



Case Report

Prenatal Diagnosis in a Family with TTN-related Limb-girdle Muscular Dystrophy (LGMDR10): A Case Report

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ABSTRACT

Background: TTN-related limb-girdle muscular dystrophy R10 (LGMDR10) is a rare autosomal recessive neuromuscular disorder caused by biallelic pathogenic variants in the *TTN* gene. Owing to the large size of *TTN* and the marked phenotypic heterogeneity of titinopathies, molecular diagnosis can be challenging. Accurate genetic diagnosis is essential for reproductive risk assessment and prenatal genetic counselling. We report the successful application of targeted prenatal diagnosis following molecular confirmation of TTN-related LGMDR10 in an affected father.

Case presentation: A 32-year-old pregnant woman with a history of poliomyelitis and two first-trimester pregnancy losses was referred for prenatal genetic counselling because her husband had progressive proximal muscle weakness suggestive of an inherited muscular dystrophy. Expanded carrier screening identified a homozygous pathogenic *TTN* variant, c.106117C>T (p.Gln35373Ter), confirming TTN-related LGMDR10 in the father. The mother did not carry the familial *TTN* variant but was heterozygous for pathogenic variants in *GYS2* and *PNKP* and a likely pathogenic variant in *DNAAF1*. During the ongoing pregnancy, non-invasive prenatal screening indicated a low-risk result. Amniocentesis was subsequently performed for chromosomal microarray analysis and targeted testing for the familial *TTN* variant. Chromosomal microarray analysis revealed no clinically significant copy number abnormalities, while targeted molecular testing demonstrated that the fetus was heterozygous for the familial *TTN* variant, indicating carrier status. These findings excluded autosomal recessive TTN-related LGMDR10 in the fetus and enabled accurate genetic counselling regarding recurrence risk and future reproductive options. **Conclusions:** This case demonstrates the clinical utility of molecular diagnosis in facilitating targeted prenatal testing for TTN-related muscular dystrophy. It further highlights the importance of integrating molecular findings with clinical evaluation, inheritance pattern, and multidisciplinary genetic counselling for accurate prenatal risk assessment and informed reproductive decision-making.

KEYWORDS: *TTN*, titinopathy, limb-girdle muscular dystrophy R10, prenatal diagnosis, genetic counselling, prenatal testing.

INTRODUCTION

Limb-girdle muscular dystrophies (LGMDs) are a heterogeneous group of inherited disorders characterized by progressive weakness and wasting of the pelvic and shoulder girdle muscles. Advances in molecular genetics have led to the identification of numerous causative

genes and have refined disease classification. Among these, pathogenic variants in the *TTN* gene are associated with a spectrum of skeletal and cardiac muscle disorders collectively known as titinopathies. *TTN* encodes titin, a giant sarcomeric protein that plays a critical role in

muscle elasticity, structural integrity, and force transmission.^[1]

LGMDR10, an autosomal recessive TTN-related limb-girdle muscular dystrophy, is characterised by significant phenotypic heterogeneity, increased serum creatine kinase levels, and increasing proximal muscle weakening.^[2] Establishing a molecular diagnosis can be challenging due to the large size of the TTN gene and the broad clinical spectrum associated with TTN variations. However, prenatal diagnosis, family screening, reproductive counselling, and prognosis all depend on an accurate genetic diagnosis.^[3]

We report a family in which molecular confirmation of TTN-related LGMDR10 in an affected father enabled targeted prenatal testing during an ongoing pregnancy and facilitated informed reproductive decision-making.

CASE REPORT

A 32-year-old pregnant woman was referred for genetic counselling during her third pregnancy. She had a history of poliomyelitis and two previous first-trimester pregnancy losses at approximately 9 and 9.5 weeks of gestation. There was no family history of neuromuscular disorders on her side of the family.

Her husband, aged 32 years, had a history of progressive muscular weakness. The weakness predominantly affected the proximal muscles of the lower limbs and gradually progressed. He experienced increasing difficulty in walking and climbing stairs and eventually became unable to ambulate independently. Clinical examination revealed proximal muscle weakness involving the lower limbs, scapular winging, foot deformities, and elevated serum creatine phosphokinase levels. No cognitive impairment was reported.

Family history revealed third-degree consanguinity between his parents. No other family members were known to be affected by a neuromuscular disorder (Figure 1).

