DOI:10.4274/tnd.2022.44788
Turk J Neurol 2023;29:79-84

A Rare Neuromuscular Disease: Limb-girdle Muscular Dystrophy-R18 Case Report

Nadir Bir Nöromusküler Hastalık: Limb-girdle Musküler Distrofi-R18 Olgu Sunumu

Gülce Coşku Yılmaz Çakan[1], Ebru Bölük[2], Yaprak Seçil[3], Aslı Subaşıoğlu[4], Özgür Tosun[5]

[1]Torbali State Hospital, Clinic of Neurology, Izmir, Türkiye
[2]University of Health Sciences Türkiye, Izmir Tepecik Training and Research Hospital, Clinic of Neurology, Izmir, Türkiye
[3]Izmir Katip Celebi University, Atatürk Training and Research Hospital, Clinic of Neurology, Izmir, Türkiye
[4]Izmir Katip Celebi University, Atatürk Training and Research Hospital, Clinic of Medical Genetics, Izmir, Türkiye
[5]Izmir Katip Celebi University, Atatürk Training and Research Hospital, Clinic of Radiology, Izmir, Türkiye

Keywords: Limb-girdle, dystrophy, proximal, muscle weakness, TRAPPC11
Anahtar Kelimeler: Limb-girdle, distrofi, proksimal, kas güçsüzlüğü, TRAPPC11

Dear editor,

Limb-girdle muscular dystrophies (LGMDs) are a heterogenous group of genetic diseases generally characterized by proximal muscle weakness (1). Among them, LGMD-R18 is an autosomal recessive form caused by a mutation on the 4q35 locus of the gene encoding transport protein particle complex 11 (TRAPPC11). The available clinical data is limited to case reports and series of Syrian, Hispanic, Chinese, and Turkish origin (1,2,3,4,5,6). Our aim was to contribute to the existing data by presenting a LGMD-R18 case, to the best of our knowledge, the first reported from Türkiye.

A 25-year-old, consanguineous male patient visited our clinic due to difficulty in walking and frequent falls. He began to walk at a normal age, but suffered a developmental delay following a single non-febrile epileptic seizure at age three. While his seizures did not recur, he started to fall behind his peers in terms of physical and intellectual development, and from the age of eight, had difficulty in climbing stairs and experienced frequent falls. He was the third of four siblings, but neither his siblings nor his parents reported similar complaints. His muscle strength was 4/5 in the bilateral forearm flexors and extensors and the wrist extensors, 4/5 in the neck flexors, 3/5 in the neck extensors, 2/5 in the hip flexors, 2/5 in the hip extensors, 2/5 in the thigh adductors, and +4/5 in the knee flexors and extensors. His deep tendon reflexes were normal and his Gower's sign was positive.

The findings indicated limb-girdle myopathy, which was supported by the electromyography findings. The cranial magnetic resonance imaging (MRI) and electroencephalography examinations returned normal results. The computed tomography (CT) (Figure 1c) imaging in the soft tissue window and the MRI (Figure 1a, b, d) indicated advanced fatty replacement in the bilateral paravertebral, periscapular, paracostal, gluteal, and proximal thigh muscles, while the bilateral posterior parascapular, trapezius, and vastus lateralis muscles were comparatively preserved. The liver ultrasonography, electroencephalography, eye, and heart examinations returned normal results. His total score was 22/30 in the mini mental state examination, with impaired time orientation and attention, and his IQ test score was consistent with borderline mental capacity. Due to the age of symptom onset and the history of parental consanguinity, a genetic examination was performed, which revealed TRAPPC11 homozygous c.2938G>A (p.Gly980Arg) missense mutation. In the subsequent family screening, a heterozygous c.2938G>A (p.Gly980Arg) mutation in one allele and a c.2944T>C (p.Tyr982His) mutation in another allele was detected in the mother, and a single allele c.2938G>A (p.Gly980Arg) mutation in the father, while the neurological examinations were normal for both parents and they had no LGMD-related complaints. In light of these findings, the diagnosis was LGMD-R18 with syndromic features, including

Address for Correspondence/Yazışma Adresi: Gülce Coşku Yılmaz Çakan MD, Torbali State Hospital, Clinic of Neurology, Izmir, Türkiye
Phone: +90 232 344 44 44 E-mail: gulcecoskuyilmaz@gmail.com ORCID: orcid.org/0000-0002-7873-0383
Received/Geliş Tarihi: 24.02.2022 **Accepted/Kabul Tarihi:** 20.08.2022

musculoskeletal deformities, neurodevelopmental, and cognitive problems.

