



Article
scientifique

Rapport de
cas

2023

Published
version

Open
Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Successful heart transplant in a child with congenital core myopathy and delayed-onset restrictive cardiomyopathy due to recessive mutations in the titin (TTN) gene

Wacker Bou Puigdefabregas, Julie Caroline; Di Bernardo, Stephanie; Lobrinus, Johannes Alexander; Jungbluth, Heinz; Gautel, Mathias; Beghetti, Maurice; Fluss, Joel Victor

How to cite

WACKER BOU PUIGDEFABREGAS, Julie Caroline et al. Successful heart transplant in a child with congenital core myopathy and delayed-onset restrictive cardiomyopathy due to recessive mutations in the titin (TTN) gene. In: Pediatric transplantation, 2023, p. e14561. doi: 10.1111/petr.14561

This publication URL: <https://archive-ouverte.unige.ch/unige:170571>

Publication DOI: [10.1111/petr.14561](https://doi.org/10.1111/petr.14561)

CASE REPORT

WILEY

Successful heart transplant in a child with congenital core myopathy and delayed-onset restrictive cardiomyopathy due to recessive mutations in the titin (*TTN*) gene

Julie Wacker^{1,2}  | Stefano Di Bernardo^{2,3} | Johannes Alexander Lobrinus⁴ |
Heinz Jungbluth^{5,6} | Mathias Gautel⁶ | Maurice Beghetti^{1,2}  | Joel Fluss⁷

¹Pediatric Cardiology Unit, University Hospitals of Geneva, Faculty of Medicine, University of Geneva, Geneva, Switzerland

²Centre Universitaire Romand de Cardiologie et Chirurgie Cardiaque Pédiatrique, University Hospitals of Geneva, Geneva, Switzerland

³Pediatric Cardiology, Department of Pediatrics, Lausanne University Hospital, Lausanne, Switzerland

⁴Neuropathology Unit, Department of Clinical Pathology, University Hospitals of Geneva, Geneva, Switzerland

⁵Department of Paediatric Neurology, Neuromuscular Service, Evelina's Children Hospital, Guy's & St. Thomas' Hospital NHS Foundation Trust, London, UK

⁶Randall Centre for Cell and Molecular Biophysics, King's College London BHF Centre of Research Excellence, London, UK

⁷Pediatric Neurology Unit, University Hospitals of Geneva, Faculty of Medicine, University of Geneva, Geneva, Switzerland

Correspondence

Julie Wacker, Pediatric cardiology, Pediatric Subspecialties Service, Children's Hospital, Geneva University Hospital, Rue Willy-Donzé 6, Geneva 1211, Switzerland.
Email: julie.wacker@hcuge.ch

Abstract

Background: Mutations in the *TTN* gene, encoding the muscle filament titin, are a major cause of inherited dilated cardiomyopathy. Early-onset skeletal muscle disorders due to recessive *TTN* mutations have recently been described, sometimes associated with cardiomyopathies.

Case Description: We report the case of a boy with congenital core myopathy due to compound heterozygosity for *TTN* variants. He presented in infancy with rapidly evolving restrictive cardiomyopathy, requiring heart transplantation at the age of 5 years with favorable long-term cardiac and neuromuscular outcome.

Conclusion: Heart transplantation may have a role in selected patients with *TTN*-related congenital myopathy with disproportionately severe cardiac presentation compared to skeletal and respiratory muscle involvement.

KEYWORDS

cardiomyopathy, pediatric heart transplant, titin

Abbreviations: ASD, atrial septal defect; DCM, dilated cardiomyopathy; NGS, next generation sequencing; PH, pulmonary hypertension; RCM, restrictive cardiomyopathy; *TTN*, titin; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. *Pediatric Transplantation* published by Wiley Periodicals LLC.

