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Prognostic impact of the findings of the genetic test in left dominant arrhythmogenic cardiomyopathy

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ABSTRACT

Background: The diagnosis of left dominant arrhythmogenic cardiomyopathy (LDAC) is sometimes complex. The Padua group recently published a document with criteria to identify patients with LDAC, requiring a compatible genetic variant for diagnosis. Due to the gaps in the knowledge of the role of genetics in its pathogenesis, our objective is to describe the findings of the genetic test in patients with LDAC in our center and its prognostic impact.

Methods: Single-center prospective cohort study, in which we recruited 77 patients diagnosed with LDAC or biventricular arrhythmogenic cardiomyopathy according to the criteria of Sen-Chowdhry et al.

Results: We obtained a positive result in the genetic test in 53.2 %. The desmoplakin gene was the most affected (16.9 %). The mean value of left ventricular (LV) ejection fraction was 45.6 ± 13.1 %, with no significant differences in the severity of the dysfunction according to genetics ($p = 0.187$). Among the patients with positive genetics there was a greater number of segments in the LV affected by fibrosis ($p = 0.043$). Regarding fatty infiltration in the LV and number of affected segments, there were no significant differences between groups ($p = 0.144$). MACE was recorded in 23 patients (29.9 %). The positive result in the genetic test was not significantly associated with the occurrence of MACE ($p = 0.902$).

Conclusion: In our study, we did not find mutations responsible for the disease in practically half of the cases. Despite the existence of a high proportion of MACE during follow-up, there were no prognostic differences according to the result of the genetic test.

1. Introduction

Arrhythmogenic cardiomyopathy (ACM) is a hereditary disease characterised by the replacement of the myocardium by fibro-fatty tissue, predisposing to the appearance of ventricular arrhythmias and systolic dysfunction [1]. Prior to the introduction of cardiac magnetic resonance (CMR), it was called ACM of the right ventricle (RV) since it showed a predominant involvement of the right side. However, in anatomopathological studies in victims of sudden death and patients who underwent heart transplantation, left ventricular (LV) involvement was observed in 76 % of cases [2]. In addition, CMR studies have consistently shown that LV involvement is identified in more than half of patients [3]. Currently, the broader term of ACM is used, allowing the distinction of three disease patterns: the classic right variant, the biventricular and the left dominant [3].

Increased knowledge of the different presentations of ACM led to a review of the International Task Force Criteria published in 2010, since they did not include variants with left dominant involvement (LDAC) [4]. Sen-Chowdhry et al [5] were the first to define the clinical and genetic profile of patients with LDAC, establishing a series of clinical characteristics that would facilitate their diagnosis. Subsequently, various studies have tried to analyse the clinical and imaging characteristics that define this entity. Motivated by this interest, the Padua group published in 2020 an expert consensus document that provides updated criteria to identify patients with LDAC [6]. The diagnosis of LDAC in the initial stages of the disease can be very complex since,

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usually, there is no significant LV dilation or dysfunction that can be detected with conventional imaging techniques. Recently, our group has described the importance of CMR [7], which has become a fundamental tool for its diagnosis, as is also reflected in the Padua criteria. On the other hand, since LDAC can be confused with entities with similar phenotypes, such as dilated cardiomyopathy, sarcoidosis or myocarditis, the Padua criteria require the presence of a compatible genetic variant to diagnose patterns with exclusive LV involvement.

Most of the initially described ACM-causing genetic variants were found in genes that code for intercellular junction proteins. In the classic right variant, the most frequent are those that affect the desmosome, but variants have also been found in non-desmosome genes, the latter being more common in LDAC [8]. However, although a family history is common in patients with ACM, incomplete penetrance and variable expressivity even within the same family lead us to think that, in addition to the genetic cause, there could be other factors influencing the expression of the ACM disease [9,10].

Despite increasing knowledge regarding the role that genetics plays in the pathogenesis of ACM, we still find gaps in the evidence on how it affects the clinical course and evolution of the disease. The objective of this study is to describe the findings of the genetic test in patients diagnosed with LDAC in our centre, and their possible prognostic impact.