In view of the clinical suspicion of an inherited muscular dystrophy, expanded carrier screening was performed. Molecular analysis identified a homozygous pathogenic variant in the TTN gene, c.106117C>T (p.Gln35373Ter). This nonsense variant introduces a premature stop codon and is predicted to result in loss of normal protein function. The molecular findings, together with the clinical phenotype, established the diagnosis of autosomal recessive TTN-related limb-girdle muscular dystrophy (LGMDR10).

Subsequent carrier screening of the spouse identified heterozygous pathogenic variants in GYS2 and PNKP, and a likely pathogenic variant in DNAAF1. She did not carry the familial TTN pathogenic variant, and no shared pathogenic variants associated with autosomal recessive disorders were identified between the couple.

Given the established molecular diagnosis in the father and the ongoing pregnancy, prenatal genetic evaluation was undertaken. Non-invasive prenatal screening demonstrated a low-risk result. Amniocentesis was subsequently performed for chromosomal microarray analysis and targeted testing for the familial TTN variant. Chromosomal microarray analysis using a 750K array did not reveal any clinically significant copy number abnormalities. Targeted molecular testing demonstrated that the fetus was heterozygous for the familial TTN variant, c.106117C>T (p.Gln35373Ter), indicating carrier status. The fetus was therefore not expected to be affected with autosomal recessive TTN-related LGMDR10.

Following disclosure of the results, comprehensive post-test genetic counselling was provided. The couple was counselled regarding the interpretation of fetal carrier status, recurrence risks, and the implications of the molecular findings for future reproductive planning. The importance of correlating molecular findings with clinical presentation and family history was emphasized, and the couple was informed about the benefits and limitations of prenatal genetic testing.

DISCUSSION

Although prenatal investigations were reassuring regarding the risk of autosomal recessive TTN-related limb-girdle muscular dystrophy type R10 (LGMDR10), interpretation of the fetal findings required careful consideration of the complex genotype-phenotype relationships associated with TTN. As one of the largest genes in the human genome, TTN has been implicated in a diverse range of skeletal and cardiac muscle disorders, including congenital myopathies, limb-girdle muscular dystrophy, myofibrillar myopathy, and dilated cardiomyopathy (DCM). Consequently, determining the clinical relevance of a TTN variant can be challenging, particularly in the prenatal setting where clinical manifestations cannot be fully assessed.^[1-5]

In the present case, the father was found to harbour a homozygous pathogenic TTN truncating variant, c.106117C>T (p.Gln35373Ter), which showed strong concordance with his clinical features of progressive adult-onset proximal muscle weakness, elevated serum creatine phosphokinase levels, scapular winging, foot deformities, and impaired ambulation. These findings supported the pathogenic role of the variant and established it as the molecular basis of his neuromuscular disorder. Targeted prenatal testing demonstrated that the fetus had inherited only one copy of the familial TTN variant and was therefore heterozygous. Since the mother did not carry the familial pathogenic variant, an autosomal recessive TTN-related disorder in the fetus was effectively excluded. Accordingly, the likelihood of the fetus developing the same recessive muscular dystrophy phenotype as the father was considered negligible.

Nevertheless, genetic counselling extended beyond the assessment of recessive neuromuscular disease risk. TTN truncating variants have also been implicated in autosomal dominant forms of cardiomyopathy, particularly DCM. Evaluation of such risk depends on multiple factors, including variant location, exon expression within cardiac tissue, segregation data, and available clinical evidence. Therefore, interpretation of TTN variants requires consideration of the broader spectrum of TTN-associated disorders rather than focusing solely on the presenting phenotype. Existing evidence indicates that the clinical consequences of TTN truncating variants may differ according to their genomic context and expression patterns, and future cardiac manifestations cannot always be excluded with certainty.

This shows a major issue in medical genetics: a specific clinical outcome is not always predicted by the discovery of a pathogenic variant. Environmental factors, age-related onset, variable penetrance, and gene-modifying factors can all have an impact on disease expression. Molecular results should therefore always be interpreted combined with clinical assessment and family history. At the time of assessment, there was no evidence of cardiomyopathy in this family, and the father's symptoms were primarily neuromuscular. However, periodic cardiac monitoring was considered to be beneficial because skeletal and cardiac involvement may coexist in TTN-related disorders. The familial variant identified in this case is located within the I-band region of TTN. Current evidence suggests that truncating variants in the I-band are generally less enriched among patients with dilated cardiomyopathy than truncating variants affecting constitutively expressed exons in the A-band region. Nevertheless, the available literature does not permit complete exclusion of future cardiac manifestations in all individuals carrying such variants.