1 | INTRODUCTION

TTN is the largest gene in humans and encodes the giant muscle filament protein titin. Titin plays a crucial role in the sarcomeric contractile apparatus in skeletal and cardiac muscle,^{1,2} notably in myocardial elasticity and passive stiffness, active force development, and cell signaling.³

Widespread introduction of next-generation sequencing (NGS) into clinical genetic diagnostic methods has led to the recognition of *TTN* as the major human disease gene for dilated cardiomyopathy (DCM), with mutations found in approximately 25% of familial and 18% of sporadic cases.^{4,5} Few reports indicate that *TTN* could also be a disease-causing gene in other types of cardiomyopathy, including restrictive cardiomyopathy (RCM).⁶ In addition, early-onset skeletal muscle disorders due to recessive *TTN* mutations have been identified, frequently combining skeletal and cardiac muscle phenotypes. Modes of inheritance, skeletal and cardiac muscle involvement, clinical severity, and histopathological features are extremely heterogeneous, accounting for the wide and evolving spectrum of the titinopathies.⁷⁻⁹ Most often, these infants present with a congenital myopathy phenotype characterized by generalized muscle weakness with axial predominance and associated variable cardiorespiratory impairment.^{10,11} Some patients may have structural cardiac defects at birth. Cardiomyopathy typically develops later in a subset of patients and carries a poor prognosis, with high mortality.^{12,13}

Individuals with neuromuscular disorders are often not considered candidates for cardiac transplantation because of concerns that the benefits might be limited by the multiple comorbidities and disease progression.

We report the case of a boy with early-onset *TTN*-related congenital myopathy who subsequently developed a rapidly evolving cardiomyopathy. He underwent successful heart transplantation at the age of 5 years, with favorable postoperative cardiac and developmental outcome.

2 | CASE REPORT

The proband, now a 13-year-old boy, was the first child of non-consanguineous parents, with no family history of note. He presented in the neonatal period with hypotonia, mild breathing difficulties, and sweating, prompting a cardiology work-up.

Echocardiography performed at the age of 6 months revealed a large atrial septal defect (ASD) with signs of pulmonary hypertension (PH). He underwent partial ASD closure with subsequent stabilization of pulmonary pressure at a borderline level.

Subsequent clinical examinations showed persistent generalized hypotonia, muscle weakness, and evolving spinal rigidity, with normal cognitive development, suggesting a possible myopathy. Skeletal muscle biopsy performed at 18 months showed histopathological features of a congenital myopathy with atrophy and predominance of type I fibers, multiple internal nuclei, and core-like structures,

corresponding to areas of sarcomeric disorganization and mitochondrial depletion on the ultrastructural level.

He developed progressive restrictive cardiac physiology by the age of 3 years, with initially preserved biventricular systolic function. He had syncopal episodes with suspected supraventricular tachycardia. A year later, he presented with acute cardiopulmonary failure in the context of a respiratory infection, requiring veno-arterial extracorporeal membrane oxygenation (VA-ECMO), which was weaned after 7 days. He could then be discharged home on oral heart failure treatment. He was put on the waiting list for cardiac transplantation. While on listing, he was able to walk short distances with support. He had normal cognitive development and was home-schooled. He had failure to thrive with a weight under the 5th centile despite hypercaloric meals. From the respiratory point of view, a restrictive pulmonary syndrome was presumed (pulmonary function tests were not feasible because of age), with multiple hospital admission due to increased oxygen requirements during viral illness. He had recurrent atelectasis caused by mucous plugs and an ineffective cough. He was managed with intense respiratory physiotherapy, a cough assist machine, dornase alpha nebulization, and occasional noninvasive ventilation as required.

After 11 months on the waiting list, heart transplantation was successfully performed at the age of 5.5 years. Immediate post-transplant period was straightforward on the cardiological point of view, and the ICU length of stay was determined by his respiratory evolution. He was extubated after 48 h but required noninvasive ventilation for 14 days with bronchoscopy performed for persistent retrocardiac atelectasis, intensive physiotherapy, cough assist, and percussion with subsequent good evolution. He was discharged home after 34 days.

