

Familial screening in case of acute myocarditis reveals inherited arrhythmogenic left ventricular cardiomyopathies

Nicolas Piriou^{1*}, Lara Marteau¹, Florence Kyndt², Jean Michel Serfaty², Claire Toquet³, Laurianne Le Gloan¹, Karine Warin-Fresse¹, Damien Guijarro⁴, Thierry Le Tourneau¹, Emilie Conan², Aurélie Thollet², Vincent Probst² and Jean-Noël Trochu²

¹*Institut du Thorax, CHU de Nantes, 44093 Nantes Cedex 1, Nantes, France;* ²*Institut du Thorax, INSERM, CNRS, UNIV Nantes, CHU Nantes, Nantes, France;* ³*Pathology Department, Nantes University Hospital, Nantes, France;* ⁴*Groupe Hospitalier Mutualiste, Institut Cardio-Vasculaire, Grenoble, France*

Abstract

Aims Several data suggest that acute myocarditis could be related to genetic variants involved in familial cardiomyopathies, particularly arrhythmogenic cardiomyopathy, but the management of patients with acute myocarditis and their families regarding their risk for having an associated inherited cardiomyopathy is unclear.

Methods and results Families with at least one individual with a documented episode of acute myocarditis and at least one individual with a cardiomyopathy or a history of sudden death were included in the study. Comprehensive pedigree, including genetic testing, and history of these families were analysed. Six families were included. Genetic analysis revealed a variant in desmosomal proteins genes in all the probands [five in desmoplakin (DSP) gene and one in desmoglein 2 gene]. In the five families identified with a DSP variant, genetic testing was triggered by the association of an acute myocarditis with a single case of apparently isolated dilated cardiomyopathy or sudden death. Familial screening identified 28 DSP variant carriers; 39% had an arrhythmogenic left ventricular (LV) cardiomyopathy phenotype. Familial histories of sudden death were frequent, and a remarkable phenotype of isolated LV late gadolinium enhancement on contrast-enhanced cardiac magnetic resonance without any other structural abnormality was found in 38% of asymptomatic mutation carriers. None of the DSP variant carriers had imaging characteristics of right ventricle involvement meeting current Task Force criteria for arrhythmogenic right ventricular cardiomyopathy.

Conclusions Comprehensive familial screening including genetic testing in case of acute myocarditis associated with a family history of cardiomyopathy or sudden death revealed unknown or misdiagnosed arrhythmogenic variant carriers with left-dominant phenotypes that frequently evade arrhythmogenic right ventricular cardiomyopathy Task Force criteria. In view of our results, acute myocarditis should be considered as an additional criterion for arrhythmogenic cardiomyopathy, and genetic testing should be advised in patients who experience acute myocarditis and have a family history of cardiomyopathy or sudden death.

Keywords Myocarditis; Arrhythmogenic cardiomyopathy; Genetics

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*Correspondence to: Nicolas Piriou, l'Institut du Thorax and Nuclear Medicine Department, CHU de Nantes, 44093 Nantes Cedex 1, Nantes, France.

Email: nicolas.piriou@chu-nantes.fr

Nicolas Piriou and Lara Marteau contributed equally to this work and are considered as first co-authors.

Vincent Probst and Jean-Noël Trochu contributed equally to this work and are considered as second co-authors.

Introduction

Myocarditis is an inflammatory disease of the myocardium. Viral infections are thought to be the most important cause

in North America and Europe, but other mechanisms such as toxic injuries or autoimmune reactions can trigger myocardial inflammation. Clinical presentations range from myocardial infarction without coronary artery obstruction to

cardiogenic shock and life-threatening arrhythmias, including sudden cardiac death (SCD). After an acute myocarditis (AMC), most of the patients fully recover; but in up to 30% of cases, AMC can progress to dilated cardiomyopathy (DCM).¹ In arrhythmogenic cardiomyopathy (AC), a heritable cardiomyopathy characterized by replacement of myocardium by fat and fibrosis,² and scattered or diffuse inflammatory cell infiltrates have been reported in two-thirds of patients analysed histologically³; and viral genomes have been detected in the myocardium of patients at higher rates than in controls.⁴ Homozygous or compound heterozygous variants in genes associated with cardiomyopathies, including AC, have been found in unrelated children with AMC.⁵ These observations suggest that myocarditis could have a genetic background⁶ and raise the question of its implication in the clinical presentation of inherited cardiomyopathies such as AC.⁷ However, data regarding genetics in myocarditis are scarce: the management of patients with AMC and their families regarding their risk of having an associated inherited cardiac disease is unclear, and AMC is not mentioned in the guidelines as a criterion to propose a genetic testing.^{1, 8, 9}

In order to determine the meaning of the occurrence of AMC in inherited cardiomyopathies, the aim of our study was to analyse the pedigrees and management of prospectively identified families with at least one individual with a documented episode of AMC and at least one individual with a cardiomyopathy or a history of sudden death.

Methods

Study population

From January 2011 to November 2018, all families followed up in our institution with a potential inherited cardiomyopathy phenotype were screened. Families with at least one individual with a documented episode of AMC and at least one individual with a cardiomyopathy or a history of SCD were included in the study. The comprehensive pedigree, including genetic testing, and history of these families were analysed.

Diagnostic criteria for cardiomyopathies included DCM, hypokinetic non-DCM (HNDCM), left ventricular non-compaction (LVNC), hypertrophic cardiomyopathy (HCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) according to current cardiomyopathies classification and definitions.^{8–12} AMC was defined as an infarct-like clinical presentation with tissue characterization of myocardial inflammation by cardiac magnetic resonance (CMR) or as an autopsy-proven myocarditis after an SCD.^{1,13} Definitely proven immune-mediated myocarditis such as cardiac sarcoidosis, vasculitis and eosinophilic syndromes, scleroderma, or systemic lupus erythematosus were excluded from the study. The study complies with the Declaration of Helsinki and was approved by the local ethics committee. Informed

consent was obtained from each patient who agreed to participate in the clinical and genetic studies.

