Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

JACC Clin Electrophysiol. Author manuscript; available in PMC 2025 May 14.

Published in final edited form as:

JACC Clin Electrophysiol. 2025 January ; 11(1): 213–216. doi:10.1016/j.jacep.2024.09.040.

TTN Variants, Dilated Cardiomyopathy, and Arrhythmic Causes by Autopsy Among Countywide Sudden Deaths

Matthew Yee, BA[a], **James W. Salazar, MD, MAS**[b], **Julianne Wojciak, MS**[c,d], **W. Patrick Devine, MD, PhD**[e], **Ellen Moffatt, MD**[e,f], **Zian H. Tseng, MD, MAS**[b]

[a]School of Medicine, University of California-San Francisco, San Francisco, California, USA

[b]Section of Cardiac Electrophysiology, Division of Cardiology, Department of Medicine, University of California-San Francisco, San Francisco, California, USA

[c]Department of Medicine, University of California-San Francisco, San Francisco, California, USA

[d]Cardiovascular Genetics Program, University of California-San Francisco, San Francisco, California, USA

[e]Department of Anatomic Pathology, University of California-San Francisco, San Francisco, California, USA

[f]Office of the Chief Medical Examiner, City and County of San Francisco, San Francisco, California, USA

Keywords

arrhythmic death; autopsy; dilated cardiomyopathy; genetics; sudden cardiac death; TTN

Truncating variants in *TTN* (TTNtvs), particularly in the A-band, are an established cause of idiopathic dilated cardiomyopathy (DCM) and have been reported in 25% of familial cases.[1] TTNtv DCM carriers have higher risk of appropriate implantable cardioverter-defibrillator therapies,[2] but these studies are limited to patients living with clinically recognized DCM and use surrogate outcomes (ie, implantable cardioverter-defibrillator therapies) rather than true out-of-hospital sudden cardiac death (SCD). Thus, we evaluated whether *TTN* variants were associated with autopsy-defined DCM and autopsy-defined arrhythmic death, leveraging the POST SCD (Postmortem Systematic Investigation of SCD) study in San Francisco County.

The POST SCD study is a prospective countywide postmortem study of out-of-hospital cardiac arrest deaths meeting World Health Organization criteria for presumed SCD in patients aged 18-90 years. Detailed methods have been previously described.[3]

THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY-NC-ND LICENSE (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ADDRESS FOR CORRESPONDENCE: Dr Zian H. Tseng, Cardiac Electrophysiology Section, University of California-San Francisco, 500 Parnassus Avenue, Box 1354, San Francisco, California 94143-1354, USA. zhtseng@medicine.ucsf.edu.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Briefly, cases underwent autopsy, histology, toxicology, and medical record review. A multidisciplinary panel of a forensic pathologist, cardiologists/cardiac electrophysiologists, cardiac pathologist, neurologist, molecular genetic pathologist, and genetic counselor adjudicated underlying arrhythmic (potentially rescuable with implantable cardioverter-defibrillator) or nonarrhythmic (tamponade, lethal toxicology/ overdose, stroke) cause of presumed SCD.[3] Heart weights were standardized with *z*-scores representing standard deviations from expected based on sex, age, body weight, and height.[4] Autopsy evidence of DCM was defined by cardiomegaly (*z*-score ≥1) and left ventricular short-axis internal diameter ≥3.5 cm, per standard pathology criteria.[4] To assess myocardial fibrosis, we performed Masson trichrome staining and quantitative Aperio ImageScope histological analysis. Burden of fibrosis (interstitial, perivascular, replacement) was calculated as a percentage of total slide area of standardized sections from the anterior, lateral, posterior, and septal left ventricle. The study was approved by the University of California-San Francisco Institutional Review Board.

Between February 1, 2011, and January 1, 2018, 856 presumed SCDs underwent autopsy. Exome sequencing was performed on cases with next-of-kin consent and interpreted using American College of Medical Genetics criteria to classify variants as pathogenic (P), likely pathogenic (LP), or variant of uncertain significance (VUS). Cases with P/LP or VUS were defined as *TTN* variant carriers. Statistical analysis was performed using chi-square and Fisher exact tests as appropriate, with a 2-tailed $P < 0.05$ considered statistically significant.

