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A homozygous DPM3 mutation in a patient with alpha-dystroglycan-related limb girdle muscular dystrophy

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Abstract

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Keywords: Limb girdle muscular dystrophy; Alpha-dystroglycan; Dolichol-P-mannose synthase; DPM

1. Introduction

Limb girdle muscular dystrophies (LGMD) represent an increasingly large and heterogeneous group of autosomal dominant and recessive disorders. In many patients, the molecular origin remains unknown and next generation sequencing has become a very important tool to hasten the genetic diagnosis and to identify variants and mutations in genes not previously associated with LGMD. Here, we report an adult female patient with autosomal recessive LGMD (LGMD2), in whom exome sequencing by inclusion in the MYO-SEQ project (Newcastle upon-Tyne, UK) revealed a homozygous substitution in DPM3, encoding dolichol-P-mannose (DPM) synthase subunit 3.

2. Case report

The patient’s medical history was uneventful. Early motor developmental milestones normally acquired and the patient started walking at the age of 1 year. At age 30 years, the patient presented with right-sided painful brachial plexopathy. Otherwise, the clinical neurological examination was normal. The neurological work-up was indicative of an inflammatory origin and the patient was diagnosed with neuralgic amyotrophy. She recovered within a few weeks. Surprisingly, serum creatine kinase (CK) activity was elevated at 4310 IU/L (N < 200). A deltoid muscle biopsy only showed mild nonspecific myopathic changes. At age 42, the patient had difficulty rising from a chair and developed an unsteady gait with tendency to fall. Because of persistingly high CK levels (2732 IU/L), a quadriceps muscle biopsy was performed, which showed a dystrophic pattern and alpha-dystroglycan (aDG) deficiency as demonstrated by immunoblotting with a IIH6C4 antibody at 1:500 dilution (Millipore SA, Overijse, Belgium)
This led to the diagnosis of aDG-related LGMD. No mutations in FKRP were found. At age 57, proximal lower limb weakness had clearly progressed. The patient could not get up from a chair without using her hands and had difficulty going upstairs. Manual muscle testing (MRC grades) showed the following abnormalities: gluteus maximus 0/5; iliopsoas and quadriceps 3/5; gluteus medius and adductors 2/5; hamstrings 4/5, tibialis anterior, tibialis posterior, peroneus longus, and triceps surae 3/5. Gowers sign was positive. Deep tendon reflexes, cranial nerves and sensation were normal. Brain MRI, respiratory, cardiac and ophthalmologic work-up were unremarkable. Nerve conduction studies were normal. EMG showed brief small amplitude polyphasic motor unit action potentials with early recruitment in the iliopsoas muscle. Muscle MRI results are shown in Fig. 2. There is no family history of neuromuscular disease. The mother died at age 94 of pancreas carcinoma. The father is healthy at age 95. One brother died at age 58 of intestinal cancer, one sister at age 39 of a brain tumour. Two other sisters and 2 sons are healthy. Serum CK levels were normal in the father and the 2 sisters.

3. Molecular analysis

Exome sequencing by inclusion into MYO-SEQ (Newcastle University, Newcastle upon-Tyne, UK) was performed at the Broad Institute’s Genomics Platform, using Illumina exome capture. A homozygous c.131T > G (p.Leu44Pro) substitution was identified in DPM3 (gene coverage 95%). DPM3 encodes DPM synthase subunit 3. This change is extremely rare in the control population (MAF = 0.00084%) and only found in the heterozygous state. Leu44 is an evolutionary highly conserved amino acid and a change to proline is predicted to be pathogenic by *in silico* tools (Mutation Taster, PolyPhen, UMD-Predictor and SIFT). Segregation studies identified heterozygosity in the father and in one of the two sisters. Maternal DNA was not available. Transferrin isoelectric focusing as well as mass spectroscopy of transferrin N-glycans in serum [1] were normal, indicating that N-glycosylation was well preserved in liver and serum. DPM synthase activity was analysed according to Barone et al [2] by measuring the formation of radio-active DPM in cultured fibroblasts and was reduced by 50% as compared to a healthy control.

4. Discussion

We report a patient with mild LGMD2 and without central nervous system involvement, caused by a homozygous substitution in DPM3. This gene encodes DPM synthase subunit 3 and we found that the enzymatic activity of DPM synthase was reduced by 50%. DMP synthase is an enzyme complex composed of 3 protein subunits, DPM1, DPM2, and DPM3. Whereas DPM2 stabilises the complex, DPM3 tethers...
the catalytic subunit (DPM1) to the endoplasmic reticulum membrane [3]. DPM synthase catalyses the synthesis of DPM from GDP-mannose and dolichol phosphate. As DPM is an essential donor substrate required in different glycosylation pathways (N-glycosylation, C- and O-mannosylation, GPI-anchor formation) [4,5], it is not surprising that O-mannosylation of aDG, catalysed by protein O-mannosyltransferase (POMT) 1 and 2, is compromised when one of the subunit-encoding genes is mutated. This was first reported in an 11-year-old female patient with mild LGMD2 and a 254T>C (p.L85S) mutation in DPM3 [6]. At age 20, she developed dilated cardiomyopathy and at age 21, she had a stroke-like episode involving the right temporo-parietal region with normal brain MRI. In addition to abnormal N-glycosylation, deficient O-mannosylation of aDG was confirmed in a muscle biopsy and the disorder was classified as DPM3-CDG. Later, Barone et al [2] reported 3 children from 2 families with DPM2 mutations with profound developmental delay, intractable seizures, microcephaly, and early fatal outcome. The patients had aDG-deficient congenital muscular dystrophy. DPM1 mutations have been reported in 7 cases with various degrees and combinations of early onset encephalopathy, seizures, microcephaly, dysmorphic features, developmental delay, optic atrophy, and cerebellar dysfunction [7–10]. These were classified as Congenital Disorders of Glycosylation (CDG) type I (DPM1-CDG) due to abnormal N-glycosylation. In 5 of these patients, CK levels were elevated but evidence of muscular dystrophy was not reported. In 2013, Yang et al [11] reported an infant with DPM1 mutations and showed deficient O-mannosylation of aDG as well, presenting with aDG-deficient congenital muscular dystrophy with seizures but otherwise minimal central nervous system involvement on MRI only. Our findings show that abnormal aDG O-mannosylation related to DPM3 mutations may lead to LGMD2 phenotype without cardiomyopathy or central nervous system involvement and with presumably normal N-glycosylation.

References