The combination of skeletal congenital myopathy with the above-mentioned features and cardiomyopathy prompted consideration of a titinopathy. Specific genetic testing revealed compound heterozygosity for two *TTN* mutations *in trans*, a maternally inherited pathogenic c.63601C>T p.(Arg21201Ter) variant and a paternally inherited likely pathogenic c.83546G>T p.(Gly27849Val) variant, confirming the diagnosis of a recessive *TTN*-related congenital myopathy. Interestingly, light microscopy on the removed heart muscle did not reveal any gross abnormalities, but later additional immunofluorescence staining on frozen specimens against N-terminal and C-terminal titin confirmed that the missense mutant allele was incorporated into the sarcomere, which appeared disrupted in multiple areas (data not shown). Of note, our patient had undergone extensive previous stepwise genetic testing based on approaches available at the time of initial diagnosis of a myopathy; this had initially included *RYR1* and *MTM1* Sanger sequencing, prompted by clinical features and the presence of cores and central nuclei on muscle biopsy and was subsequently complemented by screening through a more extensive congenital myopathy testing. The results of these tests (which did not cover *TTN* at the time) were negative.

Over the 8 years of follow-up since cardiac transplantation, the patient has maintained a normal cardiac function without any major post-transplantation complications. He is growing along the

25th centile for weight. He markedly improved his endurance and strength, with satisfactory motor development, despite major spinal surgery for scoliosis at the age of 7 years. He is active, walks independently, engages in various activities such as playing ping-pong, and rarely uses his walking aids. He developed mild respiratory insufficiency requiring nocturnal noninvasive ventilation, which had to be adjusted during respiratory infections. He was only admitted once for noninvasive ventilation and intensive physiotherapy. His pulmonary function tests show a moderate restrictive syndrome, with a decrease in total lung capacity, vital capacity, forced vital capacity (all between 50% and 55% of predicted), and decreased sniff nasal inspiratory pressure (48 cm H₂O). Of note, these parameters have been improving over the last years post-transplantation. He is attending mainstream school with good academic performance.

3 | DISCUSSION

Recent introduction of NGS has allowed previously challenging identification of *TTN* mutations in DCM and other types of cardiomyopathies, as well as in early-onset skeletal muscle disorders. However, the presence of *TTN* variants in about 3% of healthy individuals illustrates the challenge of correct pathogenicity ascertainment, especially with regard to isolated missense variants.¹⁴ In our case, a titinopathy was suspected because of clinical features combining an early-onset skeletal myopathy with delayed-onset cardiomyopathy, and typical histopathological features comprising a combination of cores and central nuclei on muscle biopsy. Other genes associated with combined skeletal and cardiac myopathies such as *MYH7*, *BAG3*, *SPEG*, or *ACTA1* were considered in the differential diagnosis,^{15–17} but not confirmed on screening through a NGS congenital myopathy panel. Although in our case the genetic diagnosis was strongly suggested by direct sequencing of the *TTN* gene, unequivocal pathogenicity ascertainment of a missense mutation in the complex recessive *TTN* genotype could only be achieved by rigorous approach combining bioinformatics prediction tools and additional functional studies.^{9,18–20} Both parents were identified as heterozygous *TTN* mutation carriers and remain asymptomatic, with normal cardiac follow-up to date.

In the few published case series of patients with *TTN*-related congenital myopathies, cardiac involvement was present in about half of them,^{8,9,12,13} with most patients presenting with DCM and heart failure in the first decade. Other reported cardiac features included left-ventricular non-compaction, ASD, ventricular septal defects, and arrhythmias. Our patient exhibited a RCM, which is intuitively plausible considering the crucial role of titin in the resting tension of the sarcomere and is also in keeping with an earlier report of a de novo *TTN* mutation in a family with RCM.⁶ The question if *TTN* mutations could account for other cases of RCM should be addressed in larger genetic studies.

