Whole exome sequencing identified a novel DAG1 mutation in a patient with rare, mild and late age of onset muscular dystrophy-dystroglycanopathy.

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Abstract

Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 9 (MDDGC9) is the rarest type of autosomal recessive muscular dystrophies. MDDGC9 is manifested with an early onset in childhood. Patients with MDDGC9 usually identified with defective glycosylation of DAG1, hence it is known as "dystroglycanopathies". Here, we report a Chinese pedigree presented with mild MDDGC9. The proband is a 64 years old Chinese man. In this family, both the proband and proband's younger brother have been suffering from mild and late onset MDDGC9. Muscle biopsy showed that the left deltoid muscle with an advanced stage of dystrophic change. Immunohistochemistry staining of dystrophin, α-sarcoglycan, β-sarcoglycan and dysferlin are normal. Molecular genetic analysis of the proband has been done with whole exome sequencing. A homozygous novel missense mutation (c.2326C>T; p.R776C) in the exon 3 of the DAG1 gene has been identified in the proband. Sanger sequencing revealed that this missense mutation is co-segregated well among the affected and unaffected (carrier) family members. This mutation is not detected in 200 normal healthy control individuals. This novel homozygous missense mutation (c.2326C>T) causes substitution of arginine by cystine at the position of 776 (p.R776C) which is evolutionarily highly conserved. Immunoblotting studies revealed that a significant reduction of α-dystroglycan expression in the muscle tissue. The novelty of our study is that it is a first report of DAG1 associated muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 9 (MDDGC9) with mild and late age of onset. In Chinese population this is the first report of DAG1 associated MDDGC9.

KEYWORDS: DAG1 gene; MDDGC9; muscular dystrophy-dystroglycanopathy; whole exome sequencing; α-dystroglycan
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