

Intragenic *TTN* Deletions in a Single Family with Dilated Cardiomyopathy

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Abstract: The *TTN* gene (MIM:188840) encodes titin, the largest human protein with exclusive expression in the cardiac and skeletal muscles. Rare variants disrupting the *TTN* gene are frequent causes of dilated cardiomyopathy and several forms of skeletal myopathy. We report a unique occurrence of two novel, distinct but overlapping intragenic *TTN* deletions in multiple relatives from a single Czech family with the clinical manifestation of dilated cardiomyopathy (DCM). After clinical exome sequencing using the custom virtual gene panel, two distinct deletions affecting the *TTN* gene (NM_001267550.2) were detected. The first deletion (3.599 kb in length) encompasses five exons with the breakpoints in exons 326 and 330. The longer one (4.859 kb in length) disrupts exon 326 only. Both deletions segregate with the cardiomyopathy phenotype, and none of the tested individuals carry both. The familial segregation of two distinct intragenic *TTN* deletions extends the broad spectrum of rare variants in the pathogenesis of DCM. The presence of severely affected carriers of the reported DNA variants and obligatory healthy non-carriers raises the debate on their ancestral origin. Our data demonstrate the clinical benefits of the family cascade screening and molecular genetic analysis in familial DCM, enabling early and effective multidisciplinary medical care.

Keywords: *TTN* gene, dilated cardiomyopathy, clinical exome sequencing, copy-number variation, deletion

Introduction

DCM is a type of myocardial disease characterized by the enlargement and dilatation of the left ventricle, as well as systolic dysfunction with an ejection fraction (EF) of less than 50%, whereas those cases with EF of less than 35% require medical intervention^{1,2} Approximately 40% of cases of DCM, particularly familial cases, have genetic basis which is documented by a broad spectrum of causative variants in more than 60 genes.³

Pathogenic variants in the *TTN* gene are responsible for 15–20% of DCM. The *TTN* gene (MIM:188840), called connectin, encodes titin, a large cardiac and skeletal muscular protein. *TTN* is primarily expressed in striated muscle tissues, including cardiac and skeletal muscle myocytes. The longest transcript (Meta) is a model transcript encompassing all possible in-frame 363 exons. At the same time, three major isoforms (N2BA, N2B, and N2A) are generated by an extensive alternative splicing in *TTN* regions encoding the Z-disk and I-band. The longest isoform, N2BA (313 exons), and other shorter isoforms (major N2B, and minor Novex-1 to 3) are exclusively expressed in the cardiac myocytes, while the N2A (312 exons) represents the longest skeletal isoform.⁴ The composition and ratios of the isoforms undergo dynamic changes as they are tissue- and developmentally specific and participate in various physiological processes.

The multidomain structure is composed of four central structural and functional regions, providing its interactions with other components (Z-line), elastic properties (I-band), stabilization of the thick filament (A-band), and a modulation of its expression and turnover (M-line).⁵ Titin constitutes an essential component of sarcomeres, the basic multiprotein units of muscle contraction, which produce the mechanical force at the Z-line and maintain resting tension in the

I-band.^{6,7} Titin closely interacts with actin filaments and motor protein myosin, which enables muscle contraction and relaxation. Last, titin is involved in chemical signalling and contributes to assembling new sarcomeres.⁸

The advent of next-generation sequencing (NGS) technologies was a key milestone for the comprehensive molecular genetic analysis of large and complex genes, when a broad spectrum of *TTN* gene variants was uncovered.

We report a rare case of familial segregation of two novel, distinct, overlapping intragenic *TTN* deletions in the region encoding the A-band in multiple affected individuals with DCM.

Materials and Methods

All procedures involving human participants were conducted per the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The genetic analyses were performed as part of a routine molecular diagnostics procedure at the Department of Biology and Medical Genetics, 2nd Faculty of Medicine, Charles University, and Motol University Hospital. The written informed consent was obtained after the primary genetic consultation and clinical genetics evaluation before the start of any genetic testing. The clinical geneticists have fully explained the risk of secondary findings (SF) and their clinical impact. The patients have been asked to opt in or out of receiving SF. The clinical geneticists have provided their interpretation and related genetic counseling.

The informed consent for publication was obtained from all living individuals who underwent genetic analyses as it is required by the Motol University Hospital and the Society Medical Genetics and Genomics of the Czech Medical Association of J. E. Purkyně.