Clinical evaluation

Clinical evaluation included review of medical history, familial pedigree, physical examination, baseline electrocardiogram (ECG), transthoracic 2D Doppler echocardiogram, exercise ECG test, 24 h Holter ECG monitoring, and CMR. Recorded ventricular arrhythmias were classified as follows: ventricular fibrillation, ventricular tachycardia (VT), non-sustained VT (NSVT), and frequent premature ventricular complexes (PVCs) (>30/h). Comprehensive CMR examination consisted of standard cine sequences to assess left and right ventricular volumes (LV and RV), function, morphology, and thickness. Tissue characterization sequences were obtained from T2-weighted sequences and T1-weighted early and late gadolinium enhancement (LGE) sequences. Diagnosis of myocardial inflammation was based on the Lake Louise Criteria that were applicable before the end of 2018.¹³

Genetic analysis and familial screening

Patients' DNA was sequenced on a targeted panel of 31 genes (*Table S1*), including DCM, HCM, and AC disease-causing genes. A custom (Sophia Genetics©) sequencing panel was used for library preparation, and DNA sequencing was performed on an Illumina© platform. The five-tier terminology system of the American College of Medical Genetics and Genomics (ACMG) was used for variant classification including: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign.¹⁴ When a pathogenic genetic variation or a suspicious genetic VUS was identified, family members were included in the study after individual consent for familial screening and segregation analysis. Familial screening was first performed in first-degree relatives and then extended as a cascade screening to other relatives if positive.¹⁵ Clinical screening of relatives included a review of the medical history, clinical examination, baseline ECG, transthoracic 2D Doppler echocardiogram, and genetic testing as described earlier. When a mutation was identified in a relative, an exercise ECG test, a 24 h ECG monitoring, and a CMR were performed. CMR protocol and analysis were the same as described earlier.

Results

Among the 600 families followed up in our institution with a potential inherited cardiomyopathy phenotype (352 HCM, 102 DCM, and 146 ARVC), six families presented with at least one individual with a documented episode of AMC and one

individual with a cardiomyopathy or a history of SCD. Genetic analysis identified a genetic variant in desmoglein 2 (DSG2) gene in one family and desmoplakin (DSP) gene in five families. One family was found with a compound heterozygosity with both DSP gene variant and MYBPC3 gene variant. The rationale for the classification of each variant according to the ACMG classification is detailed in Table S2. The six families' pedigrees are presented in Figure 1. Clinical and genetic characteristics of the 34 variant carriers and decedents from SCD or heart failure are summarized in Table 1. Regarding the predominance of desmosomal proteins genes variants in this population, Table 2 details CMR and ECG criteria for A C for each desmosomal variant carrier. The clinical presentations of patients with AMC are detailed in Table S3. Histologic samples from endomyocardial biopsies (EMBs) or autopsy were available for some of them and presented in Table S3. All relatives without mutation were asymptomatic, had no history of AMC, and exhibited normal cardiac phenotype. One hundred seventy-three other desmosomal mutation carriers, including 34 with a DSP variant, were followed up in our centre and had no history of AMC.

Family 1 (pathogenic variant in desmoplakin c.3924del)

A 34-year-old woman (IV.8), with frequent PVCs was diagnosed with HNDCM. Her ECG showed T-wave inversion from V4 to V6 (Figure 2B). Her 19-year-old cousin's daughter (V.1) was previously diagnosed with AMC after an episode of chest pain and a rise of troponin. CMR revealed high signal T2 intensity and sub-epicardial circumferential LGE, confirming AMC (Figure 2C). She had three AMC recurrent episodes. Last follow-up CMR performed 5 years later showed sub-epicardial circumferential LGE without persistent inflammation and without progress towards other phenotypic features of cardiomyopathy. Genetic analysis identified a mutation in DSP in patient IV.8, shared with patient V.1. Familial screening identified the mutation in five relatives. One (III.9) had a DCM phenotype, and three had sub-epicardial LGE without inflammation and cardiomyopathy, suggestive of isolated LV fibrosis (Figure 2). Moreover, the familial history revealed in patient III.7 an SCD at the age of 18.

Figure 1 Pedigrees of the six families.

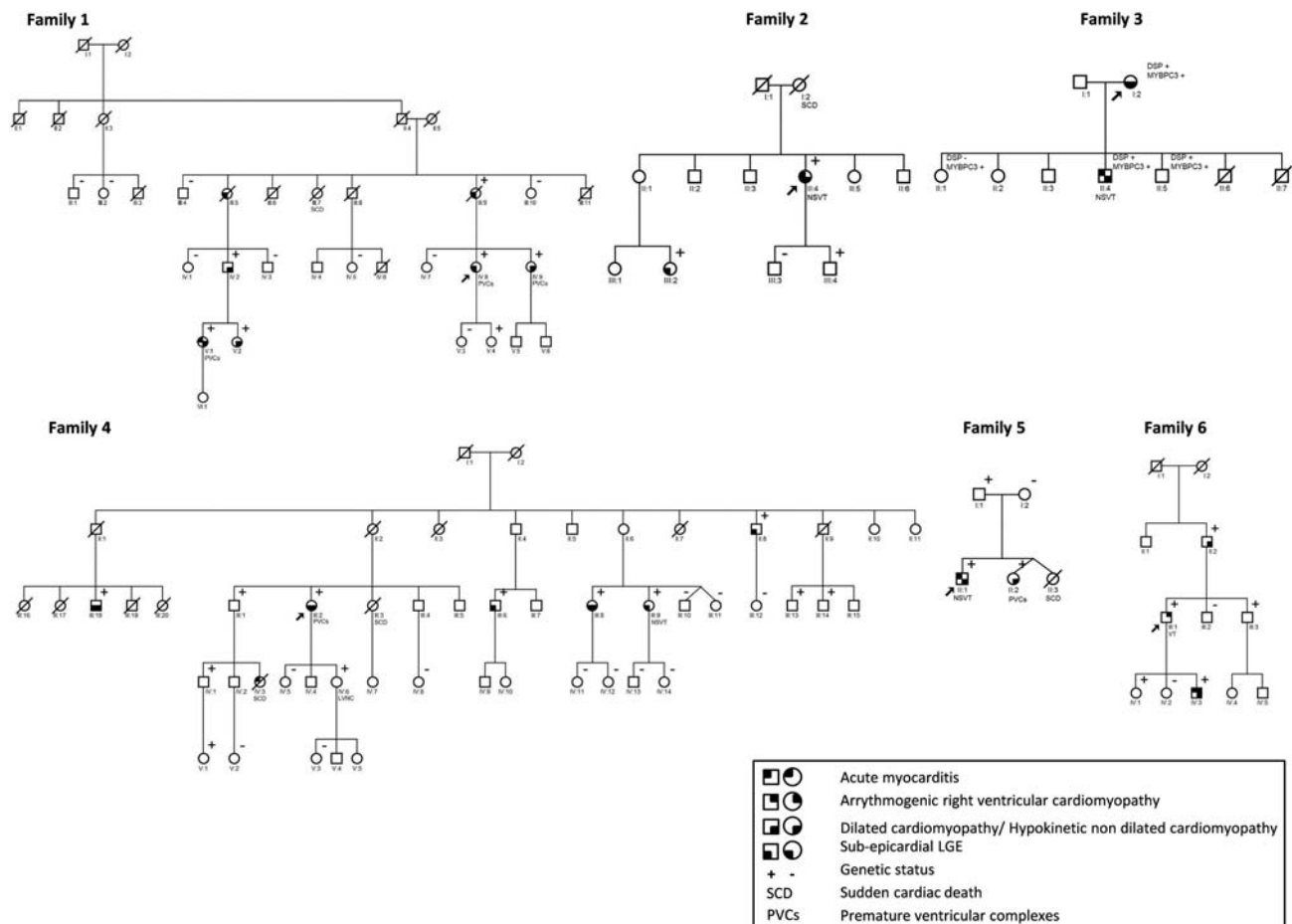


Table 1 Clinical, genetic, and cardiac magnetic resonance tissue characterization findings of the genetic variant carriers and the decedents from sudden cardiac death or heart failure

