Muscular dystrophy-dystroglycanopathy (MDDG) is a heterogeneous group of inherited muscular dystrophies caused by glycosylation defects of extracellular matrix elements. Clinically, this group of disease is characterized by progressive muscle weakness, hypotonia, and obviously elevated serum creatine kinase levels. Structural brain anomalies including agyria, hydrocephalus, cerebellar cysts, and brain stem hypoplasia or ocular defects such as cataracts and microphthalmia may also accompany.[1,2] In pathophysiological aspect, disruption in binding of cellular α-dystroglycan to its extracellular matrix ligands is the characteristic finding of the disease.[3] Thus far, some different mutations were identified especially in genes encoding α-dystroglycan or glycosyltransferases.[4] Protein O-mannose β-1,2-N-acetylglucosaminyltransferase 1 (POMGNT1) is one of the pathogenic genes involved in glycosylation defects of α-dystroglycan and responsible for the development of MDDG.[5]

Herein, we report a patient diagnosed with MDDG-A3 with the determination of a novel compound heterozygote mutation on POMGNT1 gene, which was not reported before in literature.

**Case Report**

A 20-month-old male patient was admitted to our pediatric neurology department with the complaint of having a big head. From his history, it was learnt that his head was bigger than normal since his birth. He was the first child of a consanguineous marriage (mother and father were first-degree cousins). An obvious developmental delay was observed in his physical examination. His weight was 9 kg (<3 percentile), height was 75 cm (<3 percentile), and head circumference was 55 cm (>97 percentile). He was having a dysmorphic facial appearance with flattened nasal root. Bilateral simian lines were also determined to be present in physical examination. The magnetic resonance imaging of his brain revealed cerebellar hypoplasia [Figure 1].

A genetic testing was initiated after obtaining informed parental consent. On the basis of the clinical phenotype, muscle-eye-brain disease, all coding exons and the flanking intronic regions of the POMGNT1 gene were analyzed. Sequence analysis revealed compound heterozygote mutations in POMGNT1 gene: c.635C>T and c.4241G>A, respectively.

**KEYWORDS:** Child, dystroglycanopathy, muscular dystrophy

**Address for correspondence:** Dr. Sedat İşkay, Department of Pediatric Neurology, Medical Park Hospital, 52063 street, Şekfeitkamil, Gaziantep, Turkey. Tel: +90 (342) 211 16 00, GSM: +90 546 848 1977, Fax: +90 (342) 324 88 60. E-mail: dr.sedatisikay@mynet.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

*How to cite this article:* İşkay S, Şirikçi A. Congenital muscular dystrophy due to novel compound heterozygote mutations in POMGNT1 gene. J Pediatr Neurosci 2018;13:462-4.
gene were amplified by polymerase chain reaction, and targeted sequencing analysis was performed using the MiSeq System, a next-generation sequencing platform (Illumina, San Diego, CA, USA). Sequencing analysis showed two novel missense mutations in exon 6 and exon 7 of POMGNT1 gene (c.461C>A, p.Pro154His, c.550C>T, p.His184Tyr according to NM_001243766). The proband found compound heterozygote for a paternally inherited missense variant. Both missense mutations are predicted to be disease causing by various web-based in silico prediction programs including “Mutation Taster” (http://www.mutationtaster.org/), “Sorting Intolerant From Tolerant” algorithm (http://siftdna.org/), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/index.shtml), and PANTHER (http://www.pantherdb.org/). These findings imply that the proband has molecularly confirmed MDDG (muscle-eye-brain disease), type A3 (MDDG-A3).