Clinical exome sequencing (CES) was performed in two individuals with DCM with family history of sudden cardiac death and DCM. They were counselled independently by clinical geneticists and cardiologists in two specialized centres. Their familiar relation was identified later as they both were referred to the same heart failure centre.

Peripheral blood samples were collected from all living affected familial members, and genomic DNA was extracted using the MagCore[®] Genomic DNA Large Volume Whole Blood Kit on MagCore[®] Super/HF 16 Plus Automated Nucleic Acid Extractor (RBC Bioscience Corporation, New Taipei City, Taiwan).

CES was performed for individuals III:5 and II:6, followed by the segregation analyses for an individual II:5 with cardiac phenotype and his siblings II:1, II:2, and II:4 without cardiac phenotype related to DCM. DNA samples from III:5 and II:6 were processed into libraries using the Clinical Exome Solution v3 (4727 genes) by SOPHiA GENETICS (Rolle, Switzerland), followed by 150bp paired-end sequencing on Illumina NextSeq 550 (San Diego, CA, USA). The raw data were automatically processed using the bioinformatic pipeline in the platform SOPHiA DDM[™] (SOPHiA GENETICS), reaching the QC of the standard quality (Table S1). The variants were filtered for rare single-nucleotide variants (SNVs), insertions and deletions (indels), and copy-number variations (CNVs) in the custom virtual gene panel of 389 genes related to cardiomyopathies for which coding sequences and intronic boundaries were captured together with non-coding mutation hotspot regions (Table S1). Variant analysis was focused on causative variants according to the ClinVar database records and novel rare variants for which their clinical relevance can be concluded based on the literature records and genotype-phenotype correlation. Their pathogenicity was finally evaluated according to the recommendations of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP).⁹ CNVs were called using the comparative read-depth strategy, and their pathogenicity was verified by the automated calculations using the Franklin ACMG/ClinGen CNV classification (<https://franklin.genoox.com/clinical-db/home>). Their presence and position were inspected visually using the Integrative Genomics Viewer (IGV) and then confirmed by alternative methods, such as Sanger sequencing and quantitative real-time PCR (qPCR) with custom primers (Table S2). After PCR and termination reaction, the samples were run on ABI 3130xl and SeqStudio Flex Genetic Analyzers (Applied Biosystems, Waltham, MA, USA). Chromatograms were analyzed using Chromas Lite (Technelysium Pty Ltd, South Brisbane, Australia), and the breakpoints were evaluated using the IGV and UCSC Genome Browser interface (University of California, Santa Cruz, CA, USA). The qPCR was performed using the LightCycler[®] 480 SYBR Green I Master on the LightCycler[®] 480 Instrument (Roche Diagnostics, Ltd, Basel, Switzerland). Two primer pairs were designed to estimate the relative copy number of parts of exons 326 and 330 (Table S2). The relative quantification was performed using the formula $2^{-\Delta\Delta C_q}$ with the threshold R-values <0.7 for