Next-of-kin of 306 cases (mean 62 years, 74% male, 17% Asian, 12% Black, 5% Hispanic/Latino) consented to genetic testing, reflecting San Francisco County's diverse population (Table 1). The most common comorbidities included hypertension (50%), tobacco use (41%), dyslipidemia (31%), diabetes mellitus (20%), coronary artery disease (19%), and heart failure (12%). Arrhythmic cause was adjudicated in 190 presumed SCDs (62%). Underlying etiologies of sudden death (Table 1) included chronic coronary artery disease (CAD; 25%), cardiomyopathy (13%), occult overdose (11%), acute CAD (11%), and hypertrophy (10%). Forty-seven presumed SCDs (15.4%) met DCM autopsy criteria, 13 (28%) with premortem heart failure diagnosis.

We detected 1 *TTN* P/LP variant and 102 VUSs in 83 presumed SCDs (27.1% *TTN* variant carrier rate). These included 8 (7.8%) located in the Z-disk, 36 (35.0%) in the I-band, 49 (47.6%) in the A-band, and 10 (9.7%) in the M-band. We found 5 TTNtvs, 1 the aforementioned P/LP, in 4 cases, none meeting autopsy DCM criteria and all due to arrhythmic cause: 3 due to acute CAD and 1 due to cardiomyopathy (Table 2, Figure 1). All TTNtvs were found in non–A-band regions ($P = 0.03$ via binomial test for likelihood of finding 0 A-band TTNtvs): 1 located in the Z-disk, 3 in the I-band, and 1 in the M-band (Table 2, Figure 1). None of the 47 cases meeting autopsy DCM criteria had TTNtvs.

TTN variant carriers had similar mean age and premortem comorbidities but were more likely to be Asian than noncarriers were ($P ¼ 0.001$) (Table 1). After observing a paucity of P/LP variants, we sought to explore the association of *TTN* variants in arrhythmic vs nonarrhythmic presumed SCDs. Arrhythmic cause of sudden death was associated with variant carrier status (31.1% [59 of 190] vs 20.7% [24 of 116] carrier rate for non-

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

arrhythmic cases; $P = 0.048$). Arrhythmic variant carriers had similar short axis (mean 2.9 cm vs 2.8 cm; $P = 0.75$) and heart weight (mean z-score 1.02 vs 1.18; $P = 0.47$) compared to arrhythmic noncarriers. Among arrhythmic cases with tissue available for analysis (n = 123), total myocardial fibrosis burden was similar in variant carriers (n = 36, mean 9.8%), including 3 TTNtv cases (mean 8.5%, range 1.5%-15.3%), and noncarriers (n = 87, mean 10.0%; P ¼ 0.91).

A few limitations are notable. POST SCD is derived from an entire diverse community, thus results may not be fully generalizable to other populations. Of the 4 arrhythmic TTNtv carriers, 1 had a splice variant in a lowly-expressed exon, thus only a small proportion of resulting transcripts were truncated. However, recent work suggests TTNtv messenger RNA is not subject to nonsense-mediated decay and may act via a dominant-negative mechanism, whereby even small amounts of truncated protein may exert phenotype,[5] such as potentially modifying risk of lethal arrhythmia in the setting of acute CAD, as in this case. Although none of the TTNtv carriers, including the P/LP case, met autopsy criteria for DCM, decedents may have developed DCM over time had they not suffered arrhythmic death. Lastly, we could not demonstrate a causative role for lethal arrhythmia with *TTN* variants in our study. However, the significantly higher carrier rate in precisely determined arrhythmic cases among countywide sudden deaths suggests non–A-band TTNtvs and VUSs may contribute to arrhythmic risk that may be independent of or before manifestation of DCM phenotype and myocardial fibrosis, in conjunction with other genetic and nongenetic factors. Additional studies with robust polygenic risk scores and nongenetic arrhythmic contributors could help elucidate a potential role for *TTN* variants in SCD.

