

Titin-Truncating Variants as Genetic Determinants of Chemotherapy-Induced Cardiomyopathy: A Review

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Abstract

Current risk-prediction models for Cancer Therapy–Related Cardiovascular Toxicity (CTR-CVT) rely predominantly on demographic, diagnostic, and treatment variables, lacking genetic determinants of individual susceptibility. Recent evidence suggests cardiomyopathy-associated genetic variants, particularly Titin-truncating variants (TTNtv), may be significant in CTR-CVT development. This review examines the occurrence and impact of TTNtv in CTR-CVT patients. We conducted a PRISMA-guided review analyzing TTNtv in patients with chemotherapy exposure who developed cardiomyopathy. Literature searches were performed in PubMed and Scopus using keywords: “(cardiomyopathy OR heart failure) AND (chemotherapy OR cancer therapy) AND (Titin OR TTNtv).” Quality assessment employed the Newcastle-Ottawa Scale (NOS) for observational studies and the Joanna Briggs Institute (JBI) criteria for case reports. We included 2 case-control studies and 2 case reports. TTNtv prevalence was significantly higher in chemotherapy-induced cardiomyopathy than in controls: 7.5% versus 0.6–1.1% (multicenter cohort), and 6.5% versus 0% (single-center cohort). There are conflicting results regarding symptom severity and prognosis among those with and without TTNtv mutation. One multicenter case-control study with animal model validation demonstrated that chemotherapy is poorly tolerated in TTNtv carriers. Chemotherapy-to-symptom onset ranged from 0.4 to 9 years and primarily involved anthracyclines. Among truncating variations found in the included literature, localization in the A-band of the titin protein predominated. TTNtv represents a predominant genetic determinant in CTR-CVT susceptibility, although its association with severity and recovery outcomes remains inconsistent across studies. Genetic screening could identify high-risk cancer patients benefiting from personalized cardioprotective strategies and enable assessment of prophylactic interventions. Future investigations will determine if early genetic risk recognition optimizes cancer and cardiovascular treatments, potentially transforming precision cardio-oncology care. However, cost-benefit analysis, validation in diverse populations, and comparison with non-anthracycline CTR-CVT groups are needed.

Keywords: Titin-truncating variants, Chemotherapy-induced cardiomyopathy, Cardio-oncology, Genetic predisposition, Review

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Introduction

Risk prediction for Cancer Therapy–Related Cardiovascular Toxicity (CTR-CVT), previously described in the literature as chemotherapy-induced cardiomyopathy, is a cornerstone of modern cardio-oncology. Current approaches largely depend on demographic, diagnostic, and treatment-related factors such as age, baseline cardiac function, and cumulative drug exposure. While these models help identify patients at higher risk, they still fail to explain interindividual variation of cardiotoxicity despite receiving similar treatment. This variability suggests that genetic predisposition may play a role. Yet, despite rapid progress in cardiovascular genomics, genetic factors have not been incorporated into standard cardiotoxicity risk assessments. The European Society of Cardiology (ESC) working group has noted that Titin-truncating variants (TTNtv) confer additional anthracycline-related risk, establishing groundwork for improved risk stratification.¹ This gap underscores the urgent need for studies exploring the genetic determinants of CTR-CVT.

Recent research points to sarcomeric gene variants, especially TTNtv, as possible contributors to myocardial vulnerability under stress, including exposure to chemotherapy. Titin, the largest protein in the human body, is essential for maintaining sarcomere elasticity and structural stability. Variants that truncate the TTN protein lead to incomplete or dysfunctional sarcomeric components, weakening myocardial contractility. Truncating *TTN* variants, especially those located in the A-band, shape the genetic architecture of Dilated Cardiomyopathies (DCM) and are recognized as the most frequently encountered monogenic basis of DCM. It was identified in 15-25% of familial DCM and 10-18% of sporadic ones.² Studies in both pediatric and adult populations have shown that TTNtv carriers often present with more severe disease and poorer outcomes, including progressive heart failure and need for transplantation, even without a clear family history.³

These findings suggest that TTNtv may act as genetic sensitizers, lowering the threshold for cardiac injury when the heart is exposed to external stressors. Environmental and pharmacologic stressors, including anthracycline chemotherapy, alcohol exposure, and pregnancy, can unmask latent genetic vulnerability and precipitate overt cardiomyopathy through gene–environment interactions.^{2,4} Multi-omic analyses of chemotherapy-exposed tissues have revealed that *TTN* is among the genes most frequently mutated following treatment, highlighting a potential link between cytotoxic stress and genomic instability.⁵ Altogether, this evidence supports the concept that individuals with TTNtv may have reduced myocardial resilience to the oxidative and mechanical stress induced by chemotherapy.

Despite these observations, systematic evaluation of TTNtv in CTR-CVT remains limited. In addition, *TTN* was notably excluded from genetic risk prediction for anthracycline toxicity in pediatric cancer models, unlike other genes expressed in anthracycline cardiotoxicity or cellular adaptation biological pathways.⁶ This creates a critical equipoise that necessitates a review of *TTN*'s role, specifically TTNtv, in chemotherapy-induced cardiomyopathy or CTR-CVT to inform its integration into clinical risk stratification for a more personalized risk prediction in the field of cardio-oncology.

Methods

We conducted a PRISMA-guided review analyzing the prevalence of TTNtv among patients who developed chemotherapy-induced cardiomyopathy and evaluated its clinical implications. A comprehensive literature search was performed using PubMed and Scopus databases on May 19, 2025, restricted to articles published within the last five years.

Boolean operators were employed to formulate the search terms used in the database, as shown in Table 1 below. The search terms combined concepts of cardiac toxicity ((cardiomyopathy) OR (heart failure)), cancer treatment ((chemotherapy) OR (heart failure)), cancer treatment ((chemotherapy)

Table 1. Boolean strategy.

Database	Search Terms	Number of Hits
PubMed	((cardiomyopathy) OR (heart failure)) AND ((chemotherapy) OR (cancer therapy)) AND ((Titin) OR (TTNtv))	62
Scopus	Title, abstract, keywords : cardiomyopath* OR (heart AND failure) AND chemotherap* OR cancer AND titin OR ttn	31

OR (cancer therapy)), and genetic variants ((*Titin*) OR (*TTNtv*)) using database-specific syntax for PubMed and Scopus. The initial search yielded 93 records (PubMed: 62; Scopus: 31) with 13 duplicates removed. We included original articles reporting the presence of *TTNtv* and subsequent cardiomyopathy or heart failure following chemotherapy exposure, which included observational studies and case reports. Abstract-only articles and registry data were excluded from this review due to limited methodological detail and peer review. With these selection criteria, 2 observational studies and 2

case reports were included in the review. Quality assessment of included studies was performed using the Newcastle-Ottawa Scale (NOS) for observational studies and the Joanna Briggs Institute (JBI) for case reports. Article screening, selection, and assessment, as well as data extraction, were performed independently by two authors (A.N.L. and B.A.). Any disagreements were resolved through discussion, with input from a third author (G.G.S.).

In detail, the flowchart of study selection can be seen in Figure 1 below.

