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SUPPLEMENTARY MATERIAL

The role of genetics in the prognosis of acute myocarditis: a systematic review and meta-analysis

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Key words: acute myocarditis, myocarditis, genetic myocarditis, genetic burden, positive genetic test.

Supplementary Table 1 PubMed search strategy.

#1	myocarditis [Text Word]
#2	myocarditis [MeSH]
#3	myocarditis/genetics [MeSH]
#4	#1 OR #2 OR #3
#5	genetic* [Text Word]
#6	genetic test* [Text Word]
#7	pathogenic variant* [Text Word]
#8	mutation [Text Word]
#9	#5 OR #6 OR #7 OR #8
#7	humans [MeSH]
#8	#4 AND #9 AND #7

Nº of results: 1647

Supplementary Table 2. Web of Science search strategy.

#1	myocarditis
#2	genetic
#3	genetic test*
#4	pathogenic variant*
#5	mutation
#6	#2 OR #3 OR #4 OR #5
#7	TS= #1 AND TS= #6

Nº of results: 1083

Supplementary Table 3. Characteristics of the eleven studies included in the literature review.

Study	*Country*	*Population*	*Aim and study design*	*Intervention*	*Comparison*	*Outcome*	*Results/Conclusions*
Ader et al,2020* [8]	France	Patients with clinically suspected AM associated with sustained ventricular arrhythmia or right ventricular abnormalities as first clinical manifestation (n=16; aged 13 to 75 years)	Aim: Assess the genetic basis of myocarditis (12 ARVC/D and 51 CMP associated genes) Case series	Genetic test	NA	-Recurrent myocarditis -Temporary external hemodynamic support -Heart transplantation	R: High proportion of positive genetic tests in patients with clinically suspected myocarditis and right ventricular involvement or sustained ventricular arrhythmias. C: AM can be the first clinical expression of inherited CMP.
Ammirati et al, 2022*[9]	Italy	Patients with AM and positive genetic test (n=36; aged 17 to 38 years)	Aim: Assess the risk of death, ventricular arrhythmias, recurrent myocarditis and heart failure in patients with AM and positive genetic test Retrospective study	Genetic test	Patients with AM and negative genetic test (n=25), or without genetic testing (n=36)	-Cardiovascular death -Ventricular arrhythmia -Recurrent myocarditis -Heart failure (main endpoint) -ICD implantation	R: Higher risk of the main endpoint in patients with a positive genetic test. C: Patients with AM and a positive genetic test are at high risk for recurrent myocarditis and ventricular arrhythmias.
Artico et al, 2020*[10]	Italy	Patients with AM (n=11; age= 46±15 years)	Aim: Test the hypothesis that pathogenic variants in CMP causing genes may increase susceptibility to developing left ventricle dysfunction Cohort	Genetic test	Patients with myocarditis and negative genetic test (n=25)	-LVEF normalization	R: Patients with a positive genetic test had a lower rate of LVEF normalization. C: Patients with biopsy-proven myocarditis are in a non-negligible percentage of cases with a positive genetic test.
Brown et	United	Children who	Aim: Understand	Genetic test	NA	-Death	R: Patients with a positive genetic test had severe