2. Methods

2.1. Patients and study design

This is a single-centre cohort study, in which patients diagnosed with LDAC or biventricular ACM were prospectively recruited from the CMR unit, from January 2010 to December 2020. For inclusion, patients had to present findings compatible with LDAC or biventricular variants according to the criteria of Sen-Chowdhry et al [5] (inversion in the electrocardiogram (ECG) of the T-wave in V4-V6, I and aVL; the presence of ventricular arrhythmias or frequent ventricular extrasystoles (>1% in 24 h) with complete right bundle branch block morphology; the existence of LV dilation or dysfunction detected by echocardiography; a CMR finding of late gadolinium enhancement (LGE) with a characteristic mid-subepicardial distribution; or presence in the endomyocardial biopsy of replacement of myocytes by fibrofatty tissue). Patients had to meet at least two of four criteria, and it was essential to detect characteristic alterations of LDAC in CMR to confirm the diagnosis. None of the patients required endomyocardial biopsy to reach the diagnosis.

Regarding the exclusion criteria, those with ischemic heart disease were not included, either due to a history of acute myocardial infarction or due to presenting a positive ischemia inducibility test in those with clinical symptoms suggestive of coronary ischemia.

All patients initially underwent an ECG, an echocardiogram, 24-hour monitoring with Holter-ECG and a CMR. Subsequently, they were followed up every 6–12 months, depending on the case, by a specific family heart disease unit. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and all patients gave their consent after being informed of the purpose of this study.

2.2. Cardiac magnetic resonance

2.2.1. Image acquisition

A 1.5 T scanner (Intera CV, Philips Medical Systems, Best, The Netherlands) was used in all cases. Patients were monitored with single-lead ECG and pulse oximetry, and images were obtained with ECG synchronisation and apnoea. Short-axis, 2-, 3- and 4-chamber long-axis images were acquired using a standard steady-state free precision technique. LGE images were obtained 10 min after peripheral injection of 0.1 mmol/kg gadobutrol bolus (Gadovist, Bayer Schering Pharma, Berlin, Germany) using a turbo gradient echo sequence. The inversion time was determined individually to abolish the normal myocardial signal. In cases where myocardial thinning was evident on short-axis cine images, T1 fat-saturated and T1 nonfat-saturated were also acquired on that plane.

2.2.2. Image analysis

Image analysis was performed by an experienced CMR radiologist on a workstation provided by the manufacturer (ViewForum version 6.3, Philips Medical Systems). For ventricular volume analysis, the endocardial border was determined at end systole and end diastole in all short axis images. LV end-diastolic and end-systolic volumes, stroke volume, ejection fraction and cardiac output were calculated from short-axis cine sequences (8–12 contiguous slices) using semiautomated segmentation. Volumes were indexed by body surface area. Each segment of the LV was examined to determine the presence of either fatty infiltration or LGE, or both. Data were collected on a circumferential polar plot of the 17 myocardial segments.

2.3. Genetic tests

After receipt of informed consent, blood samples were taken from the peripheral vein, which were sent to and analysed by an external genetic laboratory. In the probands, a panel of cardiomyopathies, arrhythmias and sudden death was requested from the scientific team of Health In Code S.L., which was analysed using the next generation sequencing technique. In family screening, the study of the genetic variant identified in the proband was directly requested. For data analysis, the presence of variants classified in the genetic study as pathogenic and probably pathogenic was established as positive according to the current guidelines of the *American College of Medical Genetics and Genomics*. Variants of uncertain significance from patients who presented a compatible clinical context and demonstrated familial cosegregation were also included as positive. In studies that detect more than one genetic variant in the same patient, we do not classify them as independent genes, but include a new variable to consider their overall effect.

2.4. Study evaluation criteria

The primary objective of the study was to evaluate the association of a positive result in the genetic test with a greater occurrence of major adverse cardiovascular events (MACE) during follow-up, defined as sudden death (SC), sustained ventricular arrhythmias and heart transplantation.

The secondary objectives were the study of the association of genetics with other phenotypic variables (degree of fibrosis, fatty infiltration, volumes and systolic function of both ventricles) and with the presence of arrhythmic events (and the corresponding need for implantable cardioverter-defibrillator (ICD) and administration of appropriate therapies by the ICD).

