


A homozygous mutation in the *POMT2* gene in four siblings with limb-girdle muscular dystrophy 2N

Miraç Yıldırım¹ , Hatice Koçak Eker² , Melih Timuçin Doğan³ 

¹Department of Pediatric Neurology, Konya Training and Research Hospital, Konya, Turkey

²Department of Medical Genetics, Konya Training and Research Hospital, Konya, Turkey

³Department of Pediatric Cardiology, Konya Training and Research Hospital, Konya, Turkey

What is already known on this topic?

Protein O-mannosyltransferase 2 mutations can cause Walker-Warburg syndrome, which has severe clinical findings, as well as rarely limb-girdle muscular dystrophy, which has milder clinical findings.

What this study adds on this topic?

In this study, scoliosis was first described in two siblings with protein O-mannosyltransferase 2 mutation-related limb-girdle muscular dystrophy type 2N, thus this report expands the phenotypic spectrum of limb-girdle muscular dystrophy type 2N.

Corresponding Author:

Miraç Yıldırım

✉miracyildirim81@hotmail.com

Received: 02.04.2020

Accepted: 09.10.2020

turkarchpediatr.org

Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



ABSTRACT

Mutations in protein O-mannosyltransferase 2 can cause a wide spectrum of clinical phenotypes from severe congenital muscular dystrophy such as Walker-Warburg syndrome to milder limb-girdle muscular dystrophy 2N. We aimed to describe the clinical and paraclinical features, laboratory tests, and molecular findings of four siblings with a homozygous mutation in the protein O-mannosyltransferase 2 gene. There were two sisters and two brothers, aged 4 to 17 years, with an age of onset symptoms at 3 to 12 years. The main neurologic findings were mild intellectual disability, hypoactive deep tendon reflexes, symmetrical weakness of the proximal lower and/or upper limbs, and difficulties in walking on heels and/or toes. The scoliosis found in two siblings has not been associated with protein O-mannosyltransferase 2 gene mutations related to limb-girdle muscular dystrophy 2N in previous reports. This report expands the phenotypic spectrum of protein O-mannosyltransferase 2 gene mutation-related limb-girdle muscular dystrophy 2N.

Keywords: Dystrophy, dystroglycanopathy, limb-girdle muscular scoliosis, LGMD2N, protein O-mannosyltransferase 2

Introduction

The dystroglycanopathies are a subgroup of congenital muscular dystrophy with autosomal recessive inheritance, characterized by absent or reduced functional glycosylation of α -dystroglycan, which results in decreased binding of extracellular matrix ligands (1). Protein O-mannosyltransferase 2 (*POMT2*) catalyzes the first step in the synthesis of O-mannosyl glycan with its homolog *POMT1* (2). Protein O-mannosyltransferase 2 mutations were first identified in patients with Walker-Warburg syndrome (WWS), and have also been found in patients with muscle-eye-brain (MEB)-like phenotype, Fukuyama-type congenital muscular dystrophy, and rarely limb-girdle muscular dystrophy type 2N (LGMD2N) (3-5). Mutations in the *POMT2* gene, containing 21 exons, at chromosome 14q24, can cause LGMD2N, which may occur when α -dystroglycan glycosylation is only slightly diminished (6). Limb-girdle muscular dystrophy type 2N is usually clinically characterized by childhood-onset, slow progression, intellectual disability, primarily hamstring and gluteal muscle involvement, and rarely cardiomyopathy (7, 8).

