Genomic Insights into Anthracycline Cardiotoxicity: Enhancing Survivorship Care through Early Risk Identification

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BACKGROUND

- Anthracycline chemotherapy-related cardiomyopathy **(CCM)** is a serious adverse event that can occur several years after completion of breast cancer therapy.
- Demographic and clinical risk factors have failed to predict which patients will experience CCM.
- Genetic variants can account for a significant proportion of inter-individual variation.
- Knowledge of genetic risk variants prior to chemotherapy will be informative for risk stratification and early intervention.
- The goal of our study is to identify genetic variants that predispose patients to CCM.

METHODS

- Patients were enrolled under IRB #19-002566 and #22-001501, consenting for clinical chart review and DNA sequencing.
- Eligibility to the registry and sequencing project (began in 2019) includes any patient receiving or who had previously been treated with any potentially cardiotoxic cancer therapy. Patients are enrolled either prospectively prior to therapy initiation and followed for two years to determine whether or not they develop CCM, or retrospectively when first identified with CCM.
- Cardiomyopathy and heart failure were defined according to the American college of Cardiology (ACC) and American Heart Association (AHA) Guideline for the Management of Heart Failure. Cardiomyopathy was defined as an LVEF < 50% and ACC/AHA Stage B. Heart failure was defined as an ACC/AHA Stage C or D.
- We sequenced whole exomes of the first 136 patients primarily focusing on Titin (*TTN*) truncating variants, known to be present in ~25% of patients with idiopathic cardiomyopathy, and previously reported in 7.5% of patients with CCM, followed by exploration of rare non-synonymous variants in 61 established genes for primary cardiomyopathy.

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FIGURE 1: 17% OF CCM PATIENTS CARRIED A PATHOGENIC VARIANT IN TWO OF THE KNOWN IDIOPATHIC CARDIOMYOPATHY GENES: *TTN* AND *LMNA*

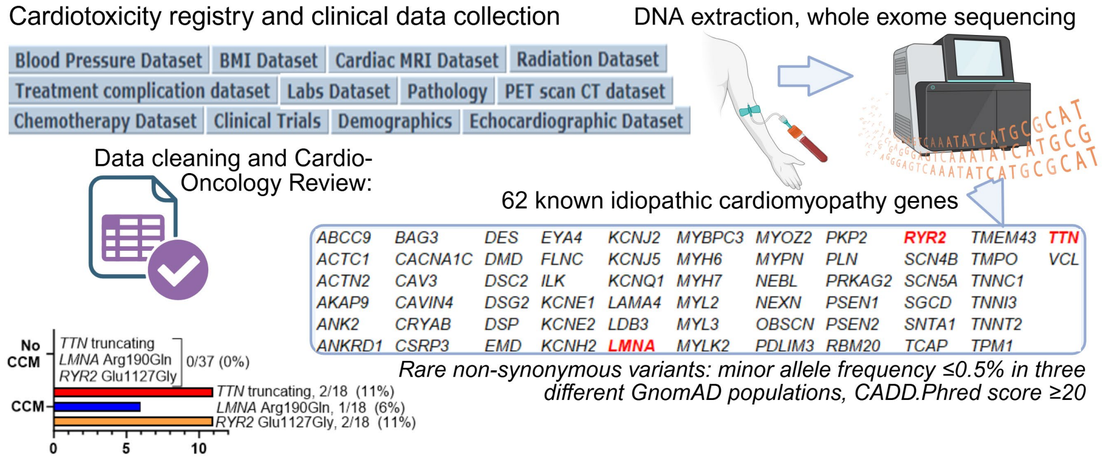


TABLE 2: MULTIPLE RARE NON-SYNONYMOUS VARIANTS WERE IDENTIFIED IN IDIOPATHIC CARDIOMYOPATHY GENES IN ANTHRACYCLINE CCM PATIENTS

