

SUPPLEMENTAL MATERIAL

Altered Desmosomal Proteins in Granulomatous Myocarditis and Potential Pathogenic

Links to Arrhythmogenic Right Ventricular Cardiomyopathy

Angeliki Asimaki, PhD,¹ Harikrishna Tandri, MD,² Elizabeth R. Duffy, MA,³
Jeffrey R. Winterfield, MD,⁴ Shannon Mackey-Bojack, MD,⁵ Maria M. Picken, MD, PhD,⁶
Leslie T. Cooper, MD,⁷ David J. Wilber, MD,⁶ Frank I. Marcus, MD,⁸ Cristina Basso, MD,⁹
Gaetano Thiene, MD,⁹ Adalena Tsatsopoulou, MD,¹⁰ Nikos Protonotarios, MD,¹⁰
William G. Stevenson, MD,⁴ William J. McKenna, MD,¹¹ Shiva Gautam, PhD,¹ Daniel G. Remick, MD³
Hugh Calkins, MD,² Jeffrey E. Saffitz, MD, PhD¹

¹Department of Pathology (AA and JES), Department of Medicine (SG) Beth Israel Deaconess
Medical Center and Harvard Medical School, Boston, MA

²Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD

³Department of Pathology, Boston University Medical Center, Boston, MA

⁴Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

⁵Jesse E. Edwards Registry of Cardiovascular Diseases, St. Paul, MN

⁶Department of Pathology (MMP), Department of Medicine (DJW),
Loyola University Health System, Maywood, IL

⁷Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN

⁸Department of Medicine, University of Arizona, Tucson, AZ

⁹Department of Medico-Diagnostic Sciences and Special Therapies, University of Padua, Padua, IT

¹⁰Yiannis Protonotarios Medical Center, Naxos, Greece

¹¹The Heart Hospital, University College London, London, UK

Address correspondence to:

Jeffrey E. Saffitz, MD, PhD
Department of Pathology
Beth Israel Deaconess Medical Center
330 Brookline Ave
Boston, MA 02215
Phone: 617-667-4343
Fax: 617-667-2943
jsaffitz@bidmc.harvard.edu

Supplemental Table 1. Sarcoidosis patients

Patient Number	Sex	Age	Clinical/Pathological Features	Junctional Immunoreactive Signal Intensity				
				N-cadherin	Plakoglobin	Cx43	desmoplakin	PKP2
1	F	46	Palpitations, syncope, multiple VT morphologies, mild RV dilatation; sarcoid on EMB	normal	decreased	decreased		
2	M	35	QRS prolongation, T wave inversions, RV dilatation, HF; sarcoid at transplantation	normal	decreased	decreased	decreased	decreased
3	M	51	ECG and echo consistent with ARVC, multiple VT morphologies; sarcoid on EMB	normal	decreased	normal		
4	M	45	ECG and echo consistent with ARVC, multiple VT morphologies; sarcoid on EMB	normal	decreased	normal		
5	M	54	Initial diagnosis DCM; sarcoid at transplantation	normal	decreased	normal		
6	M	44	Sarcoid on EMB	normal	decreased	normal		
7	F	52	Sarcoid on EMB	normal	decreased	normal		
8	M	54	Sarcoid on EMB	normal	decreased	decreased		
9	M	86	CAD, CABG, AF, cardiac arrest at catheterization; sarcoid at autopsy	normal	normal	normal		
10	M	21	Initial diagnosis DCM; ICD, SCD; sarcoid at autopsy	normal	decreased	decreased		
11	M	67	HF, COPD; sarcoid at autopsy	normal	decreased	decreased	decreased	decreased
12	F	43	Syncope, SCD; sarcoid at autopsy	normal	decreased	decreased	decreased	decreased
13	F	78	HF, COPD, hypothyroidism; sarcoid at autopsy	normal	decreased	normal		
14	F	39	SCD; sarcoid at autopsy	normal	decreased	decreased	decreased	decreased
15	F	42	Eosinophilic myocarditis diagnosed on EMB, SCD; sarcoid at autopsy	normal	decreased	normal		
16	M	37	SCD; sarcoid at autopsy	normal	decreased	decreased	normal	normal
17	M	40	Syncope, 1st degree AV block, SCD; sarcoid at autopsy	normal	decreased	normal	decreased	decreased
18	M	44	SCD; sarcoid at autopsy	normal	normal	normal		
19	M	N/A	SCD; sarcoid at autopsy	normal	decreased	normal	normal	normal
20	M	25	SCD; sarcoid at autopsy	normal	decreased	decreased	decreased	decreased
21	M	64	LV enlargement, inferobasal and septal fibrosis on MRI, VT; sarcoid on EMB	normal	decreased	decreased		
22	M	34	Basal septal and lateral fibrosis on MRI, VT; sarcoid on EMB	normal	decreased	normal		
23	M	60	Basal septal and lateral fibrosis on MRI, complete heart block, VT; sarcoid on EMB	normal	decreased	decreased		