**DISCUSSION**

MDDG is a genetic, heterogeneous group of muscular dystrophies with a broad range of clinical severity. This is the first known report of POMGNT1 c.461C>A, p.Pro154His, c.550C>T, p.His184Tyr according to NM_001243766 mutations in compound heterozygote, responsible for MDDG-A3. Although the genotype–phenotype correlation was not elucidated exactly, the clinical severity may be associated with the type of mutations.[6]

Cellular α-dystroglycan non-covalently binds with transmembrane protein β-dystroglycan; this complex attaches to dystrophin and F-actin, and by this way, extracellular matrix is connected to the cytoskeleton.[7] Any disturbances in this connection result in MDDG. POMGNT1 gene encodes a type II transmembrane protein that resides in the Golgi apparatus.[8] The product of POMGNT1 gene is essential for the proper α-glycosylation. To the best of our knowledge, this is the first reported case with compound heterozygote c.461C>A, p.Pro154His, c.550C>T, p.His184Tyr mutations in POMGNT1 gene causing MDDG-A3.

Some different genetic mutations were reported before being associated with MDDG, and it is clearly known that different genetic mutations result in a broad spectrum of phenotypes. In that aspect, mutations in POMGNT1 gene were reported to be associated with macrocephaly and epilepsy.[9] Similarly, our case was admitted with macrocephaly and a new mutation was determined in POMGNT1 gene. Intellectual disability and marked behavioral disturbances were also reported to be associated with the mutations in this gene. As our case was very young, any intellectual or behavioral troubles were not defined.

Our patient was diagnosed with MDDG with brain and eye anomalies A3 (MDDG-A3) from his clinical features and the results of genetic analyses. This disease was defined as an autosomal-recessive disorder characterized by congenital muscular dystrophy, ocular abnormalities, lissencephaly, and cerebellar and pontine hypoplasia. Patients were generally reported to have severe congenital myopia, congenital glaucoma, pallor of the optic disks, retinal hypoplasia, mental retardation, hydrocephalus, generalized muscle weakness, and myoclonic jerks.[10] Macrocephaly was the main finding in our patient with cerebellar hypoplasia.

We expand our knowledge regarding the genotypic spectrum of the disease by reporting this novel mutation, particularly in the Turkish population.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Godfrey C, Foley AR, Clement E, Muntoni F. Dystroglycanopathies: coming into focus. Curr Opin Genet Dev 2011;21:278-85.
2. Mercuri E, Muntoni F. Muscular dystrophies. Lancet 2013;381:845-60.
3. Riemersma M, Sandrock J, Boltje TJ, Büll C, Heise T, Ashikov A, et al. Disease mutations in CMP-sialic acid transporter SLC35A1 result in abnormal α-dystroglycan O-mannosylation, independent from sialic acid. Hum Mol Genet 2015;24:2241-6.
4. Bouchet-Séraphin C, Vuillaumier-Barrot S, Seta N. Dystroglycanopathies: About numerous genes involved in glycosylation of one single glycoprotein. J Neuromuscul Dis 2015;2:27-38.
5. Michele DE, Barresi R, Kanagawa M, Saito F, Cohn RD, Satz JS, et al. Post-translational disruption of dystroglycan-ligand interactions in congenital muscular dystrophies. Nature 2002;418:417-22.

6. Lommel M, Cirak S, Willer T, Hermann R, Uyanik G, van Bokhoven H, et al. Correlation of enzyme activity and clinical phenotype in POMT1-associated dystroglycanopathies. Neurology 2010;74:157-64.

7. Ibraghimov-Beskrovnaya O, Ervasti JM, Leveille CJ, Slaughter CA, Sernett SW, Campbell KP. Primary structure of dystrophin-associated glycoproteins linking dystrophin to the extracellular matrix. Nature 1992;355:696-702.

8. Pereira NA, Pu HX, Goh H, Song Z. Golgi phosphoprotein 3 mediates the Golgi localization and function of protein O-linked mannose β-1,2-N-acetylgalactosaminyltransferase 1. J Biol Chem 2014;289:14762-70.

9. Sparks SE, Quijano-Roy S, Harper A, Rutkowski A, Gordon E, Hoffman EP, et al. Congenital muscular dystrophy overview. GeneReviews 1993–2018.

10. Fu X, Yang H, Jiao H, Wang S, Liu A, Li X, et al. Novel copy number variation of POMGNT1 associated with muscle-eye-brain disease detected by next-generation sequencing. Sci Rep 2017;7:7056.