We hereby report this case to emphasize that, while LGMD-R18 is a rare disease, it has variable clinical features due to dysfunction of TRAPPC11 encoding. More than 30 pathogenic mutations were identified, and 23 of these including TRAPPC11 are related to LGMD-R (2). The *TRAPPC11* gene encodes TRAPPC, which is a cell membrane trafficking protein involved in the transport between the endoplasmic reticulum and the Golgi apparatus (1). The structural defects in TRAPPC11 mainly cause disruption of the secretory cell functions along with muscle-, brain-, liver-, and eye-related pathologies (1), with, according to a recent study, the type and severity of these pathological changes differing according to the tissue (6). Thus, *TRAPPC* gene-associated pathological diversity appears to be one of the greatest challenges to phenotyping LGMD.

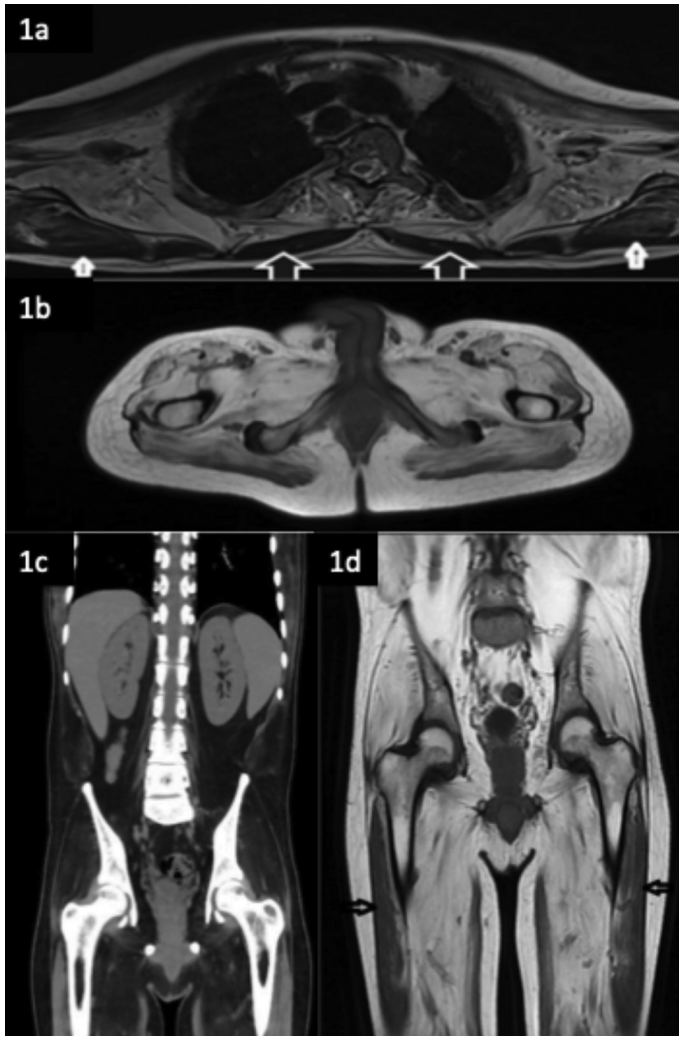

Figure 1. (a) Axial T1-weighted magnetic resonance image (MRI) of the thoracic spine showing the marked fatty replacement of the posterior paravertebral, bilateral anterior parascapular muscles. The bilateral posterior parascapular (white arrows) and trapezius muscles (black arrows) were comparatively preserved. (b) Axial T1-weighted MRI of the hip at the ischiopubic level showing marked fatty replacements in the bilateral quadratus femoris, gluteus maximus, vastus lateralis, rectus femoris, sartorius, tensor fasciae latae, and hip adductor muscles. Fatty replacement is more evident in the anterior medial muscle groups. (c) Coronal pelvic computed tomography image showing fatty replacements in bilateral psoas major, gluteal muscles, abdominal wall muscles, and medial muscle group of the proximal thigh. The vastus lateralis muscles were comparatively preserved bilaterally. (d) Coronal T1-weighted MRI at the proximal femoral bone level showing marked fatty replacement in the bilateral psoas, adductor, and gluteal muscle group. The vastus lateralis muscles were comparatively preserved (arrows)

After the first LGMD-R18 cases were published in 2013 (5), a growing number of case reports has increased our insight into the disease phenotype. Table 1 presents all the previously reported pathological features along with the differences among the individuals, and it is clear that these patients had a number of common clinical features, such as early disease onset, high creatine kinase levels, and developmental delay (7). Conversely, only two patients were born from a consanguineous marriage, while a minority of the patients, including ours, had epileptic seizures (3,4).