| Mutation | | Age at first symptoms (years) | | | Age (years) | | | Age at first symptoms (years) | | | CMR Lake Louise Criteria for myocardial inflammation ^{a,b} | | |
|-----------------|------------|-------------------------------|-------------------------------|--------|-------------------|-----|-------------------------|--|------------|--------------------|---|--|--|
| Gene | Zygoty | Age (years) | Age at first symptoms (years) | Gender | Acute myocarditis | SCD | CM phenotype (ESC 2008) | High signal T2 intensity | Hyperaemia | Sub-epicardial LGE | | | |
| Family 1 | | | | | | | | | | | | | |
| III.5 | Unknown | Deceased | Unknown | F | No | No | DCM | | | | | | |
| III.7 | Unknown | Deceased | 18 | F | No | Yes | Unknown | | | | | | |
| III.9 | Het | 72 | 60 | F | No | No | DCM | | | | | | |
| IV.2 | Het | 57 | Asymptomatic | M | No | No | No | No | No | Yes | | | |
| IV.8 | Het | 45 | 34 | F | No | No | HND | Tissue characterization sequences were not analysable owing to ICD artefacts | | | | | |
| IV.9 | Het | 42 | 41 | F | No | No | No | No | No | Yes | | | |
| V.1 | Het | 26 | 19 | F | Yes | No | No | No | No | Yes | | | |
| V.2 | Het | 18 | Asymptomatic | F | No | No | No | No | No | Yes | | | |
| V.4 | Het | 15 | Asymptomatic | F | No | No | No | No | No | Yes | | | |
| Family 2 | | | | | | | | | | | | | |
| I.2 | Unknown | Deceased | 39 | F | No | Yes | Unknown | | | | | | |
| II.4 | Het | 46 | 41 | F | Yes | No | DCM | Yes | No | Yes | | | |
| III.2 | Het | 26 | 20 | F | No | No | DCM | | | | | | |
| III.4 | Het | 18 | Asymptomatic | M | No | No | No | No | No | No | | | |
| Family 3 | | | | | | | | | | | | | |
| I.2 | DSP/MYBPC3 | 60 | 47 | F | No | No | DCM | Yes | No | Yes | | | |
| II.1 | MYBPC3 | 37 | Asymptomatic | F | No | No | No | No | No | No | | | |
| II.4 | DSP/MYBPC3 | 23 | 17 | M | Yes | No | No | Yes | Yes | Yes | | | |
| II.5 | DSP/MYBPC3 | 16 | Asymptomatic | M | No | No | No | No | No | Yes | | | |
| Family 4 | | | | | | | | | | | | | |
| II.8 | DSP | 82 | 74 | M | No | No | DCM | No | No | Yes | | | |
| III.1 | DSP | 75 | Asymptomatic | M | No | No | No | No | No | Yes | | | |
| III.2 | DSP | 69 | 65 | F | No | No | DCM | No | No | Yes | | | |
| III.3 | Unknown | Deceased | Unknown | F | No | Yes | Unknown | | | | | | |
| III.6 | DSP | 69 | 64 | H | No | No | DCM | No | No | No | | | |
| III.8 | DSP | 63 | 58 | F | No | No | DCM | No | No | Yes | | | |
| III.9 | DSP | 61 | 48 | F | No | No | DCM | No | No | No | | | |
| III.13 | DSP | 42 | Asymptomatic | M | No | No | No | No | No | No | | | |
| III.14 | DSP | 52 | Asymptomatic | M | No | No | No | No | No | No | | | |
| III.18 | DSP | 70 | 69 | M | No | No | HND | No | No | Yes | | | |
| IV.1 | DSP | 55 | Asymptomatic | M | No | No | No | No | No | No | | | |
| IV.3 | Unknown | Deceased | 22 | F | Yes | Yes | Unknown | No | No | No | | | |
| IV.6 | DSP | 39 | Asymptomatic | F | No | No | LVNC | No | No | No | | | |
| V.1 | DSP | 31 | Asymptomatic | F | No | No | No | No | No | No | | | |
| Family 5 | | | | | | | | | | | | | |
| I.1 | DSP | 51 | Asymptomatic | H | No | No | No | No | No | No | | | |
| II.1 | DSP | 18 | 15 | H | Yes | No | No | Yes | No | Yes | | | |
| II.2 | DSP | 16 | Asymptomatic | F | No | No | No | No | No | Yes | | | |
| II.3 | Unknown | Deceased | 12 | F | No | Yes | Unknown | | | | | | |

(Continues)

Table 1 (continued)

| Mutation | | Age at first symptoms (years) | Age (years) | Gender | Acute myocarditis | SCD | CM phenotype (ESC 2008) | CMR Lake Louise Criteria for myocardial inflammation ^{a,b} | | |
|----------|--------|-------------------------------|-------------|--------------|-------------------|-----|-------------------------|---|------------|--------------------|
| Gene | Zygoty | | | | | | | High signal T2 intensity | Hyperaemia | Sub-epicardial LGE |
| Family 6 | | | | | | | | | | |
| II.2 | DSG2 | Het | 83 | Asymptomatic | M | No | No | No | No | Yes |
| III.1 | DSG2 | Het | 51 | 48 | M | No | ARVC | No | No | No |
| III.3 | DSG2 | Het | 43 | Asymptomatic | M | No | No | No | No | No |
| IV.1 | DSG2 | Het | 21 | Asymptomatic | F | No | No | No | No | Yes |
| IV.3 | DSG2 | Het | 14 | 10 | H | Yes | ARVC | Yes | Yes | Yes |

-, normal; ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; Het, heterozygous; HNDCM, hypokinetic non-dilated cardiomyopathy; ICD, implantable cardiac defibrillator; LGE, late gadolinium enhancement; SCD, sudden cardiac death.