CHD and rhythm disturbances as seen in our case have also been reported in patients with *TTN*-related congenital myopathies,

however, given the incidence of CHD in the general population and the incidence of arrhythmia in patients with cardiomyopathy, it is uncertain if these observations reflect a coincidental or a causal association.

In the context of limited availability of donor hearts, decision-making around transplant candidacy is crucial. Patients with neuromuscular disorders are typically not considered candidates for heart transplantation, either because their comorbidities increase the risks of transplantation or their post-transplant overall prospect is perceived to be limited. An important consideration in this context is the expected natural history of neuromuscular disorders with cardiac involvement, some of which (for example, Duchenne muscular dystrophy) may feature relentlessly progressive muscle weakness, whereas in others (for example, *TTN*-related and other congenital myopathies) skeletal muscle power may remain stable over prolonged periods. Respiratory status is also of utmost importance as severe respiratory involvement can represent a contraindication for heart transplant listing.

Successful heart transplantation has been reported in some patients with a neuromuscular disorder in whom the cardiac phenotype was disproportionately severe compared to the degree of skeletal and respiratory muscle involvement.^{21–23} According to a statement released by the American Heart Association, cardiac transplantation may be considered in carefully selected patients with neuromuscular disorders and end-stage heart failure despite appropriate therapy.²⁴ Only a very small number of children with *TTN*-related congenital myopathy that underwent heart transplantation have been reported in the literature to date, without data on their long-term outcome.^{9,12,13}

Our patient exhibited skeletal muscle weakness from birth and followed a relatively stable neuromuscular course, whereas life-threatening cardiac dysfunction appeared later and progressed more rapidly. He had severe diastolic dysfunction and subsequently developed fluctuating left ventricular systolic dysfunction, with one episode of severe heart failure associated with a respiratory infection requiring VA-ECMO. Transplant candidacy was discussed in multidisciplinary meetings and finally made on the expectation that the skeletal myopathy would remain stable over time. Our patient is now 8 years post-heart transplant, with excellent cardiac outcome, and his motor performance continues to improve despite having undergone major surgery twice.

This case illustrates the phenotypical spectrum of early-onset titinopathies and emphasizes that cardiac transplant may have a role in selected patients with severe cardiac involvement out of proportion to the degree of skeletal and respiratory muscle involvement.

CONFLICT OF INTEREST STATEMENT

None of the authors have a conflict of interest related to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Julie Wacker  <https://orcid.org/0000-0001-5408-1107>

