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ScienceDirect
Neuromuscular Disorders 000 (2018) 1–5
www.elsevier.com/locate/nmd

Case report

A novel compound heterozygous mutation in the *POMK* gene causing limb-girdle muscular dystrophy-dystroglycanopathy in a sib pair

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Received 21 December 2017; received in revised form 5 April 2018; accepted 26 April 2018
Available online xxx

Abstract

We describe two Finnish siblings in whom an incidentally detected elevated creatine kinase activity eventually led to a diagnosis of limb-girdle muscular dystrophy-dystroglycanopathy (Type C12; MDDGC12). When diagnosed at age 10 and 13 years, they were mildly affected with a slow or non-progressive disease course. The main symptoms comprised infrequent hip cramps triggered by flexion, neck cramps triggered by yawning, transient growing pains, calf hypertrophy and mild proximal muscle weakness. Their cognitive and motor developments were unremarkable and they were physically active. Whole-exome sequencing revealed compound heterozygous mutations, both of which were novel, in the protein O-mannosyl kinase *(POMK)* gene in both siblings; a missense mutation, p.Pro322Leu (c.965C > T), and a nonsense mutation, p.Arg46Ter (c.136C > T). The results were confirmed by Sanger sequencing, showing that the parents were heterozygous carriers of one mutation each. This report adds to the literature by providing phenotype and genotype data on this ultra-rare *POMK*-related dystroglycanopathy.

Keywords: Protein-O-mannosyl kinase; *POMK*; Dystroglycanopathy; Limb-girdle muscular dystrophy-dystroglycanopathy type 12 C; MDDGC12; LGMD12C; Muscular dystrophy.

1. Introduction

Dystroglycanopathies are a group of muscular dystrophies characterised by considerable clinical and genetic heterogeneity. They are caused by disruption in the interactions between the transmembrane protein dystroglycan and extracellular matrix components. These interactions are necessary for normal muscle and brain development [1]. In these interactions, glycosylation plays a crucial role. Most known dystroglycanopathy mutations are located in genes related to the glycosylation process rather than in the dystroglycan gene itself [1].

The *POMK* gene (MIM 615247), located on chromosome 8p11, encodes the protein O-mannose kinase which is necessary for proper glycosylation and function of the dystroglycan complex [2]. Biallelic mutations in the *POMK* gene cause limb-girdle muscular dystrophy-dystroglycanopathy (type C12; MDDGC12) (MIM 616094). To our knowledge, two such families have been described; one in which two

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https://doi.org/10.1016/j.nmd.2018.04.012
0960-8966/

Jordanian sibs presented with limb-girdle muscular dystrophy (LGMD) and cognitive impairment, and another in which a child born to consanguineous parents presented with LGMD, mild learning difficulties and congenital mirror movements [1,3]. *POMK* mutations can also cause the more severe Walker–Warburg syndrome (Muscular dystrophy-dystroglycanopathy, congenital with brain and eye anomalies, type A12; MDDGA12) (MIM 615249), encompassing brain and eye abnormalities in addition to the muscular dystrophy. To our knowledge, three such families have been described in previous reports [1,2,4]. Due to the small number of cases described, little is known about the range of clinical variability of disorders caused by *POMK* mutations.

We report clinical, molecular, histological, neurophysiological and imaging data on a sib pair with limb-girdle muscular dystrophy-dystroglycanopathy type C12, caused by a novel compound heterozygous mutation in the *POMK* gene. The incidental finding of an elevated serum creatine kinase (CK) activity in the probands in infancy, which eventually led to the diagnosis, allowed for observation of the onset and the progression of the disease.