^aInflammation assessed over the presence of ≥ 3 Lake Louise criteria (oedema, hyperaemia, and/or sub-epicardial or intra-myocardial late gadolinium enhancement).

^bEmpty lines mean that CMR was not performed.

Family 2 (pathogenic variant in desmoplakin c.1865del)

A 41-year-old woman (II.4), whose mother (I.2) died suddenly at the age of 39 and whose niece (III.2) was transplanted for an advanced heart failure due to DCM, was diagnosed with AMC after an episode of chest pain associated with a rise of troponin and T-wave inversion in V5–V6. CMR revealed the presence of myocardial inflammation criteria, confirming AMC (Figure 3). She progressed towards a DCM phenotype, and follow-up CMR revealed persistent sub-epicardial circumferential LGE without inflammation. Genetic analysis identified a mutation in DSP gene in patients II.4 and III.2. Familial screening identified a mutation in her asymptomatic 18-year-old son (III.4) with a normal CMR, without inflammation nor LGE.

Family 3 (variants of uncertain significance in desmoplakin c.1396C>T and MYBPC3 c.1153G>A)

The index patient was a 57-year-old woman (I.2) diagnosed with a DCM and T-wave inversion from V3 to V6 on the ECG. CMR revealed the presence of sub-epicardial circumferential LGE and T2 myocardial enhancement suggesting associated oedema. Her son (II.4) had been hospitalized 2 years before for an AMC with episodes of NSVT. CMR at this time showed sub-epicardial inferior and inferoseptal LGE and the presence of criteria for myocardial inflammation but no additional cardiomyopathy phenotype (Figure 4). The subsequent CMR performed 3 years later showed persistence of LGE without inflammation, suggestive of LV fibrosis. Genetic analysis of both patients revealed a digenic pattern with two VUS in DSP and MYBPC3 genes. Familial screening identified the two variants in another son (II.5), asymptomatic, without cardiomyopathy phenotype on echocardiography and ECG. The CMR was not performed owing to patient refusal. One of the index case's daughters was also explored (II.1). She only carried the MYBPC3 VUS and not the DSP one and was asymptomatic, without any cardiac abnormalities including normal CMR. We hypothesized that the family phenotype was mainly driven by the DSP VUS whose pathogenicity emerged in case of digenic pattern associated with MYBPC3 VUS.

Family 4 (pathogenic variant in desmoplakin c.2610del)

The index patient was a 65-year-old woman (III.2) diagnosed with a DCM phenotype, whose niece (IV.3) died suddenly at the age of 22, with an AMC attested by post-mortem autopsy. Patient III.2's ECG showed T-wave inversion from V4

Table 2 Cardiac magnetic resonance and electrocardiogram criteria for arrhythmogenic cardiomyopathy in desmosomal variant carriers

| Patient | ARVC Task Force criteria | | | | | | Additional ALVC criteria | | | | |
|-----------------|---|---------------------------------|----------|--------|-----------------------|---|--------------------------|------------------------------|----------|--|---|
| | Regional RV wall motion abnormalities | RV volumes (ml/m ²) | RVEF (%) | RV LGE | ECG: T-wave inversion | Major depolarization conduction abnormalities | Ventricular arrhythmias | LV wall motion abnormalities | LVEF (%) | LV LGE | ECG criteria: low QRS voltage in limb leads and inverted T-waves in the inferolateral leads |
| Family 1 | | | | | | | | | | | |
| III.9 | No | 61 | 51 | No | No | No | No | No | 64 | Sub-epicardial—anterior, inferior, inferior lateral | No (LBBB) |
| IV.2 | RV volume, function, and LGE were not analysable owing to LCD artefacts, but visual assessment showed no significant abnormality, as well as echocardiography | 90 | 45 | No | No | No | PVCs (minor) | Yes | 45 | LGE sequences were not analysable owing to LCD artefacts | Yes |
| IV.8 | No | 61 | 62 | No | No | No | PVCs (minor) | No | 54 | Sub-epicardial—lateral, inferior septal, anterior septal | No |
| IV.9 | No | 88 | 46 | Yes | V1–V2 (minor) | No | No | No | 66 | Sub-epicardial—circumferential | No |
| V.1 | No | 74 | 52 | No | V5–V6 (minor) | No | NSVT | Yes | 30 | Sub-epicardial—circumferential | Yes |
| V.2 | No | 105 | 55 | No | NA | NA | NA | No | 62 | No | NA |
| V.4 | No | 73 | 45 | No | V3–V6 (minor) | No | No | Yes | 39 | Sub-epicardial—circumferential | Yes |
| Family 2 | | | | | | | | | | | |
| II.4 | No | 91 | 63 | No | No | No | NSVT | No | 58 | Sub-epicardial—inferior, inferior septal | No |
| III.2 | No | 94 | 60 | No | No | No | No | Yes | 25 | Intra-myocardial—circumferential | No |
| III.4 | No | 76 | 61 | No | No | No | No | No | 64 | Intra-myocardial, septal | No |
| Family 3 | | | | | | | | | | | |
| I.2 | No | <100 | >40 | No | V4–V6 (minor) | No | PVCs (minor) | Yes | 28 | Sub-epicardial—circumferential | Yes |
| II.4 | No | 87 | 31 | No | V4–V6 (minor) | No | No | Yes | 21 | No | No |
| II.5 | No | 58 | 42 | No | V4–V6 (minor) | No | No | Yes | 41 | Sub-epicardial—lateral | Yes |
| Family 4 | | | | | | | | | | | |
| III.8 | No | <100 | >40 | No | V4–V6 (minor) | No | NSVT | Yes | 40 | No | Yes |
| III.9 | No | 90 | 51 | No | V1 | No | No | No | 57 | No | No |
| III.13 | No | 126 | 58 | No | No | No | No | No | 58 | No | No |
| III.14 | No | Yes | Yes | No | V5–V6 | No | Yes | Yes | 45 | Yes | Yes |

(Continues)