al, 2019 [11]	States	presented with acute heart failure suspected to be AM (n=8; aged 3 weeks to 14 years)	how genetic disorders contribute to the cases of acute heart failure in children, presumed to be myocarditis in patients without structural heart defects and negative family/personal history. Retrospective review			-Cardiac transplantation	outcomes, and none of them were able to recover. C: Genetic testing should be considered in children with clinical presentation of heart failure, even in those without family/personal history/syndromic features.
Kontorovich, 2021* [12]	Germany	Patients with AM from 3 different cohorts (n=117; aged 0.6 to 62 years)	Aim: Determine the extent of the association between genetic positive test and the risk of myocarditis in children. Observational study (case-control)	Genetic test	"Heart-healthy" controls matched 4:1 by sex and ancestry to AM cases	-Death -Heart transplantation -Left ventricle assist device -Persistence of CMP -LVEF normalization	R: Higher rate of individuals with a positive genetic test in patients with myocarditis vs controls, but absence of statistically significant differences in histology, viral status, or outcomes. C: Patients with a positive genetic test in genes related to cardiomyocyte structure and function have higher episodes of myocarditis compared with "heart healthy" individuals.
Kontorovich, Tang, et al, 2021* [13]	United States	Children who died from myocarditis (n=24; aged 3 weeks to 20 years)	Aim: Evaluate if positive cardiomyopathic genetic tests were more prevalent among fatal pediatric AM cases compared to ancestry-matched controls Observational study	Genetic test	Controls without cardiovascular disease matched by genetic ancestry	-Death	R: Cases of fatal pediatric AM are associated with significantly higher rates of positive cardiomyopathic genetic tests than seen in controls. C: The finding of a positive genetic test in patients who recover from AM should justify ongoing surveillance for CMP/arrhythmia; females with TTN mutations may benefit from counseling about the risk of peripartum CMP, and relatives of these individuals may undergo cascade screening for the higher risk of developing cardiac disease related to these mutations.

Lota et al, 2022[14]*	England and Netherlands	Patients with AM (n=336; aged 25 to 60 years)	Aim: Assess the frequency and clinical consequences of positive genetic test (for DCM and ACM genetic variants) in patients with AM. Cohort	Genetic test	Healthy controls (n=1053)	-All-cause mortality -Major arrhythmia (ventricular tachycardia, aborted sudden cardiac death, ICD, second/third degree heart block) -Major heart failure (heart transplantation, left ventricle assist device, heart failure hospitalization)	R: The incidence of a positive test was higher in cases of myocarditis compared with healthy controls (8% vs <1%). 5-year-mortility risk was higher in patients with a positive genetic test (11.1% vs 3.3%). C: The results found support the potential role of genetic testing in patients with AM. It also reinforces the idea that those with a positive genotype may not manifest symptoms until exposed to a triggering environmental factor.
Ollitrault et al,2022* [15]	France	Patients with recurrent AM and no previous CMP (n=21; aged 13 to 69 years)	Aim: Evaluate the temporal association between recurrent AM and the later diagnosis of a genetic ACM. Observational study	Genetic test	NA	-Arrhythmogenic cardiomyopathy	R: A genetic positive test was found in 8/14 patients with myocarditis and ACM phenotype. C: Recurrent AM is associated with the latter diagnosis of a genetically determined arrhythmogenic cardiomyopathy, and AM episodes may justify the realization of genetic testing, particularly in the presence of suggestive family history.
Seidel et al, 2021 [16]	Germany	Pediatric patients with myocarditis (n=42; 20 with DCM phenotype; 22 without DCM phenotype; aged 1.1 to 16.4 years)	Aim: Attempt to describe the clinical and genetic characteristics in patients with myocarditis and <18 years of age to predict the outcome Cohort	Genetic test	Patients without DCM phenotype (n= 22)	-Mechanical circulatory support -Weaned from mechanical circulatory support -Resuscitation -Heart transplantation -Death	R: Myocarditis patients with DCM phenotype have a higher risk for mechanical circulatory support or heart transplantation than patients with myocarditis without a DCM phenotype. C: Genetic testing is justified in children who have recently been diagnosed with myocarditis and present with clinical features of DCM.
Seidel et al, 2022 [17]	Germany	Pediatric patients with myocarditis and DCM phenotype at admission	Aim: Understand the further impact of immune disorder gene variants in patients with	Genetic test	NA	-Malign arrhythmia -Mechanical circulatory support -Heart transplantation -All cause death	R: A positive genetic test was found in 8/12 and the screening of recessive immune disorder genes identified a PV in 3/12 patients. C: This study supports the impact that a positive genetic test has in patients with myocarditis and DCM and raises the idea that altered cilium

		(n=12; aged 0.8 to 8.0 years)	myocarditis and DCM phenotype. Retrospective study				function might play an additional role in inflammation in patients with CMP.
Tiron et al, 2022 [18]	Spain	Patients with severe and non-severe myocarditis (n=28; aged 15 to 74 years)	Aim: Clarify the value of genetic testing in patients with myocarditis Retrospective cohort	Genetic test	NA	-Sustained ventricular arrhythmia -Cardiogenic shock -Heart transplantation	R: 5/28 patients with myocarditis had a positive genetic test. C: The importance of genetic testing is confirmed in severe cases of myocarditis and in those with a family history of CMP.