When compared with others, our patient displays somewhat different clinical features, which may lead to clinical findings that are limited in scope, but nonetheless, valuable. The coexistence of LGMD and epileptic seizures is known to be common with LGMD-R23, but in most LGMD types, conditions stemming from the underlying pathological metabolic processes, such as encephalopathy and structural brain abnormalities, may predispose the individual to seizure development (6). While our patient's seizure issue is unrelated to his myopathy, it should always be borne in mind that a patient with LGMD is vulnerable to epileptic seizure.

Recent publications have noted patterns of muscle involvement and their correlation with MRI; however, differences in the localization of the affected muscles are expressed only in terms of lower or upper extremity dominance (6). The pattern of muscle group involvement detected in our patient has never been previously discussed, and is valuable in terms of illustrating the importance of imaging in phenotyping. In addition, the correlation between the CT and MRI findings confirms the sensitivity of CT in patients unable to undergo MRI.

Finally, unlike many genetic diseases, thus far, LGMD-R18 appears to exhibit no homogeneous geographical distribution pattern, which may be related to the lack of newly reported cases. However, some cases are members of ethnoreligious communities (5), suggesting that LGMD-R18 may be more common in closed societies.

In summary, the detection of *TRAPPC11* gene mutation and the related clinical syndromes not only provides a better understanding of the clinical features but is also informative in terms of inheritance characteristics and geographical distribution characteristics. Comprehensive genetic analysis is essential for accurate diagnosis, as well as for raising awareness among future generations. While disease-modifying treatment studies on LGMD currently exist, for syndromic patients, the accurate determination of treatment targets will only be possible with appropriate phenotyping.

Table 1. Demographical, clinical, and genetic characteristics of previous LGMD-R18 cases in the literature