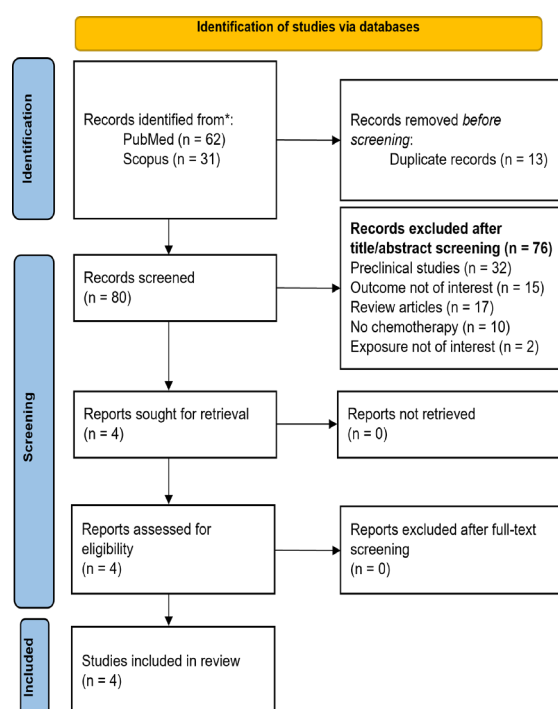


Figure 1. Study selection PRISMA flowchart.

Results

This systematic search yielded four studies processed for qualitative assessment, revealing high methodological rigor, with case-control studies scoring 7-8/9 on the Newcastle-Ottawa Scale and case reports meeting all applicable JBI criteria. The analysis included 259 patients and 2,655 controls from case-control studies, plus three patients from two case reports. Table 2 summarizes the detailed data extraction and key findings.

As the four included studies were published from 2017 to 2024, the terminology used to describe cancer therapy-related cardiovascular toxicity varies across them, reflecting evolving guideline standards during this period. Table 3 summarizes the terms used in each included study and their relationship to

the CTR-CVT framework adopted in this review per the 2022 ESC Cardio-Oncology Guidelines.⁴ Where study-specific terminology appears in subsequent sections, it is retained for source fidelity and clearly attributed to its respective study.

TTNtv Prevalence, Clinical Outcome, and Cardiac Condition on Case-Control Studies

TTNtv prevalence was significantly enriched in chemotherapy-induced cardiomyopathy cohorts compared to controls across both case-control studies. Garcia-Pavia et al. reported 7.5% *TTNtv* prevalence in Cancer Therapy-Related Cardiac Dysfunction (CTRCD) patients versus 0.6-1.1% in three control groups: unselected breast or lung cancer from The Cancer Genome Atlas (TCGA) participants (combined, $p=7.36 \times 10^{-8}$), healthy

Table 2. Data extraction and finding summary of literatures.

No	Author	Research Design and Setting	Samples	Chemotherapy	Genetic variant(s)	Outcome	Quality Appraisal Score	
							Newcastle Ottawa Score (NOS)	Joanna Briggs Institute (JBI)
1.	García-Pavia et al. (2019)	P Case-control study with animal model validation Setting: Multi-center (3 cohorts)	Cases (n=213) • Retrospective adults with diverse cancers (n=99) • Prospective adults with Breast Ca (n=73) • Prospective children with AML (n=41) Controls • The Cancer Genome Atlas / TCGA participants (n=2053) • Healthy volunteers (n=445) • Ancestry-matched reference population Characteristics: 90% received anthracyclines; adult CCM patients had CV risk factors ~ to US population	Primarily anthracyclines (90%), cumulative dosage recorded. Other cancer therapies	Rare protein-altering variants in cardiomyopathy genes via NGS (custom Agilent array) TTNtvs detected: c.101638G>T c.100731dupA c.95722+2delT c.91715dupA c.60512-2A>C c.85768C>T c.82734dupA c.78625G>T c.75179delA c.69715+6T>C c.66240delA c.63096delT c.49345+2T>C c.29042-2A>C c.13141G>T c.9693_9694delCT	Primary Findings CCM had more rare protein-altering variants than comparative cohorts (p≤1.98e-04) First chemo to CCM development: 0.4—9 years Predominance of TTNtvs: CCM cohort (7.5%) vs TCGA participants (1.1%; p=7.36e-08) vs. healthy volunteers (0.7%; p=3.42e-06) vs. reference population (0.6%; p=5.87e-14) Secondary Findings • CCM adults with TTNtvs experienced: ◦ More HF and AF (p=0.003) ◦ Impaired myocardial recovery (p=0.03) • Anthracycline-treated TTNtvs mice showed sustained contractile dysfunction (p=0.0004) compared to Wt ones All-variant prevalence in CTRCD 63.0% (29/46) vs DCM 73.9% (34/76) p=0.262; in (-) controls: 39.6% (47/111) p=0.018 Predominance of TTNtvs in CTRCD & DCM cohort: each 6.5% (all P/LP) CTRCD severity and recovery rate — no significant differences in variant-harboring individuals vs. non-variant harbouring individuals	8	N/A
2.	Boen et al. (2024)	Case-control study with retrospective design	Cases: Single-center cohort of CTRCD (cancer-therapy-related cardiac dysfunction) patients (n=46) Controls (n=157), including: • positive control matched cohort of patients with DCM (n=46) • negative control: patients without cardiac disease (n=111)	Doxorubicin (or equivalent) Dosage: Median 300 mg/m ² [IQR: 112.5-540.0]	Pathogenic (P)/Likely-Pathogenic (LP)/Variant of Unknown Significance (VUS) of known 59 cardiomyopathy genes Specific TTNtvs found: c.3867delT (p.Glu-1290Asnfs*107), c.6377G>A (p.Trp2126Ter), c.100342C>T (p.Arg33448*)		8	N/A

3.	Linschoten et al. (2017)	M	Case report	Two female patients with CCM (no control): P1: 43 years old, Ductal adenocarcinoma (cT4N1M0) of the right breast patient P2: 49 years old, Ductal adenocarcinoma (T2N1M0)	P1: (450 mg/m ²), Adriamycin (300 mg/m ²), Cyclophosphamide (3000 mg/m ²) P2: Adriamycin (240 mg/m ²), Cyclophosphamide (2400 mg/m ²), Paclitaxel (960 mg/m ²), Trastuzumab and adjuvant radiotherapy	Heterozygous truncating frameshift mutation in <i>TTN</i> (NM_133432.3), via NGS, to reveal 65 cardiomyopathy-associated genes: P1: c.27098del p.(Gly9033fs) – maternally inherited P2: c.56184_56185delinsT p.(Glu18728fs), family history (-)	Chemo-to-CCM onset (Time) : P1 : 5 months P2.: 7 months Cardiac and Follow-up outcome Echocardiography Parameters P1: LVEF 15%, borderline dilated LV of 56 mm, restrictive filling pattern (gr. III) P2: LVEF 20%, moderately dilated LV (59 mm) Follow-up Outcomes: P1: Required LVAD implantation; died from metastasis P2: Initial LVEF improvement to 41% (10 months), later deterioration (LVEF 7%), then partial recovery (LVEF 34%)	N/A	6 out of 8
4.	Yu-Wei Chang et al. (2022)	Chang	Case report	1 patient: Male (20) with acute myeloid leukemia	cytarabine (200 mg/m ² /day for 7 days) plus daunorubicin (45 mg/m ² /day for 3 days)	76 target genes in which 7 meaningful variants had been frequently detected in anthracycline-related cardiotoxicity	Severe congestive heart failure • Initial LVEF = 11% • Post-intensive care LVEF = 34% • 3 years post-treatment LVEF = 45%	N/A	6 out of 8

Table 3. Terminology used in this review and its relationship to the 2022 ESC Cardio-Oncology Guidelines Framework.