In conclusion, in this 7-year genetic study of 306 community sudden deaths using autopsy to adjudicate arrhythmic from nonarrhythmic causes, we found arrhythmic deaths had a 1.5-fold higher *TTN* variant carrier rate than nonarrhythmic deaths and 5 TTNtvs, all non–A-band, exclusively in arrhythmic deaths. *TTN* variant carriers, including TTNtvs, had a similar burden of myocardial fibrosis than noncarriers. Whereas 15% of all sudden deaths met autopsy criteria for DCM, none harbored a TTNtv, contrary to the 18%-25% yield in cohorts living with diagnosed DCM,[1] which suggests a limited contribution of TTNtvs for DCM cases identified postmortem. These findings in a large cohort of SCDs (ie, cardiac arrest nonsurvivors), systematically under-represented in existing DCM cohorts, may extend the spectrum of phenotypes potentially associated with *TTN* variants.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was funded by NIH R01 HL102090 and NIH R01 HL147035 (National Heart, Lung, and Blood Institute to Dr Tseng). Dr Salazar has received grants (Award No. R38HL13581) from the National Heart, Lung, and Blood Institute. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Jolfayi AG, Kohansal E, Ghasemi S, et al. Exploring TTN variants as genetic insights into cardiomyopathy pathogenesis and potential emerging clues to molecular mechanisms in cardiomyopathies. Sci Rep. 2024;14(1):5313. 10.1038/s41598-024-56154-7 [PubMed: 38438525]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2. Corden B, Jarman J, Whiffin N, et al. Association of titin-truncating genetic variants with life-threatening cardiac arrhythmias in patients with dilated cardiomyopathy and implanted defibrillators. JAMA Netw Open. 2019;2(6):e196520. 10.1001/jamanetworkopen.2019.6520 [PubMed: 31251381]

3. Tseng ZH, Olgin JE, Vittinghoff E, et al. Prospective countywide surveillance and autopsy characterization of sudden cardiac death: POST SCD study. Circulation. 2018;137(25):2689–2700. 10.1161/CIRCULATIONAHA.117.033427 [PubMed: 29915095]

4. Connolly AJ, Finkbeiner WE, Ursell PC, Davis RL. Autopsy Pathology: A Manual and Atlas. Third ed. Elsevier; 2016.

5. Stroeks SLVM, Van Beek D, Adriaens ME, Verdonschot JAJ. Titin allelic expression and protein processing pathways in early-stage dilated cardiomyopathy patients with truncating titin variants. Circ Genom Precis Med. 2023;16(1):e003901. 10.1161/CIRCGEN.122.003901 [PubMed: 36716182]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

What is the clinical question being addressed?

Are *TTN* variants associated with autopsy-defined dilated cardiomyopathy and autopsy-defined arrhythmic death?

What is the main finding?

In this countywide genetic study, arrhythmic deaths had a 1.5-fold higher *TTN* variant carrier rate than nonarrhythmic deaths. Titin-truncating variants, all non–A-band, were found exclusively in arrhythmic deaths.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

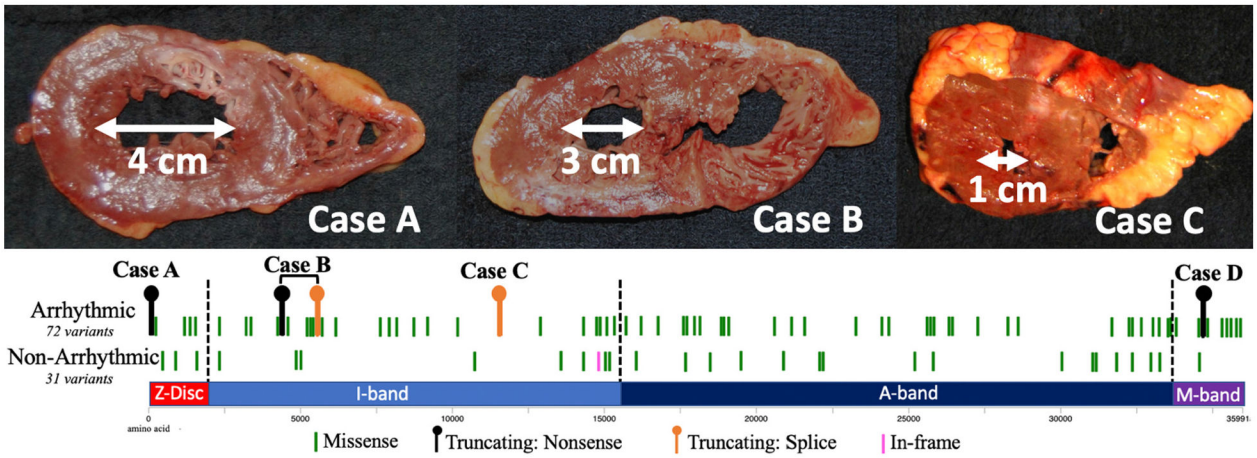

FIGURE 1. Gross Pathology of Cases With Titin-Truncating Variants and *TTN* Variant Distribution by Arrhythmic Death and Gene Region

