

CASE REPORT

Congenital muscular dystrophy a case study with a mutation in the *POMT1* gene

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ABSTRACT

Background: The congenital muscular dystrophies (CMD) are a group of heterogeneous diseases, manifested with a wide variety of clinical findings. Dystroglycanopathy is regarded as a subgroup among the CMD group of diseases. *POMT1* mutations that cause alpha-dystroglycan hypoglycosylation are reported to cause CMD diseases with autosomal recessive inheritance pattern.

Case Presentation: A 14-year-old girl patient was referred with classical symptoms for CMDs. Whole exome sequencing (WES) analysis revealed a mutation in the *POMT1* gene after the differential diagnosis of the patient. A homozygous mutation detected in the patient diagnosed muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 1 (OMIM 613155).

Conclusion: Different mutations in the *POMT1* gene have been found to cause three different types of diseases (CMDs). The differential diagnosis for these diseases clinically remains difficult, as a result, detailed clinical evaluation of patients becomes mandatory. Also, a multidisciplinary and collaborative approach involving complete clinical information and anamnesis is essential for the interpretation of genetic test results for such complex disorders.

Keywords: Muscular dystrophies, consanguinity, developmental disabilities.

Introduction

The congenital muscular dystrophies (CMD) are a highly heterogeneous group of diseases with autosomal recessive inheritance. The clinical characteristics include hypotonia in the first 6 months after birth, a long with muscle weakness, joint contractions, various degrees of mental retardation, physical disability, and muscle biopsy (1). Dystroglycan found in skeletal muscle is a central protein in the dystrophin-glycoprotein complex (DGC). DGC acts precursor for two glycoproteins: alpha-dystroglycan and beta-dystroglycan. These proteins form a link between the actin-associated cytoskeleton and the extracellular matrix. (2,3) Hypoglycosylation of alpha-dystroglycan is reported to be involved in the development of congenital muscular dystrophy. Protein-o-mannosyl transferase 1 (*POMT1*, OMIM *607423) is involved in the initiation of o-mannosyl glycan synthesis in the endoplasmic reticulum with its homolog *POMT2*. This synthesis acts as the first step in the binding of o-mannose-like glycan fragments to the alpha-dystroglycan (4). The mutation in the *POMT1* gene causes a decrease in the glycation of alpha-dystroglycan in skeletal muscles, resulting in spectrum of diseases from severe Walker-Warburg syndrome (OMIM 236670) to CMD. Muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 1 (OMIM 613155) and milder

forms of limb-girdle muscular dystrophy (LGMD) with normal brain structure and mental retardation (LGMD2K, OMIM 609308) (5). In this study, we describe a Turkish patient with CMD clinical findings. Whole exome sequencing (WES) analysis found a homozygous mutation in the *POMT1* gene. Differential diagnoses performed to compare three CMD diseases caused by the same mutation confirmed muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 1.

Case Presentation

A 14-year-old girl patient was referred with the global developmental delay, severe learning disability, skeletal muscle weakness, increased creatinine kinase level,

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macroglossia, joint contractures, spinal scoliosis, and hypertrichosis complaints. In the anamnesis information of the patient, it was learned that the prenatal period was normal. The birth information of the patient was 3100 grams with spontaneous vaginal delivery at term. The patient did not have a history of hypoxic birth, and the fifth-minute birth Appearance, Pulse, Grimace, Activity, Respiration score was 8–9. We learned that the patient's breastfeeding time was 3–4 months. The probable cause of this condition was the developing hypotonia. In the 9th month of the patient's life, head and neck control did not develop. For this reason, the patient's parents consulted the doctor. The neuromotor development retardation was determined. Then, the time of the motor development stages of the patient was questioned. According to this, the patient's head–neck control was observed during 9 months, supported sitting at 18 months, unsupported sitting at 21 months, and walking at 30 months. Neuromotor retardation was noted in the patient. A 9–10 years of age was considered as a single word speaking time of the patient. When the patient was 7–8 years old, her walking had begun to deteriorate. The difficulty of walking on the long road and the difficulty of getting up from the seat started. The walking difficulty gradually increased. But, the ability to walk and speech decreased in the last year. The patient's history of seizure, surgery, and chronic disease was not any feature present. In the analysis of the pedigree of the patient, it was found that there was 3rd-degree cousin consanguinity between the parents. In the family of the patient, there are no other cases similar to the patient (Figure 1). In the physical examination, head circumference was found within normal limits according to the age of his peers. Head circumference: 53 cm (25–50 p). Height: 151 cm (3 p). Weight: 51 kg (25–50 p). At the dysmorphic examination brachycephaly, flat occiput, triangular face, narrow forehead, prominence cheekbone, prominent nasolabial fold, broad chin, long palpebral fissure, prominent antihelix stem, prominent antitragus, expanded terminal portion of crus helix, wide nasal base, wide nasal bridge, broad nasal tip, deep philtrum, everted lower lip vermillion, thin lower lip vermillion, downturned corners of mouth, and wide mouth were found. There was a prominent macroglossia (Figures 2A, 2B, 2C). The

