# The Interplay of Infection, Pain, Locking Syndrome in LGMD-TNPO3 Related. Evidence from a Sporadic Slovakian Patient


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LGMD is a group of disorders with many subtypes categorized by disease gene and inheritance leading to progressive proximal weakness caused by loss of muscle fibers.

Among the less frequent forms of LGMD, the autosomal dominant LGMD (LGMD-D) are a genetically heterogeneous group of myopathies presenting with progressive proximal weakness

LGMD-D2, transportin 3 (TNPO3) related deficiency, is a very rare autosomal dominant myopathy, characterized by muscle fiber degeneration and progressive weakness. Genetic investigation of DNA identified a heterozygous mutation in the termination codon of the TNPO3 gene

TNPO3 gene encodes for transportin-3 (TNPO3), a protein that belongs to the importin beta family and which is directly involved in protein translocation from the cytoplasm to the nucleus

TNPO3 binds and transports proteins rich in serine/arginine domains (SR) and several of these SR proteins include essential splicing factors and proteins involved in mRNA splicing and metabolism.

## What do we know about the disease nowadays?

A total of **32** affected individuals were **initially** reported. The **age of onset** is highly variable, ranging from infancy (<1 year) to 58 years. Most patients experience juvenile onset before the age of 15, while others develop symptoms in their 20s or 30s.

Initial **muscle weakness** primarily affected **the proximal lower limbs and later progressed to the upper girdle**, with notable involvement of the triceps. A distinctive feature was the presence of abnormally long fingers (arachnodactyly), along with weakness in the neck, axial, and limb muscles

Investigations in a large Spanish family pinpointed a region on chromosome *7q32.1-32.2*. It has been identified a single nucleotide deletion in the TNPO3 gene (***c.2771delA***). Frameshift mutations in the last coding exon of TNPO3 were identified in two additional families with LGMD-D2: a Swedish family (c.2757delC) and a Hungarian family (c.2767delC)..

## Clinical aspects

### Patient characteristics

Diagnosed with a sporadic form of TNPO3-related LGMD

Heterozygous pathogenic variant c.2686 in the TNPO3 gene and a heterozygous *c.23335* mutation in the WASHC5 gene, associated with spastic paraplegia type 8.

### Patient's demographics and history

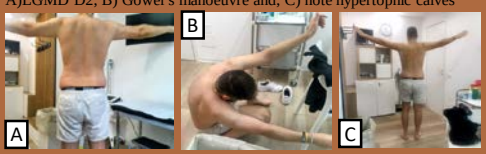
This 31-year old male patient from Slovakia developed in the third decade a weakness compatible with LGMD syndrome, he had a Gowers' sign and difficulty walking. His 'parents did not carry the mutation and appeared healthy.

Evoked potentials showed in both upper and lower limbs with bilateral cortical stimulation. He carried a pathogenic stop codon mutation of the TNPO3 gene, in exon 21, that could result in a shorter protein of the terminal part of transportin-3 from exon 22.

As a child, he had a lot of infections and such unfortunate features persisted in adulthood. He often had sinusitis, sore throat, and frequent headaches, in addition, complained of frequent sores in his feet cold hands, and tiredness.

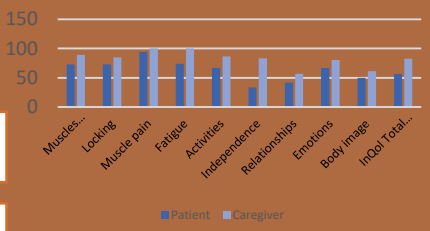
After Lyme disease he started presenting joint and muscle pain, and this pain was presented as a feeling like fibromyalgia, with a "burning sensation".

**Figure 1.** Clinical features of slovakian patient.
A)LGMD D2; B) Gower's manoeuvre and; C) note hypertophic calves




### Quality of life

**Figure 2.** Responses on the domains of INQoL by the patient and the caregiver




The domains most affected were muscle weakness, locking, muscle pain, and fatigue. Muscle symptoms also had a major impact on activities of daily living and at an emotional level.

**Table 1.** Comparison between LGMD-D2 patients and case report.

| Patient | Muscle Weakness | Locking | Muscle Pain | Fatigue | Activities | Independence | Relationships | Emotions | Body image | INQoL total score |
|---|---|---|---|---|---|---|---|---|---|---|
| *Total score of patients with LGMD-D2* | 60.52 % | 34.86 % | 23.02 % | 59.86% | 59.86% | 50.83% | 52.77% | 23.33% | 29.16 % | 38.88% |
| *Case report* | 73% | 73% | 94% | 73.68% | 66.66% | 33.33% | 41.66% | 66.66% | 50% | 56.27% |

*Note.* This patient has higher scores compared to six patients with the same diagnosis, but different mutation(s), in almost all domains except independence and impairment of social relationships. It is worth mentioning that the patient reports independence in his daily activities despite the impairments caused by the disease.

### CONCLUSIONS

- The association between TNPO3 dysfunction and susceptibility to infections, such as Lyme disease, suggests an intriguing link between the nuclear transport protein's role in muscle pathology and immune system interactions. Careful observation of transportin 3 and related proteins in LGMD-D2 muscle biopsies suggest a possible interference in the morphology and function of the myofibrillar network by mutated TNPO3.
- Quality of life assessments reveal a higher burden of symptoms in this patient compared to others with LGMD-D2, emphasizing the need for personalized management strategies.