2. Case report

2.1. Clinical phenotype

The probands comprise a Finnish sib pair born to non-consanguineous parents. The older sister was born at term with birth asphyxia due to placental abruption. She suffered a mild asphyxia-related kidney injury for which she was on follow-up. At 6 years of age, while being investigated for elevated liver enzymes, she presented with elevated CK values of 1000–4000 U/L. Her motor and cognitive developments as well as her growth were normal. She started walking at age 15 months. Her visual acuity was normal. She had unilateral high-frequency hearing loss (hearing threshold 65 decibel at 6000 and 8000 Hz). In childhood she suffered from transient growing pains. Since school age she has experienced infrequent hip cramps triggered by hip flexion when doing for instance sit-ups, and by cramps in the neck region triggered by yawning. She has, at times, suffered from exercise-induced knee ache. Testing of muscle strength at 10 years of age using myometry showed muscle power slightly below average for hip adductors and abductors, as well as for knee extensors and ankle plantar flexors, as compared with normative values. On the contrary, muscle power in other arm and leg muscle groups were equal to or even stronger than average [5]. Subsequent evaluations showed muscle strength within normal limits.

Her electromyography (EMG) findings were normal, however, only one muscle (right gastrocnemius) was examined due to her fear of needles. Neurography of the median, tibial peroneal and sural nerves gave normal results. A muscle biopsy at 7 years of age was paraffin-embedded and showed normal findings. Echocardiography (followed up every two years starting from 7 years of age, with the latest evaluation done at 14 years of age) and spirometry showed no signs of cardiac or respiratory involvement. Magnetic resonance imaging (MRI; 1,5 T scanner) with T1-weighted and STIR images of muscles in shoulders, upper arms, thighs and pelvic region was normal, without signs of fatty replacement or edema (not shown).

The younger brother was born preterm by caesarean section due to placenta praevia. His motor and cognitive developments as well as his growth were unremarkable. He started walking at age 13 months. He had normal hearing and visual acuity. As a consequence of his sisterś incidentally detected CK elevation, his CK level was determined, showing markedly increased levels of up to 6800 U/L. In childhood, he suffered from transient nocturnal growing pains. He also suffered from thigh stiffness and infrequent pain and cramps in the thighs and groins triggered by hip flexion. Like his sister, he experienced infrequent neck region cramps triggered by yawning. Muscle strength in his hip abductors and adductors as well as upper limbs was slightly weak, making it, at times, difficult for him to do sit-ups and arm push-ups.

His EMG was normal (neurography of tibial, peroneal and sural nerve, as well as myography of vastus lateralis, tibialis anterior and biceps). A muscle biopsy taken from the vastus lateralis muscle at age 6 showed moderate chronic myopathic changes, small groups of regenerating fibres, sparse inflammatory cell infiltrates, α-dystroglycan deficiency in a majority of fibres with preserved expression in single, scattered fibres and normal merosin immunolabelling (Fig. 1). The major histocompatibility complex 1 (MHC1) protein was slightly up-regulated (not shown). Electrocardiography (ECG) showed isolated persistent deep Q-waves in leads V5-6 from the age of 5 years onwards. At the age of 7 years, the boy had a history of syncope of unknown etiology (electroencephalography, echocardiography and 24-h ECG were normal). Echocardiography was normal at initial evaluation at the age of 5 years but gradually turned pathological after the age of 8 years, revealing mild enlargement and borderline weakened function of the left ventricle by the age of 12 years. No cardiac MRI was done. The boy is on regular cardiac follow-up (echocardiography and 24-h ECG) every 6–24 months and receives no treatment. There were no signs of respiratory involvement. MRI findings (1,5 T, T1-weighted and STIR images) in the muscles of the shoulder region, upper arms, thighs and pelvic region were within normal limits, without signs of fatty replacement, although with minimal high signal changes in the right shoulder and left pelvic and thigh regions (not shown).

On clinical examination at age 13 and 10 years, respectively, both the sister and brother had calf hypertrophy (Fig. 2), mild lumbar lordosis and slightly winged scapulae, brisk tendon reflexes (interpreted as normal) in the lower extremities, weakened but positive tendon reflexes in the upper extremities, absent Babinski signs and negative Gowerśigns. They had no mirror movements, which have been related to *POMK* mutations in a previous report [3]. The brother had difficulty in walking on heels. Both sibs were physically active and considered themselves symptom-free and as physically fit as their peers. Brain MRI was not performed.

Please cite this article as: S. Strang-Karlsson et al., A novel compound heterozygous mutation in the *POMK* gene causing limb-girdle muscular dystrophy-dystroglycanopathy in a sib pair, Neuromuscular Disorders (2018), https://doi.org/10.1016/j.nmd.2018.04.012