	Patient	Sex	Ethnicity	Age of onset	Clinical features	Cranial MRI	Genetic mutatiton
Bögershausen et al. (5), 2013	Family 1 Patient 1	F	Syrian	Childhood	Proximal weakness; muscle pain and cramps; hip dysplasia; scoliosis; motor delay; esotropia and myopia; elevated CK levels.	Not applicable	TRAPCC11 homozygous c.2938G>A (p.Gly980Arg)
	Family 1 Patient 2	F	Syrian	Childhood	Proximal weakness; muscle pain and cramps; hip dysplasia; scoliosis; enlarged right ventricle; elevated CK levels.	Not applicable	TRAPCC11 homozygous c.2938G>A (p.Gly980Arg)
	Family 1 Patient 3	F	Syrian	Childhood	Proximal weakness; muscle pain; hip dysplasia; scoliosis; bilateral cataracts; intellectual disability; elevated CK levels.	Not applicable	TRAPCC11 homozygous c.2938G>A (p.Gly980Arg)
	Family 2 Patient 1	M	Hutterite	Childhood	Limb asymmetry; intellectual disability; global delay; choreiform movements; ataxia; elevated CK levels.	Normal	TRAPCC11 homozygous c.1287þ5G>A (p.Ala372_Ser429del)
	Family 2 Patient 2	M	Hutterite	Childhood	Limb asymmetry; intellectual disability; global delay; choreiform movements; ataxia; elevated CK levels.	Mild cerebral atrophy	TRAPCC11 homozygous c.1287þ5G>A (p.Ala372_Ser429del)
	Family 2 Patient 3	M	Hutterite	Childhood	Limb asymmetry; intellectual disability; global delay; choreiform movements; ataxia; elevated CK levels.	Mild cerebral atrophy	TRAPCC11 homozygous c.1287þ5G>A (p.Ala372_Ser429del)
	Family 3 Patient 1	F	Hutterite	Childhood	Global delay; choreiform movements; ataxia exophoria; anisometropia and amblyopia; elevated CK levels.	Normal	TRAPCC11 homozygous c.1287þ5G>A (p.Ala372_Ser429del)
Liang et al. (1), 2015		F	Han Chinese	Childhood	Unable to stand up; speech delay; bilateral cataracts; mild lordosis; hepatomegaly; high levels of transaminases; elevated CK levels.	Normal	Heterozygous TRAPPC11, c.2938G > T (p.Gly980Arg)
Fee et al. (4), 2017	Patient 1	M		Infancy	Intrauterine growth; retardation; attention deficit; mental retardation; delayed motor domains; elevated CK levels.	Significant for subtle fluid-attenuated inversion recovery intensity increase in frontal and occipital lobe white matter.	Heterozygous TRAPPC11, c2330A.C (pGln777Pro)
	Patient 2	F		Infancy	Intrauterine growth; retardation; mental retardation; delayed motor domains; congenital cataracts; thoracic spine dysmorphism; recurrent ear infections; generalized tonic–clonic seizures.	Brachycephaly, especially flattening of the right parieto-occipital vault; borderline volume loss, especially in the cerebellum, with borderline increased signal in the midbrain.	Heterozygous TRAPPC11, c2330A.C (pGln777Pro)

Table 1. Continued

	Patient	Sex	Ethnicity	Age of onset	Clinical features	Cranial MRI	Genetic mutatiton
Koehler et al. (3), 2017	Family 1 Patient 1	M	Turkish	Infancy	Achalasia; alacrima hyperkeratosis; intellectual disability; gait abnormalities; milestones delay; epileptic seizures; scoliosis; undescended testis; nephrolithiasis.	Cerebral atrophy	TRAPPC11 homozygous splice site mutation c.1893+3A>G (p.Val588Glyfs16)
	Family 1 Patient 2	F	Turkish	Infancy	Alacrima; intellectual disability; no gait milestones delay; epileptic seizures; scoliosis.	Cerebral atrophy	TRAPPC11 homozygous splice site mutation c.1893+3A>G (p.Val588Glyfs16)
	Family 2 Patient 1	M	Turkish	Infancy	Achalasia; alacrima; intellectual disability; no gait milestones delay; scoliosis.	Cerebral atrophy	TRAPPC11 homozygous splice site mutation c.1893+3A>G (p.Val588Glyfs16)
	Family 2 Patient 2	F	Turkish	Infancy	Achalasia; alacrima; intellectual disability; no gait milestones delay; scoliosis.	Cerebral atrophy	TRAPPC11 homozygous splice site mutation c.1893+3A>G (p.Val588Glyfs16)
Wang et al. (7), 2018	Family 1 Patient 1	F	Chinese	Early childhood	Progressive proximal muscle weakness; no significant signs of extramuscular involvement; elevated CK levels.	Normal	TRAPPC11 heterozygous mutations c.1192C>T (p.Arg398*) and c.3014C>T (p.Pro1005Leu)
	Family 1 Patient 2	M	Chinese	Early childhood	Progressive proximal muscle weakness; no significant signs of extramuscular involvement; elevated CK levels.	Normal	TRAPPC11 heterozygous mutations c.1192C>T (p.Arg398*) and c.3014C>T (p.Pro1005Leu)
Chen et al. (2), 2021	Family 1 Patient 1	F	Han Chinese	Adulthood	Bilateral wing scapula; atrophy of upper extremity girdle muscles.	Normal	TTN c.19481T>G (p.Leu6494Arg) and TRAPPC11 c.3092C>G (p.Pro1031Arg)
	Family 2 Patient 1	F	Han Chinese	Adulthood	Bilateral wing scapula; atrophy of upper extremity girdle muscles; pseudohypertrophy.	Normal	TTN c.19481T>G (p.Leu6494Arg) and TRAPPC11 c.3092C>G (p.Pro1031Arg)
	Family 2 Patient 2	F	Han Chinese	Adulthood	Bilateral wing scapula; atrophy of upper extremity girdle muscles; Pseudohypertrophy.	Normal	TTN c.19481T>G (p.Leu6494Arg) and TRAPPC11 c.3092C>G (p.Pro1031Arg)