For this reason, cardiac assessment of the father, including echocardiography, was recommended to evaluate for subclinical cardiomyopathy and establish baseline cardiac function. Fetal echocardiography was also advised as part of a comprehensive prenatal evaluation despite the absence of abnormalities on routine obstetric ultrasonography. These assessments were intended to complement the molecular findings by evaluating organ systems that may potentially be affected in TTN-related disease.

The present case also emphasizes the importance of a multidisciplinary approach when interpreting complex prenatal genetic results. Combining molecular diagnostic data with detailed clinical phenotyping, prenatal investigations, and specialist assessment provided a more comprehensive evaluation of fetal risk than any single modality alone. Effective communication among the molecular laboratory, clinical geneticist, genetic counsellor, fetal medicine specialist, cardiologist, and the family was equally important. Such collaboration facilitated appropriate interpretation of the findings, clarified residual uncertainties, and helped distinguish carrier status from disease expression.

In conclusion, prenatal genetic testing should be regarded as one component of an integrated clinical assessment rather than a standalone diagnostic tool. Its greatest benefit is achieved when molecular results are interpreted in conjunction with clinical findings and communicated through a coordinated multidisciplinary framework. Ongoing dialogue between the family, genetic counsellor, and healthcare team is essential for accurate interpretation of genetic information, informed decision-making, and appropriate reproductive counselling while recognising both the capabilities and limitations of current genomic technologies.

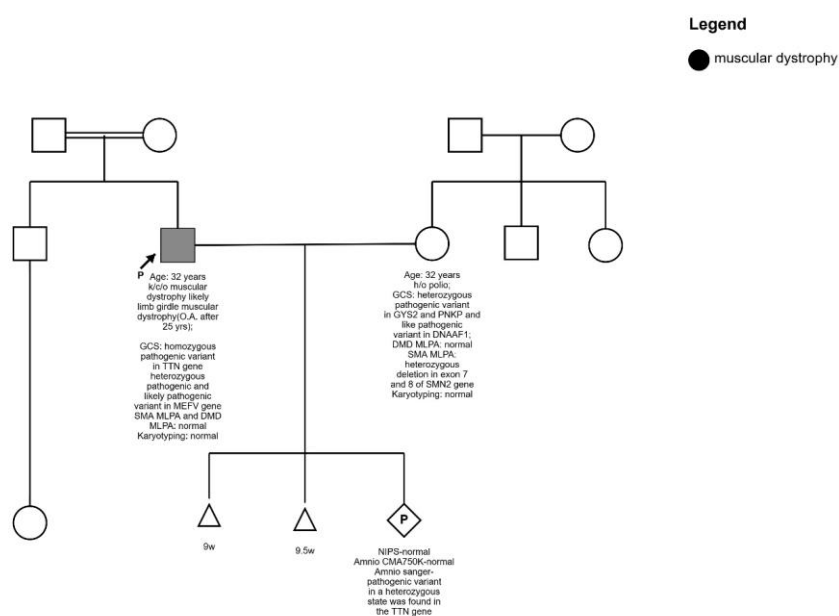


Fig. 1: Pedigree of the family with TTN related limb girdle muscular dystrophy (LGMDR10).

CONCLUSION

This case highlights the clinical utility of molecular diagnosis in hereditary neuromuscular disorders and demonstrates how identification of a homozygous pathogenic TTN variant can facilitate accurate reproductive risk assessment. Targeted prenatal testing established that the fetus was heterozygous for the familial TTN variant, thereby excluding autosomal recessive TTN-related limb-girdle muscular dystrophy type R10 (LGMDR10). The case further underscores the challenges associated with interpreting TTN variants due to their broad phenotypic spectrum and complex genotype–phenotype correlations. Integration of molecular findings with inheritance pattern, clinical phenotype, prenatal evaluation, and multidisciplinary genetic counselling is essential for accurate interpretation of prenatal genetic results and informed reproductive decision-making.

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Conflict of Interests

The authors declare no conflict of interest.

Ethical Approval

Ethical approval was not required for this case report.

Consent

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Availability of Data and Material

Not applicable. All relevant data are presented in the manuscript.

Authors' Contributions

All authors contributed to the conception, drafting, revision, and approval of the final manuscript.

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