*Studies whose data was included in meta-analysis. ACM, arrhythmogenic cardiomyopathy; AM: acute myocarditis; ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; CMP, cardiomyopathy; DCM, dilated cardiomyopathy; ICD, implantable cardiac defibrillator; LVEF, left ventricle ejection fraction; NA, not available.

Supplementary Table 4. Diagnostic criteria of myocarditis applied in each study, genetic variants found and their corresponding classification.

REFERENCE	DIAGNOSTIC CRITERIA OF MYOCARDITIS	GENETIC VARIANTS FOUND (N)	CLASSIFICATION
Ader et al, AHA 2020[8]	Clinically suspected AM according to the definition of the ESC Working Group on Myocardial and Pericardial Diseases.	*DES (1), DSG2 (1), DSP (1), DTNA (1), PKP2 (5), RYR2 (1)*	*DES*: pathogenic *DSG2, DSP, DTNA, RYR2*: likely pathogenic *PKP2*: pathogenic/ likely pathogenic
Ammirati et al, AHA 2022[9]	Diagnosis based on symptoms in association with increased troponin levels and CMR findings or histology consistent with AM.	*DSG2 (2), DSP (32), PKP2 (2)*	*DSG2, DSP*: pathogenic *PKP2*: pathogenic/ likely pathogenic
Artico et al, JACC 2020[10]	Patients with biopsy-proven active lymphocytic myocarditis according to Dallas criteria and immunohistochemical analysis.	*TTN (8), DSP (1), FLNC (1)*	*TTN, DSP, FLNC*: pathogenic/ likely pathogenic
Brown et al, Cardiology in the Young 2019[11]	Clinical evaluation which included an echocardiogram, electrocardiogram, CMR, clinical history, viral cultures, troponin-I levels, and EMB with pathological analysis.	*ALMS1 (1), MYBPC3 (1), TTN (2), TNNT2 (1), IDUA (1), LAMA4 (1), RBM20 (1), DMD (1), SCN5A (1), PRDM16 (1), MIB1 (1), DTNA (1)*	*ALMS1, MYBPC3, TNNT2, IDUA*: pathogenic *TTN*: pathogenic/likely pathogenic *SCN5A*: likely pathogenic *LAMA4, RBM20, DMD, PRDM16, MIB1, DTNA*: unknown significance
Kontorovich, et al, JACC 2021[12]	Cohort1: Clinical diagnosis of AM based on historical and diagnostic testing data recruited between 1991-2000. Cohorts 2 and 3: Clinically suspected viral myocarditis, recruited between 2015-2017 and 1997-2013, respectively, with AM proven by immunohistology criteria.	*DMD (1), DNM2 (1), DSP (3), DYSF (2), FLNC (1), MYH7 (1), PRDM16 (1), PKP2 (1), RYR1 (1), SGCG (1), TTN (7), TRDN (1), TNNT1 (1)*	*PKP2*: pathogenic *DSP, DYSF, SGCG*: pathogenic/likely pathogenic *DMD, DNM2, FLNC, PRDM16, TTN, TRDN, TNNT1*: likely pathogenic *MYH7*: unknown significance *RYR1*: pathogenic/unknown significance
Kontorovich, Tang et al, AHA, 2021[13]	Histological findings meeting the Dallas criteria revealed AM as the identified cause of death in the autopsy records.	*CTF1 (1), SCN5A (1), TTN (2)*	*SCN5A*: pathogenic *CFT1*: likely pathogenic *TTN*: unknown significance/likely pathogenic
Lota et al, AHA 2022[14]	Cohort 1: CMR or biopsy-confirmed myocarditis by ESC criteria. Cohort 3: 106 cases confirmed by EMB by ESC criteria and 103 cases underwent CMR.	*BAG3, DES, DSC2, DSG2, DSP, JPH2, JUP, LMNA, MYH7, PKP2, PLN, RMB20, SCN5A, TTN, TNNC1, TNNT2*	*BAG3, DES, LMNA, PKP2, TNNC1, TNNT2*: likely pathogenic *DSP, RMB20, TTN*: likely pathogenic/unknown significance *DSC2, DSG2, JPH2, JUP, MYH7, PLN, SCN5A*: unknown significance
Ollitrault et al,	Clinically AM presenting by at least	*DSP (5), PKP2 (2), TTN*	*PKP2*: pathogenic *DSP, TTN*: likely pathogenic