Abbreviations: VT, ventricular tachycardia; RV, right ventricular; EMB, endomyocardial biopsy; HF, heart failure; ECG, electrocardiogram; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; CAD, coronary artery disease; CABG, coronary artery bypass grafting; SCD, sudden cardiac death; AF, atrial fibrillation; ICD, implanted cardiac defibrillator; COPD, chronic obstructive pulmonary disease; AV, atrioventricular; MRI, magnetic resonance imaging

Supplemental Table 2. Giant cell myocarditis patients

Patient Number	Sex	Age	Clinical Characteristics	Junctional Immunoreactive Signal Intensity				
				N-cadherin	Plakoglobin	Cx43	desmoplakin	PKP2
1	M	57	Psoriasis, myositis, HF, AF, cardiogenic shock; GCM at autopsy	normal	decreased	normal	normal	normal
2	M	49	Biventricular dilatation, low EF; GCM at autopsy	normal	decreased	normal	normal	normal
3	F	34	EF 19%, normal CA; GCM at autopsy	normal	decreased	decreased	decreased	decreased
4	M	24	Acute febrile illness, maculopapular rash, cervical lymphadenopathy; GCM at autopsy	normal	decreased	decreased	decreased	decreased
5	N/A	N/A	GCM at autopsy	normal	decreased	normal	decreased	decreased
6	F	47	Chest pain, dypnea, syncope, VT, resuscitated cardiac arrest; GCM on EMB	normal	decreased	decreased		
7	F	44	Hives, eosinophilia, jaundice, low EF, T wave inversions, PVCs; GCM on EMB	normal	decreased	decreased		
8	M	42	VT, EF 35%; GCM at autopsy	normal	decreased	normal		
9	F	50	VT, EF 37%, GCM on EMB	normal	normal	normal		
10	M	47	VT, acute HF, GCM on EMB	normal	decreased	normal		
11	M	39	SCD; GCM at autopsy	normal	decreased	decreased		
12	M	34	SCD; GCM at autopsy	normal	decreased	decreased		
13	F	73	Acute abdominal pain, nausea/vomiting, AF; GCM on autopsy	normal	normal	normal		
14	M	64	Rapidly progressive HF; GCM at autopsy	normal	decreased	decreased		
15	M	32	HF; GCM on EMB	normal	decreased	normal	normal	normal
16	M	25	HF; GCM on EMB	normal	decreased	decreased	decreased	decreased

Abbreviations: HF, heart failure; AF, atrial fibrillation; GCM, giant cell myocarditis; EF, ejection fraction; CA, coronary arteries; VT, ventricular tachycardia; EMB, endomyocardial biopsy; PVC, premature ventricular complex; SCD, sudden cardiac death

Supplemental Table 3. Lymphocytic myocarditis patients

Sample ID	Sex	Age	Clinical Characteristics	Junctional Immunoreactive Signal Intensity				
				N-cadherin	Plakoglobin	Cx43	Desmoplakin	PKP2
1	M	18	Flu-like symptoms; LM on EMB, coxsackie B1, B3, B5	normal	normal	decreased	normal	normal
2	M	6	Flu-like symptoms; LM on EMB, influenza A	normal	normal	decreased	decreased	decreased
3	M	9	Flu-like symptoms; LM on EMB, no viral genomes detected	normal	decreased	decreased	decreased	decreased
4	F	18	SCD; LM at autopsy	normal	normal	decreased	normal	normal
5	M	25	SCD; LM at autopsy, enterovirus group B	normal	normal	decreased		
6	M	20	SCD; LM at autopsy	normal	decreased	normal	normal	normal
7	M	31	Flu-like symptoms, SCD; LM at autopsy, no viral genomes detected	normal	normal	decreased	normal	normal
8	M	24	SCD; LM at autopsy, no viral genomes detected	normal	normal	normal	normal	normal
9	F	55	VT, EF 30%, SCD; LM at autopsy	normal	normal	normal		
10	M	22	Fever, HF; LM at autopsy, no viral genomes detected	normal	decreased	decreased		
11	M	38	SCD; LM at autopsy, enterovirus group B	normal	normal	normal		
12	F	26	SCD; LM at autopsy, no viral genomes detected	normal	normal	normal		
13	F	31	SCD; LM at autopsy, enterovirus group B	normal	normal	normal		
14	F	7	SCD; LM at autopsy, no viral genomes detected	normal	normal	normal		
15	M	40	SCD; LM at autopsy, no viral genomes detected	normal	normal	decreased		
16	M	38	VT; LM on EMB, no viral genomes detected	normal	normal	normal		
17	M	69	VT; LM on EMB, no viral genomes detected	normal	normal	normal		
18	F	44	VT, HF, AV block; LM on EMB, parvovirus B19	normal	normal	normal		
19	M	55	VT, HF, AV block; LM on EMB, adenovirus	normal	normal	normal		
20	M	39	HF; LM on EMB, no viral genomes detected	normal	normal	normal		
21	M	13	HF; LM on EMB, no viral genomes detected	normal	normal	normal	normal	normal
22	M	39	Flu-like symptoms, MI-like picture; LM on EMB, no viral genomes detected	normal	normal	normal		
23	F	10	HF, AV block; LM on EMB, no viral genomes detected	normal	normal	normal		
24	M	20	HF; LM on EMB, Epstein-Barr	normal	normal	normal		
25	F	25	HF; LM on EMB, enterovirus	normal	normal	normal		