Patient and outcome	Gene, Variant	CADD PHRED score (vs1.7)	gnomAD frequency (EUR, AFR, EAS)	Previously reported as pathogenic in ClinVar
#001 **Cardiac transplant**	TTN c.89900-89903del p.Asn29967MetfsTer27	54.0	0.00, 0.00, 0.00	y: 223324
	LAMA4 c.C2603G p.Pro868Arg	23.1	0.00004, 0.00, 0.00	n
	RYR2 p.Arg1084Lys	21.2	0.0002. 0.00, 0.00	n
#079 **Cardiac transplant**	TTN c.89846-89847del p.Thr29949SerfsTer11	57.0	Not present	n
	RBM20 c.C1994G p.Ser665Cys	22.1	0.00003, 0.00, 0.00	n
	CAV3 c.C233T, p.Thr78Met	33.0	0.0027, 0.004, 0.00	n
	KCNQ1 c.G1179T: p.K393N**	21.5	0.0004, 0.001, 0.00	n
#003 **Cardiomyopathy, lowest LVEF 15, final LVEF 43**	LMNA c.G569A, p.Arg190Gln	32.0	0.000003, 0.00, 0.00	y: 66910
	LAMA4 c.G4505A, p.Arg1502His	21.0	0.00002, 0.00, 0.00007	n
	KCNE2 c.T170C, p.Ile57Thr	25.9	0.0001, 0.0001, 0.00	n
	FLNC c.G1657A, p.G553S	29.8	0.0001, 0.0000, 0.00003	n
#090 **Cardiac transplant**	RYR2 c.A3380G, p.Glu1127Gly	24.3	0.0003, 0.0002, 0.006	n
#-094 **Cardiomyopathy, Lowest LVEF 40**	RYR2 c.A3380G, p.Glu1127Gly	24.3	0.0003, 0.0002, 0.006	n

Table 2 legend: Variant details and outcomes are given for known likely pathogenic or known pathogenic variants, including additional rare non-synonymous variants found in the same patient. Rare variants in *RYR2* and *KCNQ1* that were not previously identified as (likely) pathogenic in idiopathic cardiomyopathy are reported where they occurred in more than one patient with CCM.

RESULTS

TTN truncating variants were identified in 2/18 (11%) patients who experienced CCM and/or HF following treatment with doxorubicin. *TTN* truncating variants were absent in 37 patients who were treated with doxorubicin, who did not experience CCM or heart failure.

A likely pathogenic variant in lamin A/C (*LMNA* p.Arg190Gln) was identified in one of eighteen (5.5%) patients who experienced CCM or HF following treatment with doxorubicin.

We also observed the same rare variant in *RYR2* (p.Arg1084Lys) in 2/18(11%) CCM patients, as was *KCNQ1*, p.K393N. Neither of these variants is previously reported as likely pathogenic in idiopathic cardiomyopathy.

PATIENT #079 VIGNETTE: *TTN* TRUNCATING VARIANT

#079 is a 60-year-old female treated for right-sided ductal breast cancer with mastectomy and adjuvant chemotherapy including four cycles of dose-dense doxorubicin and cyclophosphamide (ddAC-240 mg/m2 of doxorubicin) followed by four cycles of paclitaxel. Transthoracic echocardiogram completed prior to chemotherapy noted normal LVEF.

Two years following completion of chemotherapy, she presented to the Emergency Department for one week of dyspnea on exertion, paroxysmal nocturnal dyspnea, and orthopnea. She was diagnosed with acute systolic HF with an estimated LVEF of 10-15%. Subsequent testing established a diagnosis of nonischemic cardiomyopathy. She was referred to advance HF clinic for consideration of cardiac transplantation. Two months later, she was hospitalized for cardiogenic shock. She was deemed ineligible for transplant due to diagnosis of bladder cancer that as incidentally discovered during transplant work-up. With HF optimal medical therapy, LVEF improved to 52% one year later.

CONCLUSIONS

Pathogenic variants in *TTN*, *LMNA*, are enriched in patients who develop anthracycline-CCM

Further research is needed to clarify the role of additional rare variants in idiopathic cardiomyopathy genes.

Incorporating genetic risk assessments into treatment planning has the potential to enhance oncologic outcomes as well as long-term survivorship.