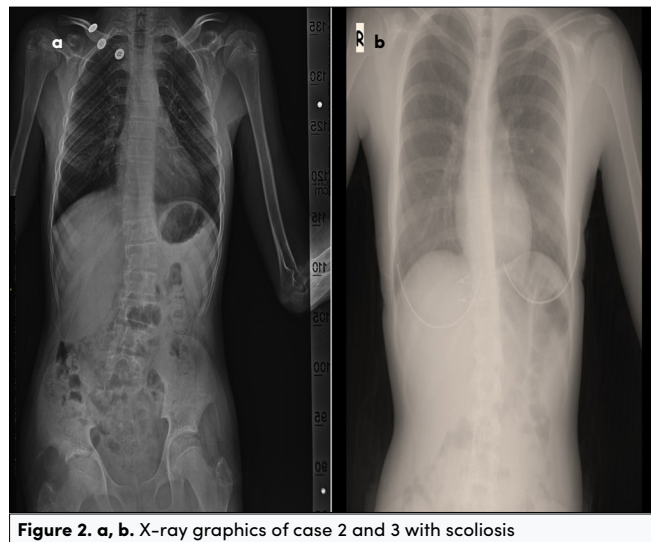
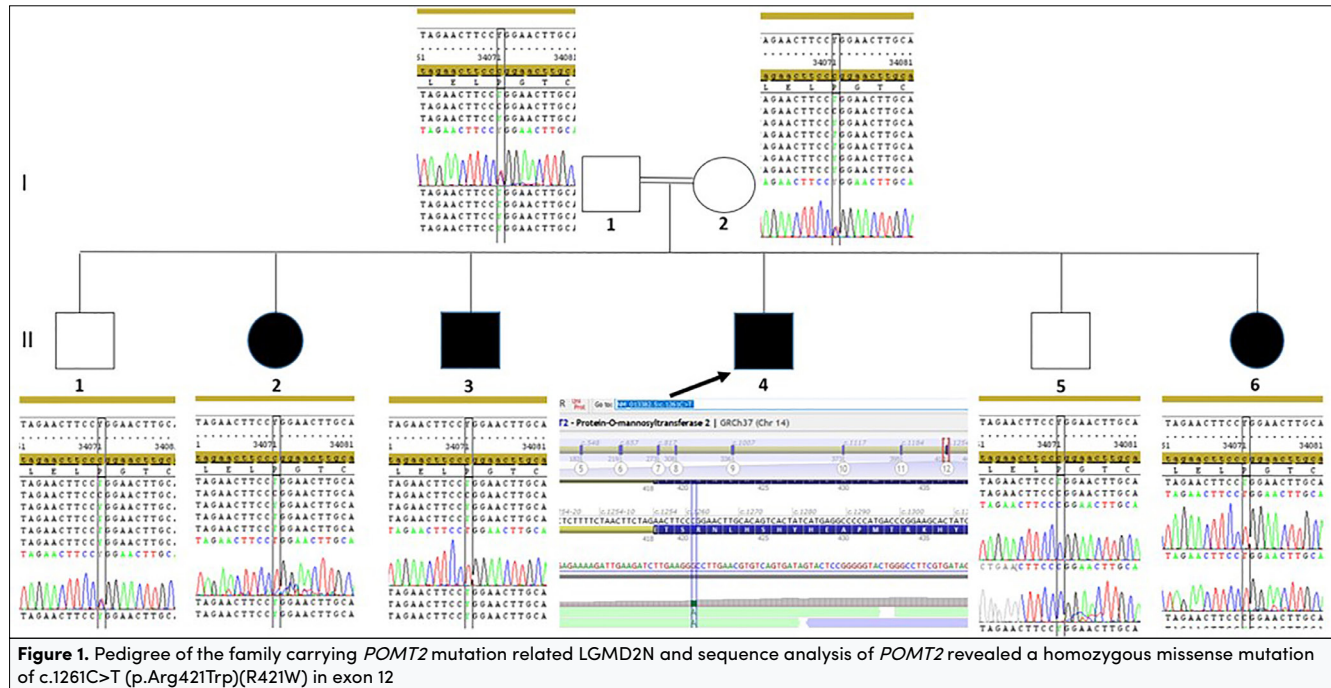
Here, we reviewed the clinical and paraclinical features, laboratory tests, and molecular findings of four siblings with LGMD2N related to a homozygous mutation in the *POMT2*, which are summarized in Table 1.