Frontiers in 2022[15]	one clinical presentation and one diagnostic criteria from ESC diagnostic criteria.	*(1)*	
Seidel et al, GPM, 2021[16]	Biopsy-proven myocarditis and clinical and diagnostic assessments including physical examination, laboratory testing, ECG, Holter, Eco and CMR.	*BAG3, DSP, LMNA, MYH7, TNNI3, TNNT2, TTN*	*LMNA, TNNI3*: pathogenic *DSP, MYH7, TNNT2, TTN:* likely pathogenic *BAG3:* pathogenic/likely pathogenic
Seidel et al, JCDD, 2022[17]	Biopsy-proven myocarditis and DCM phenotype present at admission.	Cardiomyopathy*: DMD, DSC2, FBN1, FKTN, MYH7, MYLK2, RYR2, SDHA, SGCG, TNNC1, TNNI3, TTN* Immune: *ATRX, CCDC40, DNAH9 DNAH11, FANCC, FANCM, FLNA, IRF7, PIH1D3, PLG, RAC2, RBCK1, SPAG1*	*DNAH11, RYR2, SPAG1, TNNC1, TNNI3, TTN:* likely pathogenic *ATRX, CCDC40, DMD, DNAH9, DSC2, FANCC, FANCM, FBN1, FKTN, FLNA, MYLK2, IRF7, PIH1D3, PLG, RAC2, RBCK1, SDHA, SGCG*: unknown significance *MYH7*: likely pathogenic/unknown significance
Tiron et al, 2022[18]	ESC criteria: clinical presentation, ECG, myocardial cytolysis markers, echocardiography, and tissue characterization by CMR or EMB pathology.	*BAG3 (2), FLNC (1), RMB20 (1)*	*BAG3, FLNC, RMB20*: pathogenic/likely pathogenic

ALMS1, ALMS1 centrosome and basal body associated protein; AM, acute myocarditis; *BAG3*, BAG cochaperone 3; *CTF1*, cardiotrophin 1; *DES*, desmin; *DMD*, dystrophin; *DNM2*, dynamin 2, *DSC2*: desmocollin 2, *DSG2*: desmoglein 2; *DSP*, desmoplakin; *DTNA*, dystrobrevin alpha; *DYSF*, dysferlin; *FLNC*, filamin C; *FBN1*, fibrillin 1; *FKTN*, fukutin; *IDUA*, alpha-L-iduronidase; *IRF7*, interferon regulatory factor 7; *JPH2*, junctophilin 2; *JUP*, junction plakoglobin; *LAMA4*, laminin subunit alpha4; *LMNA*, lamin A/C; *MIB1*, midbomb E3 ubiquitin protein ligase 1; *MYBPC2*, myosin binding protein C2; *MYH7*, myosin heavy chain 7; *MYLK2*, myosin light chain kinase 2; *PKP2*, plakophilin 2; *PLN*, phospholamban; *PRDM16*, PR/SET domain 16; *RMB20*, RNA binding motif protein 20; *RYR1*, ryanodine receptor 1; *RYR2*, ryanodine receptor 2; *SCN5A*, sodium voltage-gated channel alpha subunit 5; *SDHA*, succinate dehydrogenase complex flavoprotein subunit A; *SGCG*, sarcoglycan gamma; *SPAG1*, sperm associated antigen 1; *TNNC1*, troponin C1; *TNNI3*, troponin I3, cardiac type; *TNNT1*, troponin T1; *TNNT2*, troponin T2; *TRDN*, triadin; *TTN*, titin.