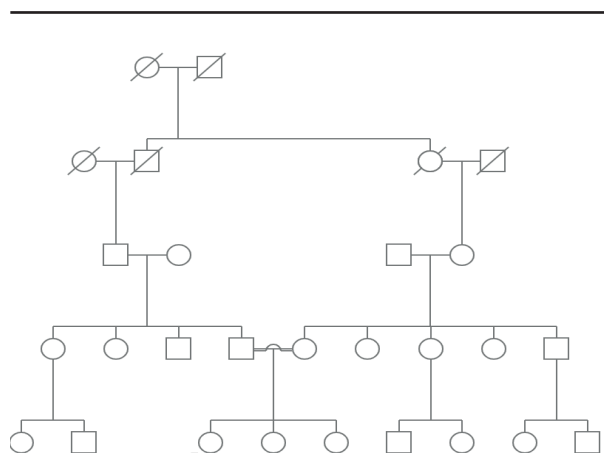


Figure 1. Family Pedigree.

patient had a severe learning disability. At the same time, muscle weakness and joint contracture were detected in four extremities. The patient had spinal scoliosis and lumbar lordosis. Hyporeflexia was found in deep tendon reflexes of the lower extremities. Calf hypertrophy was detected in hamstring muscles. Increased creatinine kinase was detected in the patient's biochemical parameters. The patient's creatinine kinase (CK) level had increased by about 15 times (CK: 3816 U/L). No pathological findings were found at the patient's magnetic resonance imaging. Homozygous [c.598G>C (p.Ala200Pro) (p.A200P)] mutation was detected in *POMT1* gene in WES analysis. This result was again confirmed by Sanger sequencing. HGVS: NM_007171.3:c.598G>C. The American College of Medical Genetics and Genomics (ACMG) previously developed guidance for the interpretation of sequence variants (6). The mutation found was classified into four categories according to ACMG criteria. PM2: Genome Aggregation Database (GnomAD) exomes allele frequency = 0.00000795 is less than 0.0001 threshold for recessive gene *POMT1* (good GnomAD exomes coverage = 99.7). The variant was not found in GnomAD genomes (good GnomAD genomes coverage = 33.7). PP3: Pathogenic computational verdict because of eight pathogenic predictions from deep neural network (DANN), FATHMM, Functional Analysis through Hidden Markov Models, FATHMM-MKL, Predict the Functional Consequences of Non-Coding and Coding Single Nucleotide Variants (SNVs), LRT, likelihood ratio test, MutationAssessor, MutationTaster, PROVEAN, Protein Variation Effect Analyzer, and SIFT, Scale Invariant Feature Transform versus no benign predictions. PP5: UniProt classifies this variant as "disease" (muscular dystrophy-dystroglycanopathy limb-girdle C1). A VarSome user has reported this variant to be classified as pathogenic in PubMed article PMID: 31311558. BP1: Missense variant in gene *POMT1* has been reported with 56 pathogenic variants, of which 25 truncating pathogenic variants contributing 44.6%, which is greater than the minimum of 33.3%, and 23 pathogenic missense variants out of 40 classified missense variants contributing 57.5%, which is less than maximum of 66.6%. The (DANN) score of this mutation was 0.9971. The value range was 0 to –1, with 1 given to the variants predicted to be the most damaging. Since the mutation in the gene caused three different diseases, anamnesis, physical examination, and laboratory and imaging tests were examined in detail. Thus, the patient was diagnosed with a definite diagnosis of "muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B1." As a result, it was evaluated as A variant of uncertain (or unknown) significance according to ACMG criteria, but since it is clinically significant, the study team consider this change as mutation since similar cases have been reported in the literature before (7). Also, the mutation we identified was previously described in a study by Tobias et al. (8) in a Turkish family.

Discussion

Whole exome sequencing is a good choice in cases of screening individuals with consanguineous marriages in



Figure 2. Dysmorphic features of the patient.

the family, especially when looking for a homozygous mutation. Here, in this study, a homozygous [c.598G>C (p.Ala200Pro) (p.A200P)] mutation was detected in the *POMT1* gene after WES analysis. The DANN score of this mutation was 0.9971. The value range is 0 to 1, with 1 given to the variants predicted to be the most damaging (9). According to The gnomAD data, the total allele frequency of this mutation in the population was 0.000008121. In the present study, a differential diagnosis was performed to compare between muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 1 (Walker-Warburg Syndrome) (OMIM 236670), muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 1 (OMIM 613155), and muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 1 (limb-girdle, Type 2K; LGMD2K) (OMIM 609308). This case is an example of phenotype to genotype determination, as CMD group diseases are broad and the detected mutation causes more than one type of disease. Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 1 is usually linked to severe neurological involvement such as severe ocular findings, cleft lip, cleft palate anomalies, severe mental retardation, agyria, lissencephaly, hydrocephalus, and cerebellar dysplasia (10). The milder symptoms in the patient made the study team exclude muscular dystrophy-dystroglycanopathy type A, 1. Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 1 has much milder clinical findings that include mild joint contractures, weakness in the proximal muscles, and mild mental retardation (11). These disease findings were much milder compared to the findings of the patient in the present study. Another disease caused by a mutation in the *POMT1* gene is muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 1 with mild eye findings, weakness in facial muscles, macroglossia, joint contractures, hypotonia, inability to walk, severe mental retardation, delayed psychomotor development, and delayed speech development. Although very few cases of muscular dystrophy-dystroglycanopathy (congenital with mental retardation), type B, 1 have been reported (12,13) the clinical features mentioned coincided with our patient clinical characteristics. Furthermore, macroglossia in the disease and the presence of this feature in our patient also became an important guide for confirmative diagnosis.