Term	Abbreviation	Definition as used in original source	Relationship to CTR-CVT	Used by
Cancer therapy-related cardiovascular toxicity	CTR-CVT	Encompasses the full spectrum of cardiovascular toxicity attributable to cancer therapy, including cardiac dysfunction, ICI (immune checkpoint inhibitors) myocarditis, cancer therapy-related vascular toxicity, cardiac arrhythmias, and arterial hypertension, as structured in Table S1 of the 2022 ESC Cardio-Oncology Guidelines supplementary data (Lyon et al., 2022)	-	ESC 2022 Guideline (Lyon et al., 2022); this review
Cancer therapy-related cardiac dysfunction	CTRCD	Decrease in LVEF to <50% with ≥10% reduction from baseline by echocardiography, per the 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity (Zamorano et al., 2016, as cited in Boen et al., 2024)	Equivalent to the cardiac dysfunction phenotype within the CTR-CVT spectrum; definition predates and differs from 2022 ESC criteria	Boen et al., 2024
Cancer therapy-induced cardiomyopathy	CCM	Diagnosed irrespective of symptoms, based on LVEF <50% (cohort B) or <53% (cohorts A and C)* with ≥10% reduction from baseline by echocardiography, or LVEF <50% with ≥10% reduction from baseline by radionuclide ventriculography, in the absence of established coronary artery disease, cardiomyopathy, primary valvular disease, or uncontrolled hypertension (Garcia-Pavia et al., 2019)	Equivalent to the cardiomyopathy phenotype within CTRCD/CTR-CVT; predates 2022 standardization	Garcia-Pavia et al., 2019
Chemotherapy-induced cardiomyopathy	CCMP	Cardiomyopathy occurring as a complication of anticancer treatment (used descriptively without formal diagnostic criteria in the source publication)	Equivalent to CCM; predates 2022 ESC standardization	Linschoten et al., 2017

*LVEF thresholds differ by cohort in Garcia-Pavia et al. (2019): <50% for prospectively enrolled adults (cohort B) and <53% for retrospectively recruited adults and children (cohorts A and C), reflecting different diagnostic protocols across study sites.

Note: Where study-specific terminology appears in this review, it reflects the original authors' nomenclature and is retained for source fidelity. Terminological variation across included studies reflects evolving guideline standards across the publication period 2017–2024. All terms are considered equivalent to or subsumed within the CTR-CVT framework as structured in the 2022 ESC Cardio-Oncology Guidelines (Lyon et al., 2022), Table S1. Sources: Lyon et al., 2022 ESC Cardio-Oncology Guidelines and supplementary data; Zamorano et al., 2016; Garcia-Pavia et al., 2019; Linschoten et al., 2017; Boen et al., 2024.

volunteers ($p=3.42 \times 10^{-8}$), and the reference population ($p=5.87 \times 10^{-14}$).⁷ Similarly, Boen et al. identified 6.5% TTNtv prevalence in CTRCD patients compared to 0% in controls, with all identified variants classified as pathogenic or likely pathogenic. TTN mutations represented the most prevalent genetic abnormality in the CTRCD cohort (43.0% of all variants detected).⁸

In terms of clinical and cardiac outcomes, Garcia Pavia et al. reported that TTNtv carriers had higher episodes of heart failure hospitalizations and atrial fibrillation ($p=0.003$ for each) as well as more

depressed final mean Left Ventricular Ejection Fraction (LVEF) recovery (39.6 ± 14.2 versus 48.9 ± 10.8 ; $p=0.03$)⁷ (Table 4).

Conversely, Boen et al. found no significant differences in CTRCD severity or recovery rates between variant-positive ($n=29$, 63.0%) and variant-negative patients. However, subgroup analysis specific to TTNtv carriers was not performed. Notably, the overall genetic variant burden in anthracycline-induced CTRCD patients was comparable to that observed in CM cohorts used as positive controls (0.0094 vs 0.0140; $p = 0.023$).⁸

Table 4. Specific Left Ventricular Ejection Fraction (LVEF) across case-control and case report cohorts.

Study	Population	LVEF at CTR-CVT or CCM Diagnosis (%)	Last/Follow-up LVEF (%)
Garcia Pavia et al.	TTNtv carriers (n=14 ⁰)	34.9 ± 7.4	39.6 ± 14.2*
	Non-TTNtv carriers (n=158)	36.8 ± 9.5	48.9±10.8*
Boen et al.	All CTRCD patients (with or without TTNtv, n=46)	30.1±11.0	46.6±10.0
Linschoten et al.	n=2 (P1 and P2)	P1 = 15%, P2 = 20%	P1 ⁰ , P2 = 34%
Chang et al.	n=1	11%	45%

*The last LVEF measured across TTNtv carriers and non-TTNtv carriers were statistically significant in the study (p=0.003).

⁰ = missing data from two patients noted in the publication of Garcia-Pavia, missing follow-up LVEF of P1 in the publication of Linschoten et al.

Preclinical Validation of the TTNtv and CTRCD

Garcia-Pavia et al. provided mechanistic validation through complementary preclinical models. Anthracycline-treated mice with knocked-in TTNtv demonstrated sustained contractile dysfunction compared to wild-type controls (p=0.00004). The results were replicated in stem-cell-derived cardiomyocytes harboring TTNtv, showing prolonged contractile impairment following anthracycline exposure (p<0.002), establishing biological plausibility for clinical observation.⁷

Individual Patient Trajectories in Case Report

The two case reports, each by Chang et al. and Linschoten et al., illustrated a heterogeneous clinical course of TTNtv. Linschoten et al. described two females diagnosed with ductal adenocarcinoma who both harbored heterozygous truncating frameshift mutations in *TTN*, with outcomes ranging from fatal progression to partial cardiac recovery.⁹ The first patient (P1), a 43-year-old with cT4N1M0 stage disease, presented with cardiac symptoms 5 months post-chemotherapy and showed severe cardiac dysfunction with baseline LVEF of 15%, borderline dilated left ventricle of 56 mm, and grade III diastolic dysfunction with restrictive filling pattern. Despite treatment, this patient still required Left Ventricular Assist Device (LVAD) implantation and ultimately died from metastasis. The second patient (P2), a 40-year-old with T2N1M0 stage disease, developed cardiac symptoms 7 months after chemotherapy initiation with a moderately dilated left ventricle (59 mm) and an LVEF of 20% at initial echocardiography. Her clinical course indicated dynamic LVEF changes: improving from 20% to 41% at 10 months, deteriorating to 7%, then partially recovering to 34%. In terms of variant inheritance, P1 carried a maternally inherited variant, while P2 had a variant with a family history of cardiomyopathy.⁹

Chang et al. reported a 20-year-old male with Acute Myeloid Leukemia (AML) who developed severe congestive heart failure following chemotherapy. Genetic analysis detected a *TTN* in-frame deletion variant (c.55637_55639delAAG). This patient presented with an initial LVEF of 11%, which improved to 34% post-intensive care, and subsequently recovered to 45% three years post-treatment.¹⁰

Temporal Symptoms Pattern and Treatment Characteristics

There was variability in symptom onset, although information is limited in all articles, with 0.4–9 years and 5 to 7 months post-initiation⁷ as documented by case reports.^{9–10} Anthracycline-based chemotherapy, with or without combinations, was the predominant regimen across all studies. Garcia-Pavia et al. reported 90% anthracycline exposure, while Boen et al. documented a median cumulative doxorubicin dose of 300 mg/m² (IQR/interquartile range 112.5–540.0).^{7–8} The treatment pattern differed in the Linschoten et al. study, with two patients receiving an anthracycline combination with a taxane and an alkylating agent as a TAC regimen (Taxotere, Adriamycin, and Cyclophosphamide), with P2 also receiving trastuzumab (anti-HER2 monoclonal antibody) and adjuvant radiotherapy. In an AML case, Chang et al. reported combination regimens of antimetabolite and anthracycline (daunorubicin).^{9–10}

Molecular Characteristics of Identified Variants

Analysis of 22 TTNtv mutations across all studies (Table 5) revealed distinct positional clustering within the Titin protein structure after adjustment with DNA transcripts. Fifteen mutations dominated the A-band (n=15), followed by the I-band (n=4), in proximity to the Z-disk region (n=2), and the M-band (n=1). This is further illustrated by Figure 2, which schematically represents *TTN* domain architecture and maps CTR-CVT-associated TTNtv across included studies.