Table 2 (continued)

| | | ARVC Task Force criteria | | | | | Additional ALVC criteria | | | | |
|---------------------------------------|--|--------------------------|--------|-----------------------|---|--------------------------------|------------------------------|----------|---|---|--|
| Regional RV wall motion abnormalities | RV volumes (ml/m ²) | RVEF (%) | RV LGE | ECG: T-wave inversion | Major depolarization conduction abnormalities | Ventricular arrhythmias | LV wall motion abnormalities | LVEF (%) | LV LGE | ECG criteria: low QRS voltage in limb leads and inverted T-waves in the inferolateral leads | |
| | RV volume and function not analysable by CMR owing to PVCs, normal diameters, and function at echocardiography | | | | | No VT or NSVT, Holter not done | | | Sub-epicardial—anterior lateral, inferior lateral, inferior | | |
| IV.1 | 144 | 54 | No | V4–V6 (minor) | No | No | No | 60 | No | Yes | |
| IV.6 | 87 | 64 | No | V1 | No | No | No | 69 | No | No | |
| V.1 | | | No | V1 | No | No | No | | | No | |
| Family 5 | | | | | | | | | | | |
| I.1 | <100 | >40 | No | No | No | No | No | 56 | No | No | |
| II.1 | No dilated | 50 | No | No | No | NSVT | Yes | 55 | Sub-epicardial—circumferential | No | |
| II.2 | No dilated | 52 | No | No | No | PVCs (minor) | No | 60 | Sub-epicardial—circumferential | No | |
| Family 6 | | | | | | | | | | | |
| II.2 | 88 | 53 | No | V1 | No | No | No | 55 | Intra-myocardial—septal | No | |
| III.1 | 76 | 41 | No | V1 | Late potentials (minor) | VT (major criteria) | No | 61 | No | No | |
| III.3 | 72 | 44 | No | V1 | No | No | No | 55 | No | No | |
| IV.1 | 90 | 52 | No | No | No | No | No | 58 | Sub-epicardial—inferior, lateral | No | |
| IV.3 | 101 (minor) | 52 | No | V1–V2 (minor) | No | No | No | 66 | Sub-epicardial—lateral | No | |

Empty lines mean that CMR was not performed. ALVC, arrhythmic left ventricular cardiomyopathy; ARVC, arrhythmic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; ICD, implantable cardiac defibrillator; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; NA, data not available; NSVT, non-sustained ventricular tachycardia (Holter); PVCs, frequent premature ventricular complexes > 500 per 24 h (Holter); RV, right ventricle; RVEF, right ventricular ejection fraction; VT, sustained ventricular tachycardia.

Table 3 Clinical and cardiac magnetic resonance characteristics of subjects with acute myocarditis

| Patient | Age (years) | Clinical presentation | Ventricular arrhythmias | Transient ST segment changes | Troponin peak | CMR | | |
|------------------------------------|-------------|-----------------------|-------------------------|--|---|-------------------------------------|---|--|
| | | | | | | T2 Hypersignal | LGE | ARVC CMR criteria |
| V.1 (Family 1) | 19 | Infarct-like | No | No | 29 µg/L (no high sensitivity troponin T, normal upper limit value 0.03) | Sub-epicardial (septal) | Sub-epicardial—circumferential | No |
| II.4 (Family 2) | 41 | Infarct-like | NSVT | Yes (transient ST segment elevation in apicolateral leads) | 892 µg/L (high sensitivity troponin T, normal upper limit value 14) | Sub-epicardial—circumferential | Sub-epicardial—circumferential | No |
| II.4 (Family 3) | 17 | Infarct-like | PVC | Yes (transient ST segment elevation in inferior leads) | 765 µg/L (high sensitivity troponin T, normal upper limit value 14) | Transmural (inferior, inferoseptal) | Sub-epicardial (inferior, inferoseptal) | No |
| IV.3 (Family 4) II.1 (Family 5) | 22 15 | SCD Infarct-like | Unknown NSVT | No | 8379 µg/L (high sensitivity troponin T, normal upper limit value 14) | Sub-epicardial—Circumferential | Sub-epicardial—Circumferential | No |
| IV.3 (Family 6) | 9 | Infarct-like | No | Yes (transient ST segment elevation in inferior leads) | 1156 µg/L (high sensitivity troponin T, normal upper limit value 14) | Sub-epicardial (inferior) | Sub-epicardial (inferior) | No (ARVC phenotype appeared 4 years later) |

ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; NSVT, non-sustained ventricular tachycardia; PVCs, frequent premature ventricular complexes > 500 per 24 h; SCD, sudden cardiac death.

to V6. ECG monitoring revealed frequent PVCs. CMR showed sub-epicardial circumferential LV LGE and genetic analysis identified a mutation in DSP. Familial screening identified a mutation in 11 relatives, among whom five had a phenotype of DCM or HNDCM (two with sub-epicardial LGE on CMR). One had an LVNC phenotype. Familial history revealed an SCD in patient III.3.

Family 5 (pathogenic variant in desmoplakin c.3211C>T)

A 15-year-old male patient (II.1), whose sister (II.3) died suddenly during exercise when she was 12, was diagnosed with AMC after an episode of chest pain with a rise of troponin. CMR revealed myocardial inflammation criteria with sub-epicardial circumferential LGE of the LV but no signs of additional cardiomyopathy phenotype. The ECG monitoring revealed episodes of NSVT. Genetic testing identified a mutation in DSP in patient II.1. Familial screening identified the mutation in his father (I.1), and his sister (II.2), both of them being asymptomatic. Clinical evaluation of the father showed no cardiomyopathy, and CMR did not show any signs of inflammation or LGE. The ECG and echocardiography showed no signs of cardiomyopathy in his sister II.2, twin of the deceased subject II.3. However, CMR revealed the presence of circumferential sub-epicardial LGE, without inflammation.

Family 6 (pathogenic variant in desmoglein 2 c.146G>A)

The index patient (III.1) was diagnosed with ARVC according to Task Force criteria after an episode of sustained VT. Genetic analysis revealed a mutation in DSG2 gene. His 14-year-old son (IV.3) presented 3 years before two episodes of chest pain with a rise in troponin. He experienced a recurrent episode of chest pain and troponin rise suggestive of an episode of AMC. CMR revealed myocardial inflammation with sub-epicardial lateral LGE of the LV confirming AMC. Genetic analysis identified the DSG2 familial mutation. After this episode, his ECG has been modified with a T-wave inversion in V1–V3, and a follow-up CMR 3 months after AMC revealed a shift towards ARVC imaging phenotype, according to Task Force criteria. LV LGE persisted without residual inflammation. Familial screening identified the mutation in three asymptomatic relatives. None of them had a phenotype of DCM or ARVC, one (IV.1) had sub-epicardial LGE of the inferior and inferolateral wall of the LV, and one (II.2) had intra-myocardial septal LGE on CMR.