Gross pathology of cases with titin-truncating variants with short axis lengths. None met dilated cardiomyopathy autopsy criteria. Beneath the gross pathology, *TTN* variant distribution by arrhythmic death and gene region. Gene regions are color-coded: red corresponds to the Z-disk, light blue to the I-band, navy to the A-band, and purple to the M-band. The top and bottom rows display variants belonging to arrhythmic and nonarrhythmic deaths, respectively. No titin-truncating variants were found in the A-band. Cases A, B, and C refer to Table 2.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

TABLE 1

Characteristics of *TTN* Variant Carriers and Noncarriers in POST SCD

	POST SCD Genetics Cohort (N = 306)	*TTN* Variant Carrier (n = 83)	*TTN* Variant Noncarrier (n = 223)	Carrier vs Noncarrier *P* Value
Age, y				
Mean	62	61	62	0.66
Range	25-89	28-89	25-89	
Male	226 (74)	66 (80)	160 (72)	0.17
Race or ethnic group				
Asian	51 (17)	23 (28)	28 (13)	0.001
Black	37 (12)	7 (8)	30 (13)	0.23
Hispanic or Latino	16 (5)	4 (5)	12 (5)	0.84
Other	2 (1)	0 (0)	2 (1)	0.39
White	200 (65)	49 (59)	151 (68)	0.16
Autopsy etiology of sudden death				
Cardiac, arrhythmic	190 (62)	59 (71)	131 (59)	0.048
Acute CAD	34 (11)	12 (14)	22 (10)	
Cardiomyopathy	39 (13)	10 (12)	29 (13)	
Chronic CAD/Prior MI	75 (25)	28 (34)	47 (21)	
Hypertrophy	31 (10)	6 (7)	25 (11)	
Primary Electrical Disease	6 (2)	1 (1)	5 (2)	
Valvular Disease	3 (1)	1 (1)	2 (1)	
Other Arrhythmic	2 (<1)	1 (1)	1 (<1)	
Cardiac, Nonarrhythmic	11 (4)	2 (2)	9 (4)	0.50
Myocardial rupture	5 (2)	1 (1)	4 (2)	
Pump failure	5 (1)	1 (1)	4 (2)	
Valvular disease	1 (<1)	0 (0)	1 (<1)	
Noncardiac	105 (34)	22 (27)	83 (37)	0.08
Infection	10 (3)	3 (4)	7 (3)	
Neurologic	20 (7)	7 (8)	13 (6)	
Occult overdose	33 (11)	4 (5)	29 (13)	
Pulmonary embolism	11 (4)	2 (2)	9 (4)	
Vascular catastrophe	12 (4)	0 (0)	12 (5)	
Other noncardiac	19 (6)	6 (7)	13 (6)	
Postmortem cardiac evaluation				
Evidence of DCM	47 (15)	15 (18)	32 (14)	0.42
Mean short axis, cm	2.7	2.9	2.7	0.27
Burden of total myocardial fibrosis, %[a]	9.5	10.3	9.3	0.58
Arrhythmic deaths[b]	10.0	9.8	10.0	0.91

Values are n (%) unless otherwise indicated. [a]Histological analysis was performed on a subset of 165 cases with available samples: 42 cases were *TTN* variant carriers and 123 were noncarriers. [b]Includes 123 cases who died of arrhythmic cause with available samples: 36 *TTN* variant carriers and 87 noncarriers.

CAD = coronary artery disease; DCM = dilated cardiomyopathy; MI = myocardial infarction; POST SCD = Postmortem Systematic Investigation of SCD.

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

TABLE 2

Cases With Titin-Truncating Variants

	Demographics	Variant Location	Type of Variant, PSI Index	Autopsy Evidence of DCM	Cause of Sudden Death
Case A	53-yo White female	c.325C>T	Nonsense 100%	No LV short axis = 4cm Heart weight = 450 g (z = 0.49)	Arrhythmic: acute CAD
Case B	77-yo Asian male	c.16621+1G>T	Splice 7%	No LV short axis = 3cm Heart weight = 395 g (z = 0.71)	Arrhythmic: acute CAD
		c.14113C>T	Nonsense 100%		
Case C	80-yo White female	c.34855+1G>A	Splice 3%	No LV short axis = 1cm Heart weight = 300 g (z = 0.21)	Arrhythmic: acute CAD
Case D	56-yo White male	c.104413C>T	Nonsense 100%	No LV short axis = 2cm Heart weight = 570 g (z = 3.65)	Arrhythmic: cardiomyopathy

LV = left ventricular; PSI = percent spliced in; yo = year old; other abbreviations as in Table 1.

JACC Clin Electrophysiol. Author manuscript; available in PMC 2025 May 14.