Case Presentations

Case 1

A 9-year-old boy (Figure 1; II-4) presented with weakness in the legs. He was born after an uneventful pregnancy and delivery with consanguineous parents. His early developmental

Cite this article as: Yıldırım M, Koçak Eker H, Doğan MT. A homozygous mutation in the *POMT2* gene in four siblings with limb-girdle muscular dystrophy 2N. *Turk Arch Pediatr* 2021; 56(1): 68-71.



motor milestones were normal. At 6 years of age, he initially had difficulties in walking on heels and climbing stairs. In a neurologic examination at age 8 years, he had symmetrical weakness of proximal lower limbs, hypoactive deep tendon reflexes, mild calf hypertrophy, mild lordosis, difficulties in walking on heels and toes, and negative Gowers maneuver. He had mild intellectual disability requiring special education. Serum creatine kinase (CK) level was 681 UI/L (normal values up to 170 UI/L). At age 8 years and six months, brain magnetic resonance imaging (MRI) was normal. An ophthalmologic evaluation revealed no abnormalities. Electrocardiogram and echocardiogram were normal. We identified a homozygous missense mutation of c.1261C>T (p.Arg421Trp)(R421W) in exon 12 of *POMT2*.

In the family history, a brother (Figure 1; II-3) and two sisters (Figure 1; II-2, II-6) had similar symptoms and two brothers had no motor or cognitive impairment.

Case 2

A 14-year-old boy (Figure 1; II-3) was born after uneventful pregnancy and delivery. His early developmental motor milestones were normal. At age 3 years, he initially had difficulties in walking and climbing stairs. He could only walk when assisted at age 12 years. On neurologic examination at age 13 years, he had symmetrical weakness of the proximal upper and lower limbs, hypoactive deep tendon reflexes, inability to walk without support, and mild scoliosis (Figure 2). He had mild intellectual disability requiring special education. Serum CK levels were 1891-5002 UI/L (normal values up to 170 UI/L). At age 13 years and six months, brain MRI was normal. An ophthalmologic evaluation revealed no abnormalities. Electrocardiogram was normal and echocardiogram showed a secundum atrial septal defect. We identified the same homozygous missense mutation in *POMT2*.

Case 3

A 17-year-old girl (Figure 1; II-2) was born after an uneventful pregnancy and delivery. Her early developmental motor milestones were normal. At 12 years of age, she initially had difficulties in climbing stairs and running. On neurologic examination at age 16 years, she had symmetrical weakness of the proximal lower limbs, hypoactive deep tendon reflexes, difficulties in walking on heels and toes, pes planus, and mild scoliosis (Figure 2). She had mild intellectual disability requiring special education. Serum CK level was 1140 UI/L (normal values up to 170 UI/L). At age 16 years and six months, brain MRI was normal. An ophthalmologic evaluation revealed no abnormalities. Electrocardiogram and echocardiogram were normal. We identified the same homozygous missense mutation in *POMT2*.

Case 4

A 4-year-old girl (Figure 1; II-6) was born after an uneventful pregnancy and delivery. Her early developmental motor milestones were normal. At age 3 years, she initially had mild cognitive impairment. On neurologic examination at age 3 years,

Table 1. Demographic, clinical, laboratory, imaging and genetic findings of cases with *POMT2* mutation related LGMD2N

Case	1	2	3	4
Age (years)	9	14	17	4
Sex	M	M	F	F
Symptom onset (years)	6	3	12	3
Presenting symptoms	Troubles in walking and climbing stairs	Troubles in walking and climbing stairs (No ambulation without support at 12 years of age)	Troubles in climbing stairs and running	Cognitive impairment
Neurological examination	Symmetrical weakness of proximal lower limbs, hypoactive DTR, mild calf hypertrophy, mild lordosis, troubles in walking on heels and toes, mild intellectual disability	Symmetrical weakness of proximal upper and lower limbs, hypoactive DTR, inability to walk without support, mild scoliosis, mild intellectual disability	Symmetrical weakness of proximal lower limbs, hypoactive DTR, troubles in walking on heels and toes, pes planus, mild scoliosis, mild intellectual disability	Hypoactive DTR, mild intellectual disability
CK	681	1891–5002	1140	1564
Brain MRI	Normal	Normal	Normal	Normal
ECG/				
Echocardiography	Normal/Normal	Normal/Secundum ASD	Normal/Normal	Normal/Secundum ASD
Mutation	c.1261C>T (p.Arg421Trp) (R421W) homozygous	c.1261C>T (p.Arg421Trp) (R421W) homozygous	c.1261C>T (p.Arg421Trp) (R421W) homozygous	c.1261C>T (p.Arg421Trp) (R421W) homozygous