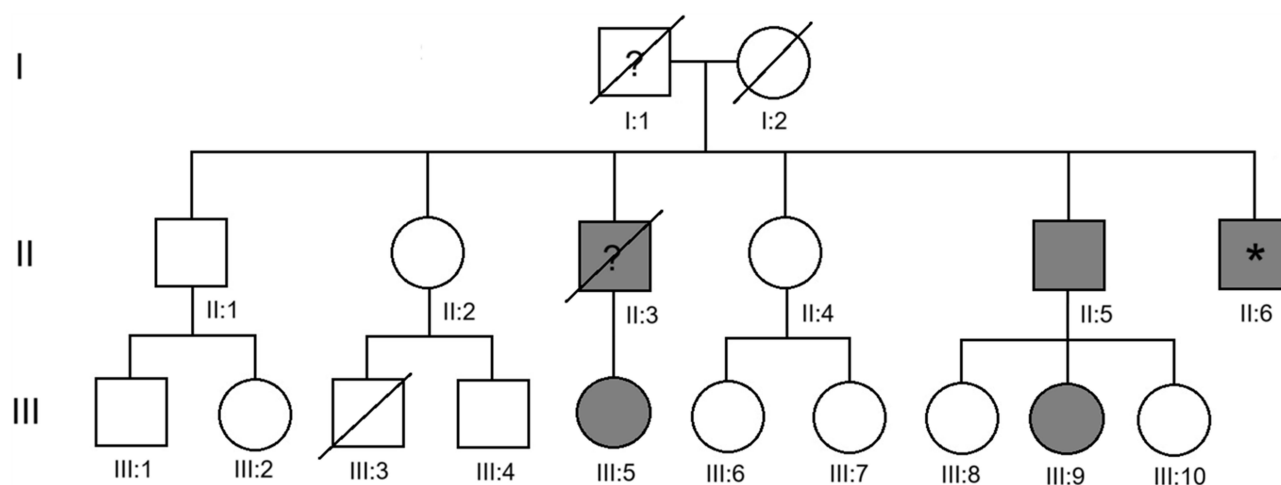


Figure 1 The three-generational pedigree of the family with the segregation of two distinct intragenic *TTN* deletions. The confirmed or obligatory affected carriers of a specific *TTN* gene deletion are filled grey (II:3, II:5, II:6, III:5, III:9), with the carrier of the shorter *TTN* gene deletion encompassing the exons 326 to 330 marked with an asterisk (*) (II:6). Finally, the untested obligatory affected carriers of unspecified deletion(s) (I:1) or a longer *TTN* gene deletion encompassing the exon 326 (II:3) are marked with a question mark (?).

DNA loss and >1.3 for DNA gain as the ratio of the relative copy numbers of the locus of interest and locus of an endogenous control.¹⁰ Finally, the causative variants were reported using the HGVS (Human Genome Variant Society) nomenclature.

Results

Family Analysis

The CES analysis documented a causative variant in individual II:6 NM_001267550.2(*TTN*):c.85464_88084del. Further CES in III:5, performed independently on the outputs of CES in individual II:6, showed NM_001267550.2(*TTN*):c.80623_85481del. Further segregation analyses by Sanger sequencing or qPCR proved a variant NM_001267550.2(*TTN*):c.80623_85481del in individuals II:5 and III:9. The other tested family members were evaluated with negative outputs. The familial segregation of distinct *TTN* gene deletions is visualized in Figure 1. The summary of clinical information of affected individuals with cardiac phenotype related to DCM and genetic results is reported in Table 1 and in the [Supplementary Material](#) (section “Detailed clinical information on investigated family members”).

Table 1 Clinical Information and Genetic Analysis in Affected Family Members

Individuals	Cardiac Pathology	Age of Onset/ Diagnosis	Genetic Results
I:1	Unknown	SD (65)	Not tested
II:3	DCM	41	Not tested (obligatory carrier) NM_001267550.2 (<i>TTN</i>): c.80623_85481del
II:5	DCM	67	NM_001267550.2 (<i>TTN</i>):c.80623_85481del
II:6	DCM	57	NM_001267550.2 (<i>TTN</i>):c.85464_88084del
III:5	DCM/LVAD/HTx	39	NM_001267550.2 (<i>TTN</i>):c.80623_85481del
III:9	M. Barlow with mild mitral valve regurgitation, no DCM	37	NM_001267550.2 (<i>TTN</i>):c.80623_85481del

Abbreviations: DCM, dilated cardiomyopathy; HTx, heart transplantation; LVAD, left ventricular assist device; SD, sudden death.