Table 5. Summary of TTNtv identified from included literatures.

No	Variant	Impact	Titin Protein Band Localization
Garcia-Pavia et al. TTN Transcript: ENST00000589042			
1	chr2:179399704 c.101638G>T	Nonsense (p.Glu3880X)	M
2	chr2:179400742 c.100731dupA	Frameshift (p.Ser33578IlefsTer15)	A
3	chr2:179410112 c.95722+2delT	Splicing	A
4	chr2:179414849 c.91715dupA	Frameshift (p.Asn30572fs)	A
5	chr2:179422284 c.60512-2A>C	Splicing	A
6	chr2:179425091 c.66625T>A	Nonsense (p.Arg28590X)	A
7	chr2:179428124 c.82734dupA	Frameshift (p.Val27579SerfsTer15)	A
8	chr2:179432234 c.78625G>T	Nonsense (p.Glu26209X)	A
9	chr2:179435679 c.75179delG	Frameshift (p.Asn25060fs)	A
10	chr2:179441250 c.69715+6T>C	Splicing	A
11	chr2:179446855 c.66240delA	Frameshift (p.Asp22081MetfsTer31)	A
12	chr2:179453355 c.63096delT	Frameshift (p.His21032fs)	A
13	chr2:179478777 c.49345+2T>C	Splicing	A
14	chr2:179571683 c.29042-2A>C	Splicing	I
15	chr2:179604819 c.13141G>T	Nonsense (p.Glu4381X)	I
16	chr2:179631116 c.9693_9694delCT	Frameshift (p.Tyr3232CysfsTer5)	I
Boen et al. TTN Transcript : (ENST00000589042; ENST00000360870 exon 46)			
1	c.3867delT	p.Glu1290Asnfs*107	Near Z-disk ⁰
2	c.6377G>A	p.Trp2126Ter	Near Z-disk/I Band ⁰
3	c.100342C>T	p.Arg33448*	A-band ⁰
Linschoten et al. TTN Transcript: ENST00000359218			
P1	TTN (NM_133432.3): c.27098del (maternal inheritance)	p.(Gly9033fs)	I-band ⁰
P2	TTN (NM_133432.3): c.56184_56185delinsT	p.(Glu18728Aspfs*3)	A-band ⁰
Exon 155			
Yu-Wei Chang et al.*			
P1	c.55637_55639delAAG	p.E18546del	A-band ⁰

⁰: No information available from the author; mutation adjusted within transcripts and Titin band localization according to the CardioDB database. Source https://www.cardiodb.org/titin/titin_transcripts.php.

*No information on a specific TTN transcript in Yu-Wei Chang et al.

Discussion

This review revealed a consistent and substantial enrichment of TTNtv among chemotherapy-induced cardiomyopathy patients, with a prevalence of 6.5–7.5% compared to 0–1.1% in controls.⁷⁻⁸ This 6–10-fold enrichment, coupled with preclinical evidence from García-Pavia et al.,⁷ confirms TTNtv as a significant genetic predisposition to CTR-CVT.

While TTNtv clearly influences CTR-CVT risk, its clinical implications for individual patients remain complex. The two case-control cohorts in our review yielded conflicting results regarding TTNtv-positive patients. One cohort demonstrated increased heart failure hospitalizations and atrial fibrillation with impaired LVEF recovery among those with TTN truncating mutations compared to

those without, while the other found no significant differences in recovery rates or disease severity. The latter finding aligns with Herman et al., who observed comparable cardiac outcomes regardless of mutation status, though notably, male TTNtv carriers experienced earlier adverse events than their female counterparts ($p=4\times 10^{-5}$).¹¹ This sex-specific difference in prognostic timing warrants further investigation, as it cannot be explained solely by inheritance patterns given TTN's autosomal dominant inheritance.

Disease mechanism of TTNtv and TTNtv-associated CTRCD

Understanding the underlying disease mechanism of TTNtv becomes essential, notably given the preclinical stem-cell and murine model

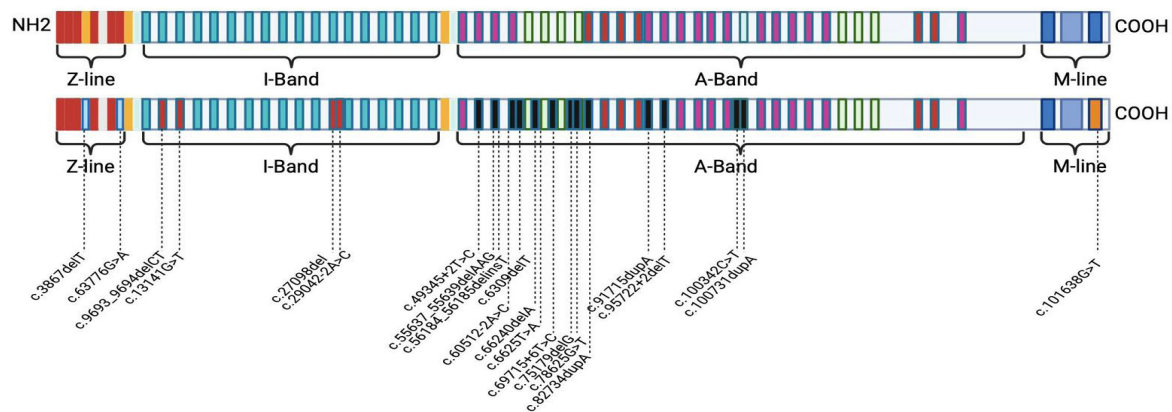


Figure 2. Schematic representation of TTN domain architecture and distribution of CTR-CVT-associated Titin Truncating Variants (TTNtv) identified across included studies.

The titin (TTN) protein is depicted linearly from its N-terminus (NH2) to C-terminus (COOH), spanning four functional domains: the Z-disk, I-band, A-band, and M-line. The upper schematic illustrates the canonical domain structure. The lower schematic maps all TTNtv identified in patients with cancer therapy-related cardiovascular toxicity (CTR-CVT) across the included studies ($n = 4$ studies; 22 unique variants), annotated by their Human Genome Variation Society (HGVS) nomenclature at the genomic DNA level. Variants are distributed across the Z-disk ($n = 2$), I-band ($n = 4$), A-band ($n = 15$), and M-line ($n = 1$), with a predominance observed in the A-band region. This A-band predominance is consistent with established pathogenicity in dilated cardiomyopathy, as discussed in the text. Figure created using BioRender.com.