Figure 2 Different DSP-related ALVC phenotypes observed in a family. (A) Family 1 pedigree. The red circle indicates the subject who had an acute myocarditis, blue squares outline individuals with a DCM or HNDCM phenotype, red squares for individuals with a history of sudden cardiac death, and green squares for individuals with isolated LGE on CMR without any other structural or functional abnormality. Red arrows indicate individuals with frequent PVC. (B) Twelve-lead ECG showing T-waves inversion in V4 to V6 and low QRS voltage in the index patient (IV.8) of the family with a phenotype mimicking HNDCM. (C) CMR findings showing focal myocardial oedema (a) and LGE (b) outlined by blue arrows in subject V.1 at the time of acute myocarditis, oedema regression (c), and persistent LGE (d) at follow-up. Similar LGE pattern in subjects IV.9 (e) and V.2 (f) without any other structural abnormality. ALVC, arrhythmogenic left ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; DSP, desmoplakin; ECG, electrocardiogram; HNDCM, hypokinetic non-dilated cardiomyopathy; LGE, late gadolinium enhancement; LGE, late gadolinium enhancement; PVC, premature ventricular complex.

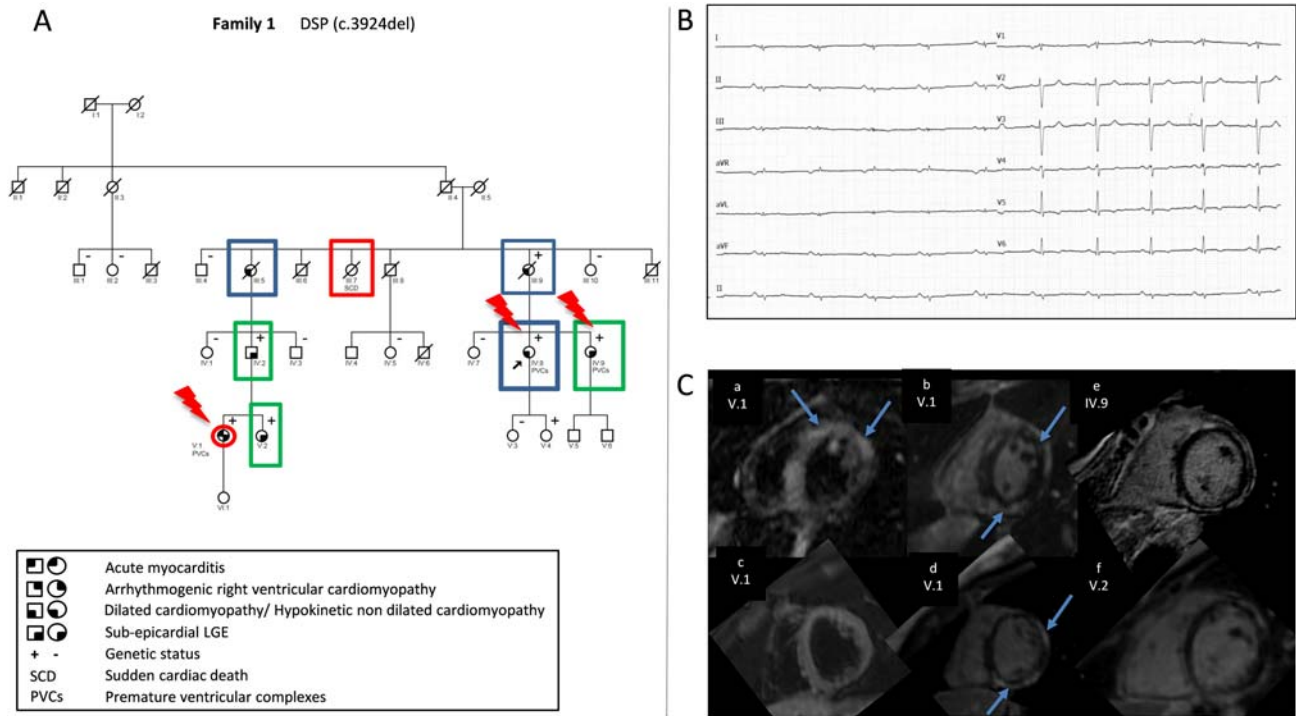


Figure 3 CMR findings in subject II.4 from Family 2. (A) Short-axis slice T2-weighted images at the time of acute myocarditis showing focal hypersignals on the left ventricle in favour of myocardial oedema (blue arrows). (B) LGE sequences at the same time showing a circumferential midwall and sub-epicardial ring-like LGE pattern. (C) Follow-up CMR 3 months after acute myocarditis showing persistent LGE at the site of initial T2 signals. At this time, there was no LV T2 hypersignal and LVEF dropped. CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction.

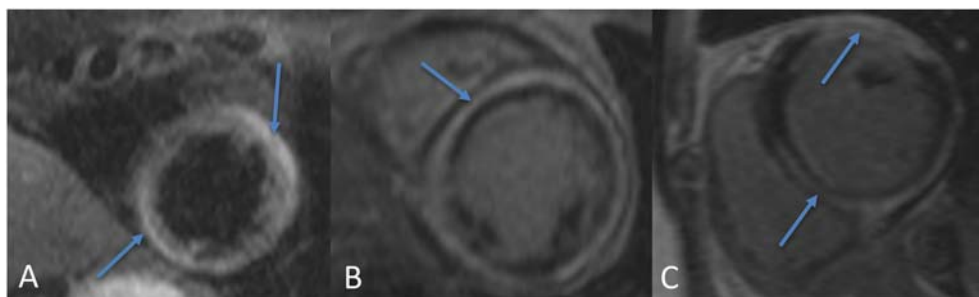
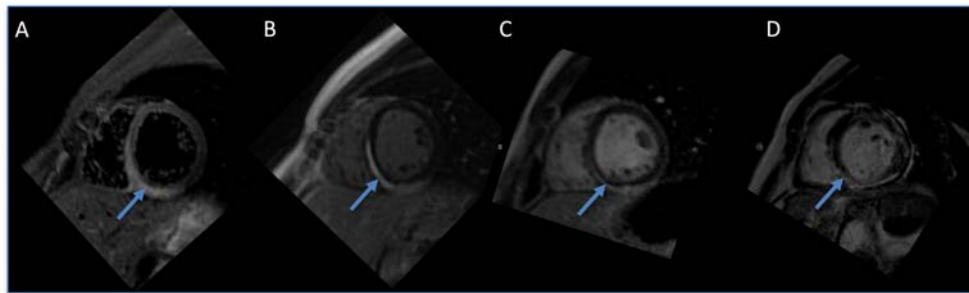


Figure 4 CMR findings in subjects II.4 (A–C) and I.2 (D) from Family 3. (A) and (B) respectively show T2 hypersignals and LGE of LV inferior and inferoseptal walls at the time of acute myocarditis in subject II.4. (C) Persistence of LGE at the same sites despite no residual T2 hypersignals at 2 years' follow-up. (D) Similar LGE lesions in her mother (subject I.2) with a DCM phenotype and similar genetic status. CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular.