Conclusion

Different mutations in the *POMT1* gene have been found to cause three different types of diseases (CMDs). The differential diagnosis for these diseases clinically remains difficult, as a result, detailed clinical evaluation of patients becomes mandatory. Also, a multidisciplinary and collaborative approach involving complete clinical information and anamnesis is essential for the interpretation of genetic test results for such complex disorders.

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Declaration of conflicting interests

None.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication

Informed consent was obtained from the parents.

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References

1. Brockington M, Blake DJ, Prandini P, Brown SC, Torelli S, Benson MA, et al. Mutations in the fukutin-related protein gene (FKRP) cause a form of congenital muscular dystrophy with secondary laminin $\alpha 2$ deficiency and abnormal glycosylation of α -dystroglycan. *Am J Hum Genet* 2001;69(6):1198–209. <https://doi.org/10.1086/324412>

2. Hayashi YK, Ogawa M, Tagawa K, Noguchi S, Ishihara T, Nonaka I, et al. Selective deficiency of α -dystroglycan in Fukuyama-type congenital muscular dystrophy. *Neurology* 2001;57(1):115–21. <https://doi.org/10.1212/WNL.57.1.115>
3. 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(6896):417. <https://doi.org/10.1038/nature00837>
4. Bello L, Melacini P, Pezzani R, D'amico A, Piva L, Leonardi E, et al. Cardiomyopathy in patients with POMT1-related congenital and limb-girdle muscular dystrophy. *Eur J Hum Genet* 2012;20(12):1234. <https://doi.org/10.1038/ejhg.2012.71>
5. Messina S, Mora M, Pegoraro E, Pini A, Mongini T, D'Amico A, et al. *POMT1* and *POMT2* mutations in CMD patients: a multicentric Italian study. *Neuromuscul Disord* 2008;18(7):565–71. <https://doi.org/10.1016/j.nmd.2008.04.004>
6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17(5):405. <https://doi.org/10.1038/gim.2015.30>
7. Kopanos C, Tsiolkas V, Kouris A, Chapple CE, Aguilera MA, Meyer R, et al. VarSome: the human genomic variant search engine. *Bioinformatics* 2019;35(11):1978. <https://doi.org/10.1093/bioinformatics/bty897>
8. Geis T, Rödl T, Topaloglu H, Balci-Hayta B, Hinreiner S, Müller-Felber W, et al. Clinical long-time course, novel mutations and genotype-phenotype correlation in a cohort of 27 families with *POMT1*-related disorders. *Orphanet J Rare Dis* 2019;14(1):179. <https://doi.org/10.1186/s13023-019-1119-0>
9. Quang D, Chen Y, Xie X. DANN: a deep learning approach for annotating the pathogenicity of genetic variants. *Bioinformatics* 2014;31(5):761–3. <https://doi.org/10.1093/bioinformatics/btu703>
10. de Bernabé DB, Currier S, Steinbrecher A, Celli J, van Beusekom E, van der Zwaag B, et al. Mutations in the O-mannosyltransferase gene *POMT1* give rise to the severe neuronal migration disorder Walker-Warburg syndrome. *Am J Hum Genet* 2002;71(5):1033–43. <https://doi.org/10.1086/342975>
11. Dinçer P, Balci B, Yuva Y, Talim B, Brockington M, Dinçel D, Torelli S, Brown S, Kale G, Haliloğlu G, Gerçeker FÖ. A novel form of recessive limb girdle muscular dystrophy with mental retardation and abnormal expression of α -dystroglycan. *Neuromuscul Disord* 2003;13(10):771–8. [https://doi.org/10.1016/S0960-8966\(03\)00161-5](https://doi.org/10.1016/S0960-8966(03)00161-5)
12. Balci B, Uyanik G, Dincer P, Gross C, Willer T, Talim B, et al. An autosomal recessive limb girdle muscular dystrophy (LGMD2) with mild mental retardation is allelic to Walker-Warburg syndrome (WWS) caused by a mutation in the *POMT1* gene. *Neuromuscul Disord* 2005;15(4):271–5. <https://doi.org/10.1016/j.nmd.2005.01.013>
13. Godfrey C, Clement E, Mein R, Brockington M, Smith J, Talim B, et al. Refining genotype-phenotype correlations in muscular dystrophies with defective glycosylation of dystroglycan. *Brain* 2007;130(10):2725–35. <https://doi.org/10.1093/brain/awm212>