Maurice Beghetti  <https://orcid.org/0000-0002-1841-0927>

REFERENCES

1. Furst DO, Osborn M, Nave R, Weber K. The organization of titin filaments in the half-sarcomere revealed by monoclonal antibodies in immunoelectron microscopy: a map of ten nonrepetitive epitopes starting at the Z line extends close to the M line. *J Cell Biol.* 1988;106(5):1563-1572.
2. Gautel M, Djinić-Carugo K. The sarcomeric cytoskeleton: from molecules to motion. *J Exp Biol.* 2016;219(Pt 2):135-145.
3. Granzier HL, Labeit S. The giant protein titin: a major player in myocardial mechanics, signaling, and disease. *Circ Res.* 2004;94(3):284-295.
4. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. *N Engl J Med.* 2012;366(7):619-628.
5. Fang HJ, Liu BP. Prevalence of TTN mutations in patients with dilated cardiomyopathy: a meta-analysis. *Herz.* 2020;45(Suppl 1):29-36.
6. Peled Y, Gramlich M, Yoskovitz G, et al. Titin mutation in familial restrictive cardiomyopathy. *Int J Cardiol.* 2014;171(1):24-30.
7. Udd B. The constantly evolving spectrum of phenotypes in titinopathies—will it ever stop? *Curr Opin Neurol.* 2020;33(5):604-610.
8. Oates EC, Jones KJ, Donkervoort S, et al. Congenital Titinopathy: comprehensive characterization and pathogenic insights. *Ann Neurol.* 2018;83(6):1105-1124.
9. Rees M, Nikoospour R, Fukuzawa A, et al. Making sense of missense variants in TTN-related congenital myopathies. *Acta Neuropathol.* 2021;141:431-453.
10. Ceyhan-Birsoy O, Agrawal PB, Hidalgo C, et al. Recessive truncating titin gene, TTN, mutations presenting as centronuclear myopathy. *Neurology.* 2013;81(14):1205-1214.
11. Savarese M, Vihola A, Oates EC, et al. Genotype-phenotype correlations in recessive titinopathies. *Genet Med.* 2020;22(12):2029-2040.
12. Chauveau C, Bonnemant CG, Julien C, et al. Recessive TTN truncating mutations define novel forms of core myopathy with heart disease. *Hum Mol Genet.* 2014;23(4):980-991.
13. Carmignac V, Salih MA, Quijano-Roy S, et al. C-terminal titin deletions cause a novel early-onset myopathy with fatal cardiomyopathy. *Ann Neurol.* 2007;61(4):340-351.
14. Roberts AM, Ware JS, Herman DS, et al. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. *Sci Transl Med.* 2015;7(270):270ra6.
15. Jungbluth H, Treves S, Zorzato F, et al. Congenital myopathies: disorders of excitation-contraction coupling and muscle contraction. *Nat Rev Neurol.* 2018;14(3):151-167.
16. Claeys KG. Congenital myopathies: an update. *Dev Med Child Neurol.* 2020;62(3):297-302.
17. Konersman CG, Bordini BJ, Scharer G, et al. BAG3 myofibrillar myopathy presenting with cardiomyopathy. *Neuromuscul Disord.* 2015;25(5):418-422.
18. Laddach A, Gautel M, Fraternali F. TITINdb—a computational tool to assess titin's role as a disease gene. *Bioinformatics.* 2017;33(21):3482-3485.
19. Savarese M, Johari M, Johnson K, et al. Improved criteria for the classification of titin variants in inherited skeletal myopathies. *J Neuromuscul Dis.* 2020;7(2):153-166.
20. Savarese M, Maggi L, Vihola A, et al. Interpreting genetic variants in titin in patients with muscle disorders. *JAMA Neurol.* 2018;75(5):557-565.
21. Finsterer J, Bittner RE, Grimm M. Cardiac involvement in Becker's muscular dystrophy, necessitating heart transplantation, 6 years before apparent skeletal muscle involvement. *Neuromuscul Disord.* 1999;9(8):598-600.
22. Wu RS, Gupta S, Brown RN, et al. Clinical outcomes after cardiac transplantation in muscular dystrophy patients. *J Heart Lung Transplant.* 2010;29(4):432-438.
23. Hanke SP, Gardner AB, Lombardi JP, et al. Left ventricular non-compaction cardiomyopathy in Barth syndrome: an example of an undulating cardiac phenotype necessitating mechanical circulatory support as a bridge to transplantation. *Pediatr Cardiol.* 2012;33(8):1430-1434.
24. Feingold B, Mahle WT, Auerbach S, et al. American heart association pediatric heart failure committee of the council on cardiovascular disease in the Y, council on clinical C, council on cardiovascular R, intervention, council on functional G, translational B, stroke C. Management of cardiac involvement associated with neuromuscular diseases: a scientific statement from the American heart association. *Circulation.* 2017;136(13):e200-e231.

How to cite this article: Wacker J, Di Bernardo S, Lohrinus JA, et al. Successful heart transplant in a child with congenital core myopathy and delayed-onset restrictive cardiomyopathy due to recessive mutations in the titin (TTN) gene. *Pediatric Transplantation.* 2023;00:e14561. doi:[10.1111/petr.14561](https://doi.org/10.1111/petr.14561)