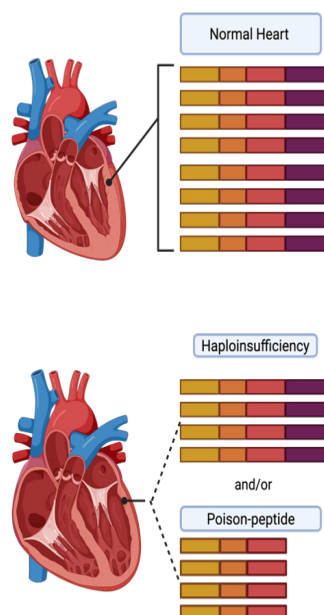


Figure 3. Two explanatory model on TTNtv disease mechanism.

In this picture, the normal heart has complete set of functional proteins, while haploinsufficiency results in reduced protein levels. 'Poison-peptide' mechanism produces truncated set of protein which may interacts with other normal protein in the sarcomere. The picture was a modified version from Ghahremani et al.¹² and created in Biorender.

data reported in this review. Research into TTNtv disease mechanism has centered on two explanatory models: haploinsufficiency and dominant-negative (poison-peptide) effects, as seen in Figure 3 below. The first mechanism posits that a single functional *TTN* allele produces insufficient normal titin protein. Meanwhile, the dominant-negative model suggests that truncated proteins either

form harmful aggregates or interfere with normal sarcomere assembly.¹² Current evidence, including experimental data, supports both mechanisms operating independently or in combination.¹²⁻¹³

Determining whether *TTN* mutations are pathogenic has evolved from positional effects in the protein to employing a more objective measure, the proportion spliced in (PSI) score. The

Table 6. Domain-based pathogenicity framework of TTN Truncating Variants (TTNtv) in Dilated Cardiomyopathy (DCM).

Domain	Category	Mechanism	Odds Ratio/OR ¹⁵	P-Value ¹⁵
Z-disk	Constitutive exon	Unclear ¹⁵	5.3 (2.3—11.9)	0.001
I-band	Proximal Constitutive	Haploinsufficiency ¹⁴	19.0 (10.9—33.0)	1.1 x 10 ⁻¹⁷
	Distal Post-Cronos Promoter		32.0 (11.9—85.9)	2.5 x 10 ⁻⁹
A-band	Constitutive	Haploinsufficiency and truncated peptide generation ¹⁴	49.8 (40.6—61.1)	2.4 x 10 ⁻²⁶⁰
M-band	Constitutive	Unclear ¹⁵	3.7 (1.6—8.8)	0.01

Table 6 above shows domain-based pathogenicity framework of TTNtv in constitutive exons throughout the gene within DCM architecture. Constitutive exons are defined as those spliced into titin isoforms with an efficiency of at least 90% in adult cardiac tissue (Proportion Spliced In, PSI ≥ 90%). Odds ratios reflect DCM association derived from a meta-analysis of 2,495 DCM cases and 61,834 population controls.¹⁵ As Schafer et al. demonstrated, TTNtv in constitutive exons are significantly associated with DCM across all sarcomere domains from the Z-disk to the M-band, although A-band and distal I-band variants carry the highest odds ratios; the reasons why Z-disk and M-band variants carry lower odds ratios remain unclear.¹⁵ The mechanistic basis for the A-band and I-band domain-specific gradient was subsequently clarified by Romano et al. (2022), as discussed in “Disease mechanism of TTNtv and TTNtv-associated CTRCD” in this manuscript’s Discussion. The proximal-distal subdivision of I-band variants reflects the position of an internal TTN promoter (Cronos) within the distal I-band.¹⁵

PSI quantifies each *TTN* exon, representing how frequently it is included across the range of TTN isoforms. The existence of TTNtv in highly used exons, defined as having PSI >0.9, warrants a more likely pathogenic mutation than those in low-scoring exons.¹³ While PSI information is not available in our included CTR-CVT cohorts, TTNtv localization data revealed predominance of A-band mutations relative to other domains (I-band, M-band, Z disk), which overlap myosin heavy chain-binding domains. This structural localization has been known to be associated with DCM-associated TTNtv.^{3,11,13–16} Disease modeling and functional assays have confirmed these position-dependent effects.

A-band TTNtv leads to both haploinsufficiency and dominant-negative effects through truncated peptide production, impairing myofibril formation and sarcomere function, whereas I-band TTNtv leads only to haploinsufficiency.¹⁴ It must be explicitly noted, however, that the pathogenic significance attributed to A-band predominance in this review is extrapolated from the established DCM literature, assuming TTNtv follows DCM genetic architecture (see Table 6). Direct PSI evidence from chemotherapy-exposed populations is not yet available, and this interpretation should therefore be regarded as hypothesis-generating pending future CTR-CVT-specific cohort studies.

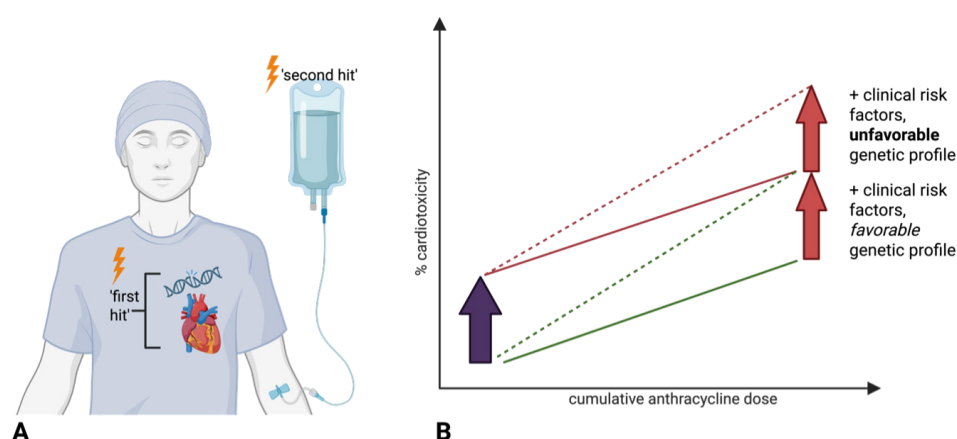


Figure 4. Illustration of ‘second hit’ model of TTNtv and interrelated determinants of CTR-CVT event.

Panel A illustrates the ‘second hit’ model, where the TTNtv acts as initial hit (genetic component) and chemotherapy as the ‘second hit’ (environmental component), altogether allow clinical manifestation of CTR-CVT. Panel B is a graph that illustrates Linschoten et al.’s model on interrelated determinants of CTR-CVT where patients carrying unfavorable genetic profiles and having clinical risk factors are at greater risk of having cardiotoxicity, despite receiving anthracycline dose. Graph on panel B is modified from Linschoten et al.’s original publication,¹⁷ both panels were created with Biorender.