Data summary from all pedigrees

Phenotypes observed in subjects with desmosomal genetic variants are summarized in *Table 4*. In the five families identified with a DSP variant, the association of one case of AMC with one case of CM or SCD in the family triggered genetic testing. None of the 28 DSP variant carriers had imaging criteria for an ARVC phenotype according to the 2010 Task Force.

Discussion

We prospectively identified six families, each presenting with one case of AMC and at least one case of cardiomyopathy or SCD in the family history. Genetic analysis revealed a variant in desmosomal proteins genes in all the probands

Table 4 Data summary from the desmosomal genes variant carriers

| | Family 1–5 (n = 28) | Family 6 (n = 5) |
|--|------------------------|---------------------|
| Involved gene | DSP | DSG2 |
| Acute myocarditis | 4/28 (14%) | 1/5 (20%) |
| Arrhythmias (VT, NSVT, frequent PVCs) | 9/28 (32%) | 1/5 (20%) |
| T-wave inversion in V5, V6 ± V4, I and aVL | 8/28 (28.5%) | 0/5 (0%) |
| Cardiomyopathy phenotype: | | |
| Imaging criteria for ARVC | 0/28 (0%) | 2/5 (40%) |
| DCM—HNDCM | 11/28 (39%) | 0/5 (0%) |
| No AMC, no CM | 13/28 (46%) | 3/5 (60%) |
| Isolated LV LGE | 5/13 (38%) | 2/3 (67%) |
| Healthy phenotype | 8/13 (62%) | 1/3 (33%) |

AMC, acute myocarditis; ARVC, arrhythmogenic right ventricular cardiomyopathy; CM, cardiomyopathy; DCM, dilated cardiomyopathy; HNDCM, hypokinetic non-dilated cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; NSVT, non-sustained ventricular tachycardia; PVCs, premature ventricular complexes; VT, sustained ventricular tachycardia.

(five in DSP gene and one in DSG2). The analysis of comprehensive pedigrees and management of these families leads to address clinical situations in which considering AMC in the diagnostic workup of inherited cardiomyopathies, and particularly AC, appears critical to accurately detect the disease.

Acute myocarditis as a diagnostic criterion for desmoplakin-related arrhythmogenic left ventricular cardiomyopathy

In five of the six families, the occurrence of a myocarditis, or a familial history of myocarditis, is associated with an apparently isolated DCM or SCD, which triggered genetic testing. A genetic variation in DSP gene was found in all these families (four pathogenic variants and one VUS associated with another VUS in MYBPC3).

None of the probands had a previous diagnosis of ARVC. Among all the DSP variant carriers, 39% presented global LV dysfunction meeting the definition of DCM or HNDCM phenotype. One was diagnosed with an LVNC. Among the 11 patients with a DCM or HNDCM, six out of the nine patients who had a CMR exhibited circumferential or lateral sub-epicardial LGE. Moreover, three relatives were found to have died from SCD, and 32% of the mutation carriers experienced frequent ventricular arrhythmias (four with a cardiomyopathy phenotype, three with AMC without cardiomyopathy phenotype, and two with isolated LGE); 28.5% presented T-wave inversion beyond V2 on ECG. This phenotype is consistent with previous description of DSP mutation-related cardiomyopathy, with frequent LV involvement and a high prevalence of ventricular arrhythmias with high occurrence of SCD as the initial event.¹⁶ It corresponds to arrhythmogenic left ventricular cardiomyopathy (ALVC) phenotype, with unexplained T-wave inversion in V5, V6 ± V4, I and aVL, ventricular arrhythmias, mild LV dilation, and/or systolic impairment¹⁷ but frequent LV wall

motion abnormalities and extensive LV LGE on CMR with a sub-epicardial ring-like pattern, particularly reported in DSP and filamin C genotypes,¹⁸ which correlates with the presence of fibro-fatty replacement on histology.¹⁹ Phenotypic descriptions of ARVC with LV involvement and isolated ALVC led to introduce the terminology of arrhythmogenic cardiomyopathy to include both RV and LV in the spectrum of the disease,^{3,7} while current European Society of Cardiology classification of the cardiomyopathies and current diagnostic Task Force criteria still only address the classical ARVC phenotype with dominant RV involvement.^{8,10} DSP-related ALVC is reputed to frequently escape the classical diagnostic criteria for ARVC.¹⁶ In fact, in our population of DSP variant carriers, a strict and retrospective application of the 2010 ARVC Task Force Criteria that includes the identification of a pathogenic mutation as a major criterion⁸ leads to classify only four subjects with a definite diagnosis of ARVC based on the presence of two additional minor criteria. Those minor criteria are consistently represented by repolarization abnormalities in V4 to V6 leads that are related to LV involvement, plus ventricular arrhythmias. Of note, none of these subjects, and none of all the DSP variant carriers, have any sufficient RV dilatation or functional abnormalities to qualify for a RV morphologic major or minor criteria. Only one had RV LGE as a sign of RV involvement. These observations reinforce the importance of the recent critical reappraisal of the 2010 Task Force criteria by an international experts panel, which highlight their potential limitations.²⁰ They identify potential areas of improvement among which the issue of the diagnosis of left-sided phenotypes, that, in case of the absence of clinically detectable RV involvement, may be supported by the evidence of RV or LV LGE on contrast-enhanced CMR or by the demonstration of a pathogenic mutation of ARVC-related genes. From a clinical point of view, the management of the families depicted in our paper is a practical demonstration of the accuracy of this approach in order to not misdiagnose left-dominant AC.

In addition, the pedigrees and histories of these families, where considering AMC to trigger genetic testing in presence of one case of CM or SCD revealed unknown or misdiagnosed individuals with ALVC, ask the question whether AMC should not be discussed as an additional diagnostic criterion for AC.

Isolated LV fibrosis without any RV or LV functional or volumetric abnormality is not uncommon in AC and can be the only manifestation of the disease before SCD.^{21,22} In our population, among the relatives with a DSP variant identified during familial screening, 13 did not have an AMC history or cardiomyopathy phenotype, but five (38%) were found to have LV sub-epicardial LGE on CMR, suggesting isolated LV fibrosis. Similarly, in the family with DSG2 mutation, two on the three asymptomatic relatives carrying the mutation had isolated LV LGE on CMR. Of note, none

of these seven desmosomal variant carriers with isolated LGE on CMR had T-wave inversion beyond V2 on ECG. Only one was symptomatic (PVCs). This highlights the value of contrast-enhanced CMR in the initial evaluation of ARVC-related gene mutation carriers, even asymptomatic, without structural and functional ventricular abnormalities, in order to detect individuals with at-risk isolated fibrosis.