F: female; M: male; DTR: deep tendon reflex; CK: creatine kinase; MRI: magnetic resonance imaging; ECG: electrocardiogram; ASD: atrial septal defect

she had only hypoactive deep tendon reflexes. She was noted to toe and heel walk without support. She had mild intellectual disability. Her serum CK level was 1564 UI/L (normal values up to 170 UI/L). At age 3 years and six months, brain MRI was normal. An ophthalmologic evaluation revealed no abnormalities. Electrocardiogram was normal and echocardiogram showed a secundum atrial septal defect. We identified the same homozygous missense mutation in *POMT2*.

Serum CK levels were normal in her two brothers (Figure 1; II-1, II-5) who had no motor or cognitive impairment. One (Figure 1; II-5) had the heterozygous mutation and the other (Figure 1; II-1) had no mutation. Genetic counseling was given to the family in accordance with autosomal recessive inheritance. Figure 1 shows the pedigree and sequence analysis.

Written informed consent was obtained from the patients' parents.

Discussion

Mutations in *POMT2* can cause a wide spectrum of clinical phenotypes from frequently severe congenital muscular dystrophy such as WWS to rarely milder LGMD2N. Protein O-mannosyltransferase 2 mutations lead to LGMD2N without brain or eye involvement except for mild intellectual disability, as first described by Biancheri et al. (3) in 2007 (6, 7).

In our series, all patients had homozygous mutations of c.1261C>T in exon 12 of *POMT2*, as previously reported by Østergaard et al. (7). The family we described herein is the second family with recessively inherited LGMD2N due to mutations in the *POMT2* gene. There are eight members, all of whom were sequenced using next-generation sequencing, and four were genetically and clinically affected. The age at disease onset, predominant clinical findings, and serum CK levels were differ-

ent in each sibling. Therefore, we suggest that the same mutation can be associated with different clinical severities, even among members of the same family, which is probably owing to epigenetic, other genetic or environmental factors that influence clinical features.

In a recent study, Østergaard et al. (7) found that disease-onset in *POMT2* mutation-related LGMD2N varied from birth to 55 years. They showed that the presenting symptoms were in most cases related to ambulatory function, such as a delay in the ability to walk, or difficulties in walking, climbing stairs or running. Three of the four patients in our series had ambulatory dysfunction and one had cognitive impairment as a presenting symptom. Moreover, they determined that 83% of cases were ambulatory. Similarly, we found that three of four patients were ambulatory, but one could only walk when assisted after the age of 12 years.

Østergaard et al. (7) showed that all 12 patients had various degrees of cognitive impairment. However, brain MRI scans were abnormal in only three of 10 patients, showing minor changes to the structure such as ventricular enlargement, periventricular hyperintensities, and unilateral frontal atrophy. They observed that cognitive impairment was not related to the MRI findings. In our series, brain MRI scans were normal, and all patients had mild cognitive impairment. We support that abnormal major changes to the brain structure in MRI should exclude LGMD2N.

Serum CK levels were elevated around 5–15 times those of normal in LGMD2N (8). Østergaard et al. (7) detected that serum CK levels were markedly elevated in ten of 12 patients, except in two cases with slightly elevated. Similarly, we found that three had markedly and one had slightly elevated in our series.