Beyond structural considerations, *TTN*tv phenotypic variability is determined not only by variant characteristics, but also by gene-environment interactions.¹³ In this case, the *TTN*tv-associated CTR-CVT exemplifies a “second-hit” model, whereby *TTN*tv carriers possess genetic vulnerability (‘first-hit’) to heart failure that manifests clinically upon exposure to chemotherapy as an environmental stressor (‘second hit’),⁸ as illustrated in Figure 4. This concept is demonstrated in Garcia-Pavia’s pre-clinical model⁷ and Boen et al.’s cohort. In the cohort, the prevalence of *TTN*tv is enriched in CTR-CVT and genetic DCM groups compared to the negative control (healthy) group, supporting environment-dependent expression rather than environment-independent expression. The latter pattern was exhibited by *FLNC* gene mutations, one of the known high-risk DCM genes, which were found exclusively in the DCM cohort but not in CTR-CVT and healthy controls.⁸ Pregnancy and alcohol consumption represent other examples of secondary stressors for *TTN*tv patients, associated with peripartum and alcoholic cardiomyopathy phenotypes, respectively.¹

Finally, Linschoten et al. proposed three interrelated determinants of CTR-CVT development: genetic profile, treatment-related factors (especially cumulative anthracycline dose), and patient-related clinical risk factors. Their model suggested that patients with unfavorable genetic profiles exhibit increased reactive oxygen species, elevated topoisomerase-2 β expression, greater cardiotoxic anthracycline metabolite accumulation, and impaired sarcomere performance (Figure 4). These molecular alterations eventually render patients susceptible to CTR-CVT even at low anthracycline dose.¹⁷

Optimal Timing and Current Guidelines on Genetic Testing

The current ESC Cardio-oncology Guidelines recommend pre-treatment risk assessment using the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) system, which incorporates patient history, cardiovascular risk factors, and cardiac biomarkers.⁴ Yet, despite acknowledging genetic factors’ potential role in CTR-CVT susceptibility, these guidelines have not yet formally incorporated genetic testing, thus representing a significant gap in precision cardio-oncology care delivery.

The optimal timing for genetic risk evaluation occurs at cancer diagnosis, before initiating cardiotoxic chemotherapy.¹⁷ This pre-treatment

window enables personalized cancer care through comprehensive risk stratification. Genetic testing for CTR-CVT risk profiling is technically feasible at multiple levels: exome sequencing, whole-genome sequencing, and population stratification.¹⁸

Pre-treatment genetic risk screening offers multiple benefits. Patients with favorable genetic profiles, as described and illustrated before by Linschoten et al.¹⁷ (see Figure 4, Panel B), might safely receive higher cumulative doses to maximize desired anti-neoplastic effects. Meanwhile, those harboring high-risk variants could benefit from modified regimens or alternative agents. This approach also provides opportunities to identify patients who would benefit from intensive cardiac surveillance for early detection of subclinical dysfunction.¹⁷ In addition, Garcia Pavia et al. argued that genetic testing opens new avenues to assess the efficacy of prophylactic cardioprotective interventions among high-risk CTR-CVT patients.⁷ Bespoke strategies for managing CTR-CVT high-risk patients are now feasible through multiple options. These range from cardiac-sparing chemotherapy regimens, anthracycline alternative analogs (e.g, liposomal doxorubicin), cardioprotective medications (e.g, carvedilol and dexrazoxane), even minimized cardiac radiation exposure techniques.¹⁸⁻¹⁹

Expanding Beyond *TTN*tv: Future Directions in Genomic Risk Assessment

Available genetic association studies, including recent cohort analyses of *TTN* and *BAG3* variants, are largely derived from populations exposed to anthracyclines and/or chest-directed radiation, with limited representation of non-anthracycline therapies. Consequently, data evaluating *TTN*tv in the context of immune checkpoint inhibitors or targeted therapies remain scarce.²⁰ Evidence from non-anthracycline settings is indirect. In a clinical trial of HER2-positive breast cancer, variants in cardiomyopathy-associated genes, including *TTN*, were associated with treatment-related decline in LVEF in patients receiving trastuzumab-based therapy; nevertheless, concomitant anthracycline exposure in this cohort limits attribution of these findings to non-anthracycline agents alone.²¹ These findings suggest that *TTN*-related genetic susceptibility may act as a modifier of cardiotoxic risk across different therapeutic contexts. Still, current evidence does not allow definitive conclusions outside anthracycline-associated cardiomyopathy. Clarifying the role of *TTN*tv across contemporary cancer therapies, including immune checkpoint inhibitors and targeted agents, therefore represents a priority for future investigation.

While *TTN*tv demonstrates strong CTR-CVT associations, improving predictive accuracy requires consideration of multiple genetic variants. The *TTN* gene itself presents unique analytical challenges due to its immense size and complexity. It consists of 363 coding exons producing multiple isoforms owing to variable splicing. These encode over 100 kilobases of transcripts, ultimately producing a 4,200 kDa protein.^{12,22-23} On top of that, sequencing and localizing variants in the I-band domain is challenging, especially when processed by short-read sequencing technology, as this domain is subject to repetitive sequences with 99% homology.²⁴

The 2022 ESC Guidelines on Cardio-Oncology further identified several Single Nucleotide Polymorphisms (SNPs) associated with CTRCD in Supplementary Table S9, including *CELF4* rs1786814 (sarcomere function), *RARG* rs2229774 (topoisomerase-2 β expression), *SLC28A3* rs7853758 (anthracycline drug transport; protective variant), *UGT1A6* rs17863783 (drug metabolism), and the intergenic variant rs28714259.⁴ However, the strength of evidence underlying these associations varies considerably. rs2229774 in *RARG* represents the most robustly validated non-*TTN* variant, having achieved conventional genome-wide significance ($p = 5.9 \times 10^{-8}$, OR 4.7) in a Genome-Wide Association Study (GWAS) of 280 European patients with independent replication in European and non-European populations.²⁵ rs7853758 in *SLC28A3* was found at $p = 1.8 \times 10^{-5}$ across 440 patients in three international cohorts using a targeted pharmacogenomic approach, below the conventional GWAS threshold.²⁶ A subsequent GWAS meta-analysis of 852 oncology patients confirmed a suggestive novel intergenic locus near *TP63*, rs7652759 ($p = 5.64 \times 10^{-6}$), validated in an independent cohort of 1,191 patients,²⁷ though conventional genome-wide significance was not reached. In this cohort, another SNP, rs28714259, showed only nominal association ($p = 1 \times 10^{-3}$). Overall, GWAS-level evidence for non-*TTN* CTRCD markers remains limited. These markers should therefore be interpreted as additive contributors to risk stratification when combined with *TTN*tv status within a multimodal genomic risk framework. In resource-limited settings where *TTN* sequencing is not yet feasible, non-*TTN* markers, especially with strong and replicated evidence, may serve as a complementary first-line screening approach, but should not be considered a substitute for *TTN*tv evaluation where sequencing capacity exists.

Complementing genomic markers, an RNA-based approach may offer additional predictive value through dynamic gene expression profiling. This was revealed in an oncology study where mRNA-based models outperformed DNA-only approaches.²⁸ Micro-RNA (miRNA), a form of non-coding RNA in the body, has been shown to be a promising biomarker for detecting subclinical cardiotoxicity, as chemotherapy alters miRNA expression patterns that influence cardiotoxicity pathways.¹⁸ In pediatric cancer populations, Leger et al. found dose-dependent elevations of cardiac-related plasma miRNAs (miR-29b and miR-499) following anthracycline therapy, which correlated with elevated high-sensitivity cardiac troponin T levels. Similarly, Oatmen et al. found three miRNAs associated with LVEF reduction in their case-control study.²⁹⁻³⁰ However, it should be noted that the requirement for myocardial tissue to achieve optimal *TTN* RNA expression likely limits clinical feasibility.³¹

Clinical Implementation Strategy

Effective implementation requires integrating cardiac genetic profiling with existing oncology workflows. The ideal approach combines tumor and cardiac genetic assessment at diagnosis, enabling an opportunity window for integrated comprehensive risk-benefit analysis³² when both tumor responsiveness and cardiac vulnerability can be evaluated simultaneously. In fact, the growing field of cardio-oncology already benefits from advances in intraoperative sequencing with rapid turnaround times.³³⁻³⁴

Recent evidence supports dual-sample profiling approaches. Iams et al. showed that concurrent blood and tissue profiling in 3,209 patients identified significantly more actionable variants than tissue sampling alone.³⁵ Extending this, Gimeno-Valiente et al. emphasized that germline analysis from blood prevents missing hereditary syndromes that tumor sample-only approaches overlook.³⁶ This germline component, already necessary for somatic variant calling, presents an opportunity for simultaneous *TTN*tv screening without additional sampling burden.