Abbreviations: LM, lymphocytic myocarditis; EMB, endomyocardial biopsy; SCD, sudden cardiac death; VT, ventricular tachycardia; EF, ejection fraction; HF, heart failure; AV, atrioventricular; MI, myocardial infarction

Supplemental Table 4. ARVC patients for immunoperoxidase studies

Sample ID	Sex	Age	Clinical Characteristics/ Pathological Findings	Desmosomal gene mutation	Signal for IL-17	Signal for TNF α
1	F	35	Palpitations, syncope, SCD; ARVC at autopsy	desmoplakin R1113X	increased	increased
2	F	28	>15,000 PVCs and NSVT on Holter, SCD; ARVC at autopsy	desmoplakin S1015fsX1023	increased	increased
3	M	42	TWI V1-V3, >1000 PVCs and NSVT on Holter, RV dilatation; ARVC on EMB	none identified	increased	absent
4	M	37	SCD; ARVC at autopsy	plakophilin2 V570fs576X	increased	increased
5	M	20	Syncope, NSVT, TWI, SCD; ARVC at autopsy	plakophilin2 G324fsX348	increased	increased
6	M	61	TWI V1-V3, RV hypokinesis, SCD; ARVC at autopsy	none identified	increased	increased
7	F	40	Pre-syncope, TWI V1-V6, WMA both ventricles, LV apex aneurysm; ARVC on EMB	desmoglein2 C591X	increased	increased
8	M	15	SCD; ARVC at autopsy	desmoglein2 829_840delCTTGAAGGGATG	increased	increased
9	M	24	Syncope, biventricular enlargement, EF 15%, VT, ICD; ARVC on EMB	none identified	increased	increased

Abbreviations: SCD, sudden cardiac death; ARVC, arrhythmogenic right ventricular cardiomyopathy; PVC, premature ventricular complex; NSVT, non-sustained ventricular tachycardia; RV, right ventricular; TWI, T wave inversions; WMA, wall motion abnormalities; LV, left ventricular; VT, ventricular tachycardia

Supplemental Table 5. ARVC patients for blood cytokine studies

Patient ID	Sex	Age	Electrophysiological Abnormalities	Structural/ Functional Abnormalities
1	M	60	TWI, VT, multiple ICD shocks	Marked RV enlargement
2	F	60	TWI, VT, no ICD shocks	Not available
3	M	45	TWI V1-V4, VT, multiple ICD shocks	RV EF 20%, mild RV dilatation
4	F	26	TWI V1-V6, VT, multiple ICD shocks	Mild RV dilatation and basal dyskinesia
5	M	52	TWI V1-V4, VT, multiple ICD shocks	RV EF 40%, mild RV dilatation
6	F	57	TWI, VT	Dilated hypokinetic RV
7	F	31	TWI V1-V3, VT, multiple ICD shocks	Borderline RV dilatation, normal RV function
8	F	49	TWI V1-V3, VT, multiple ICD shocks	RV aneurysms
9	F	40	TWI V1-V4, VT, no ICD shocks	Moderate RV enlargement and basal hypokinesia
10	F	44	TWI V1-V4, >4500 PVCs on Holter	Borderline RV dilatation
11	M	36	TWI V1-V5, VT, multiple ICD shocks	Mild RV dilatation, focal RV dyskinesia, RV EF 38%
12	F	31	TWI V1 only, no PVCs on Holter, no ICD shocks	Normal RV dimensions
13	M	50	TWI V1 only, 1473 PVCs on Holter, no ICD shocks	Global RV hypokinesia, focal RV outpouchings
14	M	45	TWI V1-V5, VT, multiple ICD shocks	Severe RV enlargement and dysfunction
15	M	18	TWI V1-V3, inducible NS VT, no ICD shocks	LV enlargement and mild dysfunction
16	F	65	TWI V2-V6, NS VT on Holter, no ICD shocks	LGE of LV, normal RV
17	M	42	TWI V1-V6 II and AVF, NS VT, multiple ICD shocks	Mild LV and RV dilatation, LV EF 47%
18	F	28	TWI V4-V6, biphasic T waves V1-V3, >6000 PVCs on Holter, NS VT, multiple ICD shocks	Mild biventricular enlargement, posterior and apical LV WMA, LGE in most of RV

Abbreviations: TWI, T wave inversions; VT, ventricular tachycardia; ICD, internal cardiac defibrillator; RV, right ventricular; EF, ejection fraction; PVC, premature ventricular complex; NS VT, non-sustained ventricular tachycardia; LGE, late gadolinium enhancement on magnetic resonance imaging; WMA, wall motion abnormality