Table 1. Continued

	Patient	Sex	Ethnicity	Age of onset	Clinical features	Cranial MRI	Genetic mutatiton
Munot et al. (6), 2022	Patient 1	M		Infancy	Proximal muscle weakness; gait retardation; pseudohypertrophy; mild contractures at elbows and ankles; bilateral cataracts; elevated CK levels.	Not applicable	TRAPPC11 c.100C > T and TRAPPC11 c.2938G > A (p.Arg34) and (p.Gly980Arg)
	Patient 2	F		Infancy	Proximal muscle weakness; gait retardation; bilateral cataracts; liver disease; borderline intellectual capacity; elevated CK levels.	Equivocally reduced white matter volume	TRAPPC11 c.661-1G > T and TRAPPC11 c.2938G > A p.(Leu240Alafs*10) or p. (Leu240Valfs*7) & p.(Gly980Arg)
	Patient 3	M		Infancy	Proximal weakness; gait retardation; mild calf hypertrophy; no joint contractures; elevated CK levels.	Not applicable	TRAPPC11 c.1816C > T and TRAPPC11 c.2938G > A p.(Gln606X) and p.(GLy980Arg)
	Patient 4	F		Infancy	Proximal weakness; gait retardation; slight pseudohypertrophy; no contractures; elevated CK levels.	Not applicable	TRAPPC11 c.2644delA and TRAPPC11 c.2938G > A p.(G980R) and p.(T881fs)
	Patient 5	M		Infancy	Able to roll, never achieved unsupported sitting; pseudohypertrophy of thigh and calf muscles; intellectual disability; elevated CK levels; strabismus; oral-motor and limb choreiform movements; microcephaly; dilated cardiomyopathy. Post-mortem: liver disease	Global cerebral and cerebellar atrophy, immature myelination	TRAPPC11 c.829A > G and TRAPPC11 c.2234C > A p.(Lys277Glu) and p.(Thr745Lys)
Current case report	Family 1 Patient 1	M	Turkish	Early childhood	Proximal muscle weakness; cervicothoracic scoliosis; mild intellectual disability; generalized tonic–clonic seizure in early childhood.	Normal	TRAPPC11 homozygous missense mutation c.2938G>A (p.Gly980Arg)

CK: Creatine kinase; TRAPPC11: Transport protein particle complex 11, F: Female, M: Male

Ethics

Informed Consent: Written informed consent was obtained from the patient for this publication.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.B., Y.S., A.S., Ö.T., Concept: G.C.Y.Ç., Y.S., Design: G.C.Y.Ç., Y.S., Data Collection or Processing: G.C.Y.Ç., Y.S., Analysis or Interpretation: E.B., Y.S., A.S., Ö.T., Literature Search: G.C.Y.Ç., Y.S., Writing: G.C.Y.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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