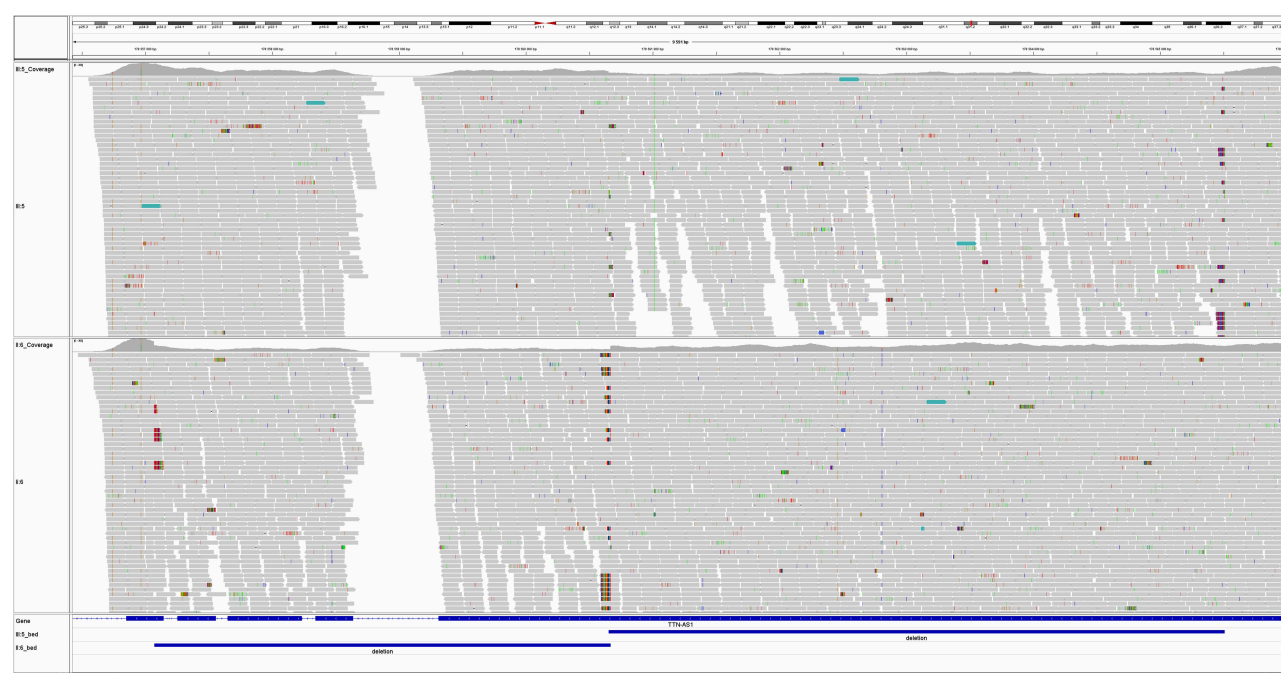


Figure 2 The alignment of two distinct intragenic *TTN* deletions. The processed outputs of clinical exome sequencing (bam files) of individuals III:5 (up) and II:6 (down) were imported to the Integrative Genomics Viewer to visualize mapped reads with *TTN* gene deletions. The breakpoints are visible as the remarkable coverage decrease in the fields above the mapped reads (III:5_Coverage, II:6_Coverage). Their ranges are represented by blue lines (III:5_bed and II:6_bed) at the bottom of the Figure.

Clinical Exome Sequencing and Segregation Analysis

CES restricted to the virtual custom panel of 389 genes related to cardiomyopathy was performed in individuals III:5 and II:6. The molecular analysis led to the identification of two distinct intragenic, out-of-frame deletions in the *TTN* gene encompassing exons 326 to 330, NM_001267550.2(*TTN*):c.85464_88084del (3599 bp) in II:6, and single exon 326, NM_001267550.2(*TTN*):c.80623_85481del (4859 bp) in III:5 (Figure 2). The breakpoint positions were visually inspected using the IGV and verified using Sanger sequencing. Moreover, the alignment of the BAM files revealed the overlap of 15 bp between the deletions (Figure S1). No other potential rare DNA variants contributing to the phenotypic manifestation of DCM have been found in CES.

The segregation analysis was impossible in deceased family members I:1 and II:3 due to the absence of DNA samples. However, the deceased individual II:3 was supposed to be an obligatory carrier of the longer deletion as a father of III:5. The oldest living sibling II:1 was tested with a negative result for both deletions using qPCR; moreover, his cardiac phenotype does not meet typical signs for DCM. Without signs of DCM, the siblings II:2 and II:4 tested negative for both deletions. Finally, the segregation analysis was conducted in three sisters III:8, III:9, and III:10, with a positive result in III:9, carrying the same deletion as her father II:5.

Discussion

Two novel, distinct, but overlapping, intragenic *TTN* gene (NM_001267550.2) deletions were identified as a cause of familial DCM with accompanying comorbidities leading to heart failure with reduced left ventricular ejection fraction. The *TTN* truncating variants (*TTN*tv) are common molecular genetic causes of DCM. They are predominantly located in the distal part encoding the sarcomeric A-band and in exons with enriched expression in cardiac muscles.^{5,11} The first identified *TTN*tv known to cause DCM was a 2-bp deletion in the largest exon 326, which was then recognized as the mutational hotspot located in the region encoding the A-band region.¹²

Large CNVs in the *TTN* gene, mostly represented by deletions affecting the gene regions important for cardiac isoforms, were proven to co-segregate with familial DCM.¹³ However, rare CNVs in the compound heterozygosity with single-nucleotide or insertion/deletion causative variants were also observed in those cases of recessive myopathies.^{14,15}

