-matched healthy control (C).

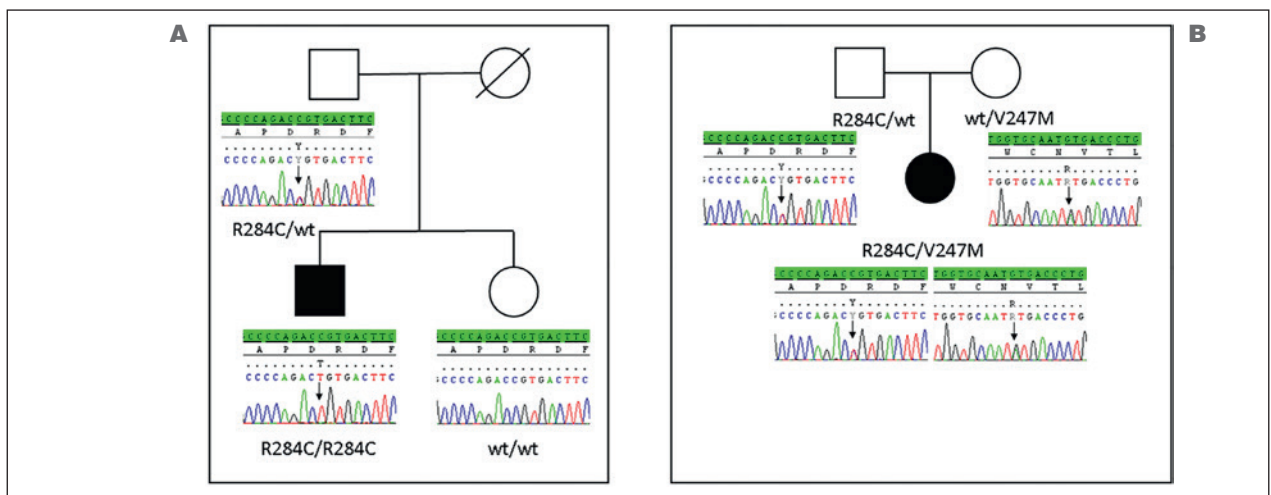


Figure 3(A-B) Genetic studies. Pedigree of the family and electropherograms showing the segregation of the variants in the family members.

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