Cardiac evaluations usually reveal no alterations (3, 4, 7). Østergaard et al. (7) found that two of 12 patients had reduced left ventricular ejection fraction and suggested that patients with LGMD2N were at risk of developing pump failure. Brun et al. (9) also showed similar cardiac findings. Moreover, other studies showed mild mitral and tricuspid valve deficiency with stable cardiac features (10, 11). In our series, no patient had reduced left ventricular ejection fraction or cardiac pump failure, but two had secundum atrial septal defects, which we think was coincidental.

Scoliosis has been associated with *POMT2* mutation-related WWS and MEB-like diseases, but not associated with LGMD2N in previous reports (6, 10). We found that scoliosis occurred in the older siblings aged 14 and 17 years. Therefore, we suggest that patients with LGMD2N should be evaluated for scoliosis during adolescence. This report expands the phenotypic spectrum and provides that *POMT2* mutation-related LGMD2N can be associated with mild phenotypes including scoliosis. Further case reports of this disease are required to expand the phenotypic and genotypic spectrum.

Informed Consent: Written informed consent was obtained from patients' parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.Y., H.K.E.; Design – M.Y., H.K.E.; Supervision – M.Y., M.T.D.; Fundings – M.Y., H.K.E.; Data Collection and/or Processing – M.Y., H.K.E., M.T.D.; Analysis and/or Interpretation – M.Y., M.T.D.; Literature Review – M.Y.; Writing – M.Y., H.K.E., M.T.D.; Critical Review – M.Y., M.T.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

- Muntoni F, Torelli S, Wells DJ, Brown SC. Muscular dystrophies due to glycosylation defects: diagnosis and therapeutic strategies. *Curr Opin Neurol* 2011; 24: 437–42. [\[Crossref\]](#)
- Manya H, Akasaka–Manya K, Nakajima A, Kawakita M, Endo T. Role of N-glycans in maintaining the activity of protein O-mannosyltransferases POMT1 and POMT2. *J Biochem* 2010; 147: 337–44. [\[Crossref\]](#)
- Biancheri R, Falace A, Tessa A, et al. POMT2 gene mutation in limb-girdle muscular dystrophy with inflammatory changes. *Biochem Biophys Res Commun* 2007; 363: 1033–7. [\[Crossref\]](#)
- Murakami T, Hayashi YK, Ogawa M, et al. A novel POMT2 mutation causes mild congenital muscular dystrophy with normal brain MRI. *Brain Dev* 2009; 31: 465–8. [\[Crossref\]](#)
- Mercuri E, D'Amico A, Tessa A, et al. POMT2 mutation in a patient with 'MEB-like' phenotype. *Neuromuscul Disord* 2006; 16: 446–8. [\[Crossref\]](#)
- Godfrey C, Clement E, Mein R, et al. Refining genotype phenotype correlations in muscular dystrophies with defective glycosylation of dystroglycan. *Brain* 2007; 130: 2725–35. [\[Crossref\]](#)
- Østergaard ST, Johnson K, Stojkovic T, et al. Limb girdle muscular dystrophy due to mutations in POMT2. *J Neurol Neurosurg Psychiatry* 2018; 89: 506–12. [\[Crossref\]](#)
- Nigro V, Savarese M. Genetic basis of limb-girdle muscular dystrophies: the 2014 update. *Acta Myol* 2014; 33: 1–12.
- Brun BN, Willer T, Darbro BW, et al. Uniparental disomy unveils a novel recessive mutation in POMT2. *Neuromuscul Disord* 2018; 28: 592–6. [\[Crossref\]](#)
- Martinez HR, Craigen WJ, Ummat M, Adesina AM, Lotze TE, Jeffries JL. Novel cardiovascular findings in association with a POMT2 mutation: three siblings with α -dystroglycanopathy. *Eur J Hum Genet* 2014; 22: 486–91. [\[Crossref\]](#)
- Saredi S, Gibertini S, Ardisson A, et al. A fourth case of POMT2-related limb girdle muscle dystrophy with mild reduction of α -dystroglycan glycosylation. *Eur J Paediatr Neurol* 2014; 18: 404–8. [\[Crossref\]](#)