Long-read sequencing technologies, in particular nanopore platforms, address *TTN*'s technical challenges by accurately sequencing repetitive regions and generating reads capable of spanning complete *TTN* transcripts.^{24,37} These platforms enable targeted enrichment of cardiac risk genes while processing both tissue and blood samples simultaneously, potentially incorporating both

DNA and RNA analysis for comprehensive risk assessment.

A key limitation of this review is the small number of eligible studies, which may reduce the robustness of evidence and limit the generalizability of the findings. This likely reflects the emerging nature of research on *TTN*tv and related sarcomere variants in CTR-CVT. This highlights the need for further investigations, particularly large-scale and well-characterized studies, to better define the role of these genetic variants in CTR-CVT, which can direct future clinical pathways and treatment strategies.

Future Directions

Advancing genetically informed risk stratification for cancer therapy-related cardiovascular toxicity requires coordinated efforts across multiple domains. First, it is essential to expand the evidence base through research, including larger, ethnically diverse cohorts and a broader range of chemotherapy regimens beyond anthracyclines. Genetic panels should also incorporate variants across complementary sarcomeric genes and drug metabolism pathways to capture the full spectrum of pharmacogenomic risk factors.

Second, clinical translation demands rigorous validation frameworks. Decision support tools that integrate *TTN* truncating variant status with established clinical risk factors must be validated across diverse populations to ensure general applicability. Standardization of *TTN* truncating variant pathogenicity assessment, such as through incorporation of proportion spliced in scores and positional effects, will be essential to ensure consistent interpretation across institutions and enable reliable risk stratification.

Third, implementation science research is crucial for clinical adoption. Cost-effectiveness analyses comparing genetic screening strategies with current standard care, alongside real-world impact assessments of genetically guided cardioprotective interventions, will provide the economic and clinical evidence necessary for healthcare system integration. Despite these ongoing efforts, *TTN* truncating variant screening remains associated with important practical limitations, including cost, infrastructure requirements, and turnaround time, as well as disparities in access to genomic testing, specifically in low- and middle-income settings.³⁸

From a clinical perspective, *TTN* truncating variant screening is unlikely to become a universal upfront test in all cancer patients soon. A more pragmatic approach may involve targeted genetic

testing in high-risk populations, such as those with a family history of cardiomyopathy or those planned for high-dose cardiotoxic therapy. As sequencing costs decrease and turnaround times improve, *TTN* truncating variant screening may gradually evolve into a clinically actionable tool within precision cardio-oncology.

These translational efforts will be instrumental in embedding genetic risk assessment into routine cardio-oncology practice, delivering the tailored cardioprotective strategies that precision medicine promises.

Conclusion

This review addresses the critical equipoise regarding *TTN*tv's role in CTR-CVT predisposition, providing evidence to support its integration into genetic risk assessment, a future potential suggested by the ESC. Our findings establish *TTN*tv as a significant genetic determinant; however, prognostic implications (symptom severity/recovery) need further clarification. Pre-treatment genetic screening for *TTN*tv offers the potential to identify patients with reduced myocardial resilience who would benefit from personalized cardioprotective strategies, including prophylactic medications and modified treatment regimens.

Combining *TTN*tv status with emerging biomarkers, including relevant and validated SNPs as well as circulating miRNAs, could transform risk prediction in cardio-oncology from a primarily clinical model to a comprehensive precision medicine approach. That said, this potential should be complemented with continued investment in translational research to bridge the gap between genomic discovery and clinical implementation. Such efforts will translate the potential of genomic-guided medicine into tangible benefit, especially for cancer patients at risk of CTR-CVT.

List of Abbreviations

CTR-CVT	Cancer Therapy–Related Cardiovascular Toxicity
CTRCD	Cancer Therapy-Related Cardiac Dysfunction
DCM	Dilated Cardiomyopathies
ESC	European Society of Cardiology
GWAS	Genome-Wide Association Study
IQR	Interquartile Range
JBI	Joanna Briggs Institute
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction

NOS	Newcastle-Ottawa Score
P1	First patient
P2	Second patient
SNPs	Single Nucleotide Polymorphisms
T*TNtv	Titin-truncating variants

Ethical Clearance

Not applicable.

Publication Approval

All authors consent to the publication of this manuscript.

Authors' Contributions

The authors confirm their contributions to the paper as follows: Study concept and methodology: ANL and BA; Literature search, study selection, data collection, and bias risk assessment were performed independently by ANL and BA, with disagreements resolved through discussion and input from GGS; Manuscript preparation (including interpretation and analysis of results), review, and finalization: ANL, BA, GGS, and MAPS; Figure creation: ANL and GGS; Project supervision: ANL. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of Interest

None.

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References

1. Magavern EF, Kaski JC, Turner RM, et al. The role of pharmacogenomics in contemporary cardiovascular therapy: A position statement from the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. *Eur Heart J Cardiovasc Pharmacother*. Oxford University Press. 2022;8(1):85-99. doi:10.1093/ehjcvp/pvab018
2. Hershberger RE, Cowan J, Jordan E, Kinnammon DD. The Complex and Diverse Genetic Architecture of Dilated Cardiomyopathy. *Circ Res*. 2021;128(10):1514-1532. doi:10.1161/CIRCRESAHA.121.318157
3. Khan RS, Pahl E, Dellefave-Castillo L, et al. Genotype and Cardiac Outcomes in Pediatric Dilated Cardiomyopathy. *J Am Heart Assoc*. 2022;11(1). doi:10.1161/JAHA.121.022854
4. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229-361. doi:10.1093/eurheartj/ehac244
5. Yin G, Liu L, Yu T, et al. Genomic and transcriptomic analysis of breast cancer identifies novel signatures associated with response to neoadjuvant chemotherapy. *Genome Med*. 2024;16(1). doi:10.1186/s13073-024-01286-8
6. Chaix MA, Parmar N, Kinnear C, et al. Machine Learning Identifies Clinical and Genetic Factors Associated With Anthracycline Cardiotoxicity in Pediatric Cancer Survivors. *JACC CardioOncol*. 2020;2(5):690-706. doi:10.1016/j.jacc.2020.11.004
7. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, et al. Genetic Variants Associated With Cancer Therapy-Induced Cardiomyopathy. *Circulation*. 2019;140(1):31-41. doi:10.1161/CIRCULA-