The clinical manifestation of a particular phenotype likely strongly depends on the affected gene region, moreover the in-frame and out-of-frame CNVs may have a different effect on the gene's function. The preserved reading frame may produce in-frame transcripts through exon skipping as demonstrated in individuals with dominant and recessive titinopathies.^{13,16} However, rare familial case of out-of-frame heterozygous deletion (16.430 kb) spanning part of A- and M-bands segregating with skeletal myopathy with facial weakness, gait disturbance and DCM was reported and documented possible unrecognized phenotypic outcomes in individuals with *TTN*tv.¹⁷

Both reported deletions affect exon 326, while the shorter one encompasses adjacent exons up to 330. With its length of 17,106 bp, exon 326 represents the largest exon of the *TTN* gene and was evaluated as the most common hotspot for deleterious protein-truncating variants (PTVs).¹¹ The localization and length of deletion do not seem to be prognostic factors of the disease onset, its course, and outcome in the reported family and elsewhere.¹⁸

The origin of both overlapping *TTN* deletions could not be evaluated; nevertheless, the sudden cardiac death in the male ancestor at the age of 65 (I:1) could implicate malignant arrhythmia associated with inherited cardiomyopathy. If the deceased individual I:1 was considered as an obligatory carrier of both *TTN*tv at least in his gonadal tissues, there must have been three types of sperm produced. However, the short overlap of deleted regions in the exon 326 suggests no complex *TTN* gene rearrangements.

The absence of cardiac phenotype in the female ancestor (I:2) does not imply its negative genotype since the incomplete penetrance for DCM due to *TTN*tv was repeatedly observed with sex- and age-related differences.^{19,20} The median age of disease onset is significantly lower in men than women. It is not uncommon to diagnose men under 30 years of age with DCM, while most females typically develop symptoms of DCM much later or remain asymptomatic for their life. A similar trend was observed for the cumulative risk of DCM, when men have almost three times higher risk in their 30s and two times higher risk in their 60s to manifest the clinical symptoms.

However, the most severe disease progression and manifestation, together with the earliest onset of DCM in the affected female III:5 in this family, deny these statements. While we cannot exclude the influence of other genetic and/or non-genetic factors as modifiers of disease onset and outcome, no other potential DNA variants responsible for the variability in the phenotypic manifestation and age-related disease onset in affected family members have been found in CES. Complementary transcriptome and epigenome analysis could elucidate the phenomena of the incomplete penetrance and variable expressivity of DCM in general; however, the cardiac muscle biopsies should be performed to obtain relevant outputs of those analyses.^{21,22}

Conclusion

Our family report on a unique familial segregation of two distinct overlapping *TTN*tv leading to DCM extends the broad spectrum of reported causative *TTN*tv. Moreover, it underlines the possibility of a heterogeneous molecular cause of DCM in one family and suggests the utility of NGS for segregation analysis in selected cases. Furthermore, our data demonstrate that individuals >60 years of age with DCM could have hereditary aetiology, and the family cascade screening and molecular genetic analysis are eligible for them.

Abbreviations

ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; CES, clinical exome sequencing; CNVs, copy-number variations; DCM, dilated cardiomyopathy; EF, ejection fraction; IGV, Integrative Genomics Viewer; NGS, next-generation sequencing; PTV, protein-truncating variants; qPCR, quantitative real-time PCR; SF, secondary findings; SNVs, single-nucleotide variants; *TTN*tv, *TTN* truncating variants.

Data Sharing Statement

The reported *TTN* gene truncating variants were submitted to the ClinVar database under the Variation IDs: 3358865 (<https://www.ncbi.nlm.nih.gov/clinvar/variation/3358865/>) and 3358866 (<https://www.ncbi.nlm.nih.gov/clinvar/variation/3358866/>). The data from clinical exome sequencing that support this study's findings are available from the corresponding author upon reasonable request. However, the data are not publicly available due to privacy or ethical restrictions.

The data from the segregation analyses by Sanger sequencing and real-time PCR that support this study's findings are available from the corresponding author upon reasonable request.

Consent for Publication and Ethics Approval

All procedures involving human participants were conducted per the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The genetic analyses were performed as part of a routine molecular diagnostics procedure at the Department of Biology and Medical Genetics, 2nd Faculty of Medicine, Charles University, and Motol University Hospital. The institutional informed consent was obtained after the primary genetic consultation and clinical genetics evaluation before the start of any genetic testing. The consent for publication was obtained from all living individuals who underwent genetic analyses.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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