Supplementary Table 5. Classification of genetic variants: OMIM codification, inheritance and number of carriers reported.

Gene	OMIM	Inheritance	Number of carriers reported across studies**
ALMS1 - ALMS1 Centrosome and Basal Body Associated Protein	606844	AR	(1) [11]
BAG3 - BAG Cochaperone 3	603883	AD	(1) [18] / + [14,16]
CTF1 - Cardiotrophin 1	600435	*	(1) [13]
DES - Desmin	125660	AD, AR	(1) [8] / + [14]
DMD - Dystrophin	300377	XL, XLR	(2) [11,12]
DNM2 - Dynamin 2	602378	AD, AR	(1) [12]
DSC2 - Desmocollin 2	125645	AD, AR	+ [14,17]
DSG2 - Desmoglein 2	125671	AD, AR	(3) [8,9] / + [14]
DSP - Desmoplakin	125647	AD, AR	(42) [8,9,12,15] / + [14,16]
DTNA - Dystrobrevin alpha	601239	AD	(1) [8,11]
DYSF - Dysferlin	603009	AR	(2) [12]
FLNC - Filamin C	102565	AD	(3) [10,12,18]
FBN1 - Fibrillin 1	134797	AD	+ [17]
FKTN - Fukutin	607440	AR	+ [17]
IDUA - Alpha-L-Iduronidase	252800	AR	(1) [11]
IRF7 - Interferon Regulatory Factor 7	605047	AR	+
JPH2 - Junctophilin 2	605267	AD, AR	+ [14]
JUP -Junction Plakoglobin	173325	AD, AR	+ [14]
LAMA4 - Laminin Subunit Alpha4	600133	AD	(1) [11]
LMNA - Lamin A/C	150330	AD, AR	+ [14,16]
MIB1 - Midbomb E3 Ubiquitin Protein Ligase 1	608677	AD	(1) [11]
MYBPC3 - Myosin Binding Protein C3	160795	*	(1) [11]
MYH7 - Myosin Heavy Chain 7	160760	AD, AR, DD	(1) [12] / + [14,16,17]
MYLK2 - Myosin Light Chain Kinase 2	606566	AD, DD	+ [17]
PKP2 - Plakophilin 2	602861	AD	(10) [8,9,12,15] / + [14]
PLN - Phospholamban	172405	AD	+ [14]
PRDM16 - PR/SET Domain 16	617692	*	(2) [11,12]
RMB20 - RNA Binding Motif Protein 20	400006	*	(1) [18] / + [14]
RYR1 - Ryanodine Receptor 1	180901	AD, AR	(1) [12]
RYR2 - Ryanodine Receptor 2	180902	AD	(1) [8]
SCN5A - Sodium Voltage-Gated Channel Alpha Subunit 5	600163	AD, AR	(2) [11,13] / + [14]
SDHA - Succinate Dehydrogenase Complex Flavoprotein Subunit A	600857	AD, AR	+ [17]
SGCG - Sarcoglycan Gamma	608896	AR	(1) [12]
SPAG1 - Sperm Associated Antigen 1	603395	AR	+ [17]

TNNC1 - Troponin C1	191040	AD	+ [14,17]
TNNI3 - Troponin I3, cardiac type	191044	AD, AR	+ [16,17]
TNNT1 - Troponin T1	191041	AD, AR	(1) [12]
TNNT2 - Troponin T2	191045	AD	(1) [11] / + [14,16]
TRDN – Triadin	603283	AR	(1) [12]
TTN - Titin	188840	AD, AR	(20) [10,11,12,13,15] / + [14,16,17]

AD, autosomal dominant; AR, autossomal recessive; DD, digenic dominat; OMIM, *Online Mendelian Inheritance in Man* codification; XL, X-linked; XLR, X-linked recessive

*Unavailable data

**The number of patients carrying genetic variants was not quantified in all studies. Only data provided was summed and included here.

+Reported but unquantified