- TIONAHA.118.037934
8. Boen HM, Alaerts M, Goovaerts I, et al. Variants in structural cardiac genes in patients with cancer therapy-related cardiac dysfunction after anthracycline chemotherapy: a case control study. *Cardio-Oncology*. 2024;10(1). doi:10.1186/s40959-024-00231-3
 9. Linschoten M, Teske AJ, Baas AF, et al. Truncating Titin (TTN) Variants in Chemotherapy-Induced Cardiomyopathy. *J Card Fail*. 2017;23(6):476-479. doi:10.1016/j.cardfail.2017.03.003
 10. Chang YW, Weng HY, Tsai SF, Fan FS. Disclosing an In-Frame Deletion of the Titin Gene as the Possible Predisposing Factor of Anthracycline-Induced Cardiomyopathy: A Case Report. *Int J Mol Sci*. 2022;23(16). doi:10.3390/ijms23169261
 11. Herman DS, Lam L, Taylor MRG, et al. Truncations of Titin Causing Dilated Cardiomyopathy. Vol 366. 2012. www.uniprot.org
 12. Ghahremani S, Kanwal A, Pettinato A, et al. CRISPR Activation Reverses Haploinsufficiency and Functional Deficits Caused by TTN Truncation Variants. *Circulation*. 2024;149(16):1285-1297. doi:10.1161/CIRCULATIONAHA.123.063972
 13. Santiago CF, Huttner IG, Fatkin D. Titin-related Cardiomyopathy: Is it a Distinct Disease? *Curr Cardiol Rep*. Springer. 2022;24(9):1069-1075. doi:10.1007/s11886-022-01726-0
 14. Romano R, Ghahremani S, Zimmerman T, et al. Reading Frame Repair of TTN Truncation Variants Restores Titin Quantity and Functions. *Circulation*. 2022;145(3):194-205. doi:10.1161/CIRCULATIONAHA.120.049997
 15. Schafer S, De Marvao A, Adami E, et al. Titin-truncating variants affect heart function in disease cohorts and the general population. *Nat Genet*. 2017;49(1):46-53.
 16. Kim Y gon, Ha C, Shin S, Park J ho, Jang JH, Kim JW. Enrichment of titin-truncating variants in exon 327 in dilated cardiomyopathy and its relevance to reduced nonsense-mediated mRNA decay efficiency. *Front Genet*. 2023;13:1087359.
 17. Linschoten M, Teske AJ, Cramer MJ, Van Der Wall E, Asselbergs FW. Chemotherapy-Related Cardiac Dysfunction: A Systematic Review of Genetic Variants Modulating Individual Risk. *Circ Genom Precis Med*. Lippincott Williams and Wilkins. 2018;11(1):E001753. doi:10.1161/CIRCGEN.117.001753
 18. Chong JH, Chuah CTH, Lee CG. Revolutionising Cardio-Oncology Care with Precision Genomics. *Int J Mol Sci. Multidisciplinary Digital Publishing Institute (MDPI)*. 2025;26(5). doi:10.3390/ijms26052052
 19. Leong DP, Waliany S, Abdel-Qadir H, et al. Cardiovascular Considerations During Cancer Therapy: Gaps in Evidence and JACC: CardioOncology Expert Panel Recommendations. *JACC CardioOncol*. Elsevier Inc. 2024;6(6):815-834. doi:10.1016/j.jacc.2024.06.005
 20. Neupane A, Petrykey K, Li K, et al. TTN and BAG3 in Cancer Therapy-Related Cardiomyopathy Among Long-Term Survivors of Childhood Cancer. *JAMA Netw Open*. 2025;8(6):e2515793.
 21. Serie DJ, Crook JE, Necela BM, et al. Breast cancer clinical trial of chemotherapy and trastuzumab: Potential tool to identify cardiac modifying variants of dilated cardiomyopathy. *J Cardiovasc Dev Dis*. 2017;4(2):6.
 22. Bang ML, Centner T, Fornoff F, et al. The complete gene sequence of titin, expression of an unusual ≈ 700 -kDa titin isoform, and its interaction with obscurin identify a novel Z-line to I-band linking system. *Circ Res*. Lippincott Williams and Wilkins. 2001;89(11):1065-1072. doi:10.1161/hh2301.100981
 23. Chauveau C, Rowell J, Ferreira A. A rising titan: TTN review and mutation update. *Hum Mutat*. 2014;35(9):1046-1059. doi:10.1002/humu.22611
 24. Perrin A, Van Goethem C, Thèze C, et al. Long-Reads Sequencing Strategy to Localize Variants in TTN Repeated Domains. *Journal of Molecular Diagnostics*. 2022;24(7):719-726. doi:10.1016/j.jmoldx.2022.04.006
 25. Aminkeng F, Bhavsar AP, Visscher H, et al. A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. *Nat Genet*. 2015;47(9):1079-1084.
 26. Visscher H, Ross CJD, Rassekh SR, et al. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *Journal of clinical oncology*. 2012;30(13):1422-1428.
 27. Martínez-Campelo L, Blanco-Verea A, López-Fernández T, et al. Meta-analysis of genome-wide association studies for cancer therapy-related cardiovascular dysfunction and functional mapping highlight an intergenic region close to TP63. *Sci Rep*. 2024;14(1). doi:10.1038/s41598-024-69064-5
 28. Ravkin HD, Givton O, Geffen DB, Rubin E.

- Direct comparison shows that mRNA-based diagnostics incorporate information which cannot be learned directly from genomic mutations. *BMC Bioinformatics*. 2020;21(1). doi:10.1186/s12859-020-3512-z
29. Leger KJ, Leonard D, Nielson D, de Lemos JA, Mammen PPA, Winick NJ. Circulating microRNAs: Potential Markers of Cardiotoxicity in Children and Young Adults Treated With Anthracycline Chemotherapy. *J Am Heart Assoc*. 2017;6(4). doi:10.1161/JAHA.116.004653
 30. Oatmen KE, Toro-Salazar OH, Hauser K, et al. Identification of a novel microRNA profile in pediatric patients with cancer treated with anthracycline chemotherapy. *Am J Physiol Heart Circ Physiol*. 2018;315:1443-1452. doi:10.1152/ajpheart.00252.2018.-Anthracycline
 31. 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):270ra6-270ra6. doi:10.1126/scitranslmed.3010134
 32. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: The need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst*. 2010;102(1):14-25. doi:10.1093/jnci/djp440
 33. Emiliani FE, Ismail AAO, Hughes EG, Tsongalis GJ, Zanazzi GJ, Lin CC. Nanopore-based random genomic sampling for intraoperative molecular diagnosis. *Genome Med*. 2025;17(1). doi:10.1186/s13073-025-01427-7
 34. Deacon S, Cahyani I, Holmes N, et al. ROBIN: A unified nanopore-based assay integrating intraoperative methylome classification and next-day comprehensive profiling for ultra-rapid tumor diagnosis. *Neuro Oncol*. 2025;27(8):2035-2046. doi:10.1093/neuonc/noaf103
 35. Iams WT, Mackay M, Ben-Shachar R, et al. Concurrent Tissue and Circulating Tumor DNA Molecular Profiling to Detect Guideline-Based Targeted Mutations in a Multicancer Cohort. *JAMA Netw Open*. 2024;7(1). doi:10.1001/jamanetworkopen.2023.51700
 36. Gimeno-Valiente F, Martín-Arana J, Tébar-Martínez R, et al. Sequencing paired tumor DNA and white blood cells improves circulating tumor DNA tracking and detects pathogenic germline variants in localized colon cancer. *ESMO Open*. 2023;8(6). doi:10.1016/j.esmoop.2023.102051
 37. Uapinyoying P, Goecks J, Knoblaich SM, et al. A long-read RNA-seq approach to identify novel transcripts of very large genes. *Genome Res*. 2020;30(6):885-897. doi:10.1101/gr.259903.119
 38. Tekola-Ayele F, Rotimi CN. Translational genomics in low-and middle-income countries: opportunities and challenges. *Public Health Genomics*. 2015;18(4):242-247.