Acute myocarditis as a 'hot phase' of inherited arrhythmogenic cardiomyopathy with left ventricular involvement

The association between myocarditis and AC has previously been described.^{3,4,23–25} It has been hypothesized that these acute episodes could be part of the natural history of AC, being an active phase of the disease referred as 'hot phase'. Chatterjee *et al.* demonstrated a high prevalence of anti-DSG2 antibodies in ARVC patients cohorts, likely participating to inflammatory phases.²⁶ Another hypothesis is that genetic alteration in the desmosome renders the myocardium more susceptible to viral infection.²⁷ Martins *et al.* described the relationship between myocardial inflammation detected by CMR and ARVC in a paediatric population and showed that AC with both RV and LV involvement can present as recurrent myocarditis-like episodes with evidences of myocardial inflammation, which often lead to disease progression.²⁸ This emphasizes the fact that a diagnosis of an underlying cardiomyopathy such as AC should be considered in the presence of recurrent myocarditis, especially in children. In one of the families we depicted here (Family 6, DSG2 mutation), recurrent AMC was associated with the progression towards ARVC phenotype in one child. LV LGE persisted despite inflammation resolution in favour of associated LV involvement, and familial screening also identified two of the three relatives carrying the mutation having isolated LV LGE without symptoms nor CM phenotype.

The few histologic data obtained in some of our AMC patients have mainly showed no florid inflammation but coexistence of slight inflammatory infiltrates, interstitial fibrosis, and presence of viral genomes without overt systemic viral infection. Myocardial inflammation has been reported in up to 75% of hearts at autopsy,² particularly in DSP-related ARVC.¹⁶ As in our patients, the detection of viral genomes led to consideration of an infective viral cause, but it is most hypothesized that either viruses are innocent bystanders or myocardial cell degeneration may serve as a milieu favouring viral attachment.² Rather than being a continuous process, disease progression in AC may occur through hot phases mediated by myocyte degeneration and loss that trigger an inflammatory response that can mimic clinical presentations of AMC.

In a previous series of seven paediatric cases ranging from 32 months old to 16 years old at the time of onset AMC, genetic testing revealed either homozygosity or compound heterozygosity for genes previously associated with typically dominant genetic cardiomyopathies, mainly AC.⁵ The authors concluded that AMC occurrence was mediated through a recessive autosomal mechanism. In contrast, our patients were adults or young adults when they had their first onset AMC, apart the one with DSG2 mutation, and carried simple heterozygosity for a desmosomal variant. Based on these observations, one can hypothesize that AC hot phases are mediated through several inflammatory mechanisms for a certain amount of myocardial damage that is reached early in case of homozygous or compound heterozygosity for AC-related mutations, but this can occur later in life and be linked to classical presentations of autosomal dominant diseases, as in our population. On the other hand, as we can suspect a role for the digenic pattern with two VUS in DSP and MYBPC3 triggering AC and AMC phenotypes in Family 3, one can ask whether other genetic variations, even of uncertain significance, associated with simple heterozygosity in a desmosomal variant, could contribute to the occurrence of the phenotype in young adult and adult patients.

Considering acute myocarditis in the diagnostic workup of arrhythmogenic cardiomyopathy

Our data reinforce the need to include LV pathological markers in the spectrum of Task Force criteria for the diagnosis of AC, like sub-epicardial LGE pattern on CMR.^{18,20} Among the research priorities of the expert panel report on AC is the determination of the role of myocarditis on disease presentation.⁷ From our results, it is not possible to affirm that all cardiomyopathy populations are more prone to myocarditis than the general population. Nevertheless, the prevalence of clinically overt AMC appears to be particularly high in our desmosomal variant carriers population, ~3/100, in contrast with the usually estimated incidence of myocarditis of one to two per 10 000 per year.²⁹ Thus, AMC occurrence in a familial history with at least one case of CM or unexplained SCD could be a relevant additional criterion for the diagnosis of AC, including ALVC with isolated LV involvement, and genetic testing should be advised in this context. CMR should be performed in asymptomatic variant carriers during familial screening in search of at-risk isolated LV LGE, even when echocardiography and ECG are normal. The question of whether genetic testing should be performed systematically after new onset apparently isolated AMC should be addressed in future studies, but our results underscore the importance of assessing the family pedigree in patients presenting with AMC.

Limitations

We did not perform an EMB in all AMC patients. The biopsy site on the RV side of the septum was not optimal, as the disease mainly involves the LV. Moreover, EMB was performed at the time of AMC in only two patients. For these reasons, we cannot determine if these acute episodes were active phases of the disease as described in AC, or if they were viral AMC episodes promoted by genetic susceptibility to infection for instance. The term of AMC in this paper refers to the clinical presentation of myocardial inflammation confirmed by CMR, without histological confirmation. Four on the five myocarditis subjects were not the index case of the family, so they have only been tested for the familial variant accordingly. It is thus not possible to assess the role of compound heterozygosities in the occurrence of AMC in these patients. Only variant carriers have had a CMR. For that reason, we cannot rule out the presence of isolated LV LGE in asymptomatic relatives without the pathogenic variant. Signal averages ECG have not been done except in Family 6, who had a clear ARVC phenotype and could not be included in the assessment of ARVC Task Force criteria in DSP population.

Conclusions

Considering AMC as an additional diagnostic criterion to help recognize heritable cardiac diseases in case of the association with a familial history of cardiomyopathy or SCD allowed to early diagnose at-risk AC-causing genetic variant carriers with exclusive LV involvement forms, which currently evade ARVC Task Force criteria. In view of our results, AMC should be considered in the diagnostic spectrum of AC, and genetic testing should be advised in patients who experience AMC and have a family history of cardiomyopathy or SCD.

Conflict of interest

J.N.T. reports grants from Novartis, Carmat, and Abbott and personal fees from Novartis, Resmed, Amgen, Bayer, and Abbott. N.P., L.M., F.K., J.M.S., C.T., L.L.G., K.W.F., D.G., T.L.T., E.C., A.T., and V.P. have no conflict of interest to declare.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 panel of the 31 genes analyzed in the study.

Table S2. Rationale for the classification of each genetic variant according to the ACMG classification.**Table S3.** Histologic and virologic data obtained from endomyocardial biopsy or autopsy subjects with acute myocarditis.

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