2.5. Statistical analysis

The normality of continuous variables was analysed using the Kolmogorov-Smirnov test. Quantitative variables are presented as mean and standard deviation. For continuous variables, T-Student test or Mann-Whitney test were used, as appropriate. Discrete variables are presented as relative frequencies and were compared using the Chi-square test or Fisher's exact test, as appropriate. A value of $p < 0.05$ was considered statistically significant. Analyses were performed with SPSS (version 27).

3. Results

Of the 105 patients with LDAC or biventricular ACM recruited in our hospital from January 2010 to December 2020, the genetic study was performed on 77 of them. The remaining 28 patients were not included in our study because the genetic test was not requested due to different

reasons (doctor's or patient's decision, or due to a fatal arrhythmic event).

3.1. Genetic study and baseline characteristics

Regarding the 77 patients included in the study, a positive result was obtained in the genetic test in 41 patients (53.2 %), of whom 10.4 % presented more than one variant in different genes that cause LDAC. Variants of uncertain significance were detected in 8 patients and pathogenic or probably pathogenic variants were detected in 33 patients. Fig. 1 illustrates the distribution based on the genetic variant detected. Detailed information on the variants identified in patients with a positive genetic test is provided in *Supplementary* Table 1. The desmoplakin gene was the most affected, with genetic variants being found in 16.9 % of the patients. The second most frequent was the desmoglein-2 gene, which was affected in 5.2 %.

The baseline characteristics are described in Table 1. The mean age at diagnosis was 54.5 ± 13.7 years. The proportion of males in the group with negative genetics was 77.8 %, which was significantly higher than in the group with positive genetics, 53.7 %; (p = 0.027). In the group with negative genetics, 83.3 % of the patients were identified as probands, with the remaining cases being detected through family screening (5 patients due to a family history of LDAC, and 1 patient due to a study of SD in a first-degree relative). The proportion of probands was lower among the patients with a positive result in the genetic test (70.7 %) compared to patients with a negative genetic result, with family screening detecting 12 patients (11 of them due to a family history of LDAC, and 1 due to SD in a first-degree relative). However, this difference was not statistically significant (p = 0.192). A total of 11 families were included in the study. The presence of a family history of LDAC was significantly higher among patients with a positive genetic test compared to patients with a negative genetic result (p = 0.040).

3.2. Phenotypic findings

The mean value of LV ejection fraction (LVEF) at diagnosis was 45.8 ± 13.1 %. The severity of LVEF was evaluated following the current classification published by the *European Society of Cardiology* in 2021 in heart failure guidelines (normal LV function: ≥50 %; midly depressed: 41–49 %; depressed: ≤40 %) [11]. To consider LV dilation, an LVEDV index value ≥ 90 ml/m2 was established. In the analysis, we did not obtain statistically significant differences in the severity of LV dysfunction based on genetics (p = 0.782). There were also no significant differences observed according to the result of the genetic test in relation to LV volumes (p = 0.891).

Regarding the RV, we consider dilation or dysfunction based on the criteria established by Maceira *et at* [12]. No significant differences were observed according to the result of the genetic test in relation to RV volume and ventricular function. In both groups, a similar percentage of cases with RV involvement was observed, either due to the presence of sacculations, systolic dysfunction or ventricular dilation, and these cases were considered biventricular variants (Table 2).

Table 1
Baseline characteristics.

Variable	Total (n = 77)	Negative Genetics (n = 36)	Positive Genetics (n = 41)	*p*
Age at diagnosis (y)	54.5 (SD 13.7)	54.8 (SD 11.2)	54.24 (SD 15.7)	0.873
Men	50 (64.9 %)	28 (77.8 %)	22 (53.7 %)	0.027
Body mass index (kg/m2)	27.0 (SD 4.9)	26.5 (SD 4.8)	27.5 (SD 4.9)	0.388
Hipertension	20 (26.0 %)	11 (30.6 %)	9 (22.0 %)	0.390
Diabetes	6 (7.8 %)	3 (8.3 %)	3 (5.3 %)	0.868
Index case	59 (76.6 %)	30 (83.3 %)	29 (70.7 %)	0.192
Family history of LDAC	19 (24.7 %)	5 (13.9 %)	14 (34.1 %)	0.040
Family history of SCD	20 (26.0 %)	7 (19.4 %)	13 (31.7 %)	0.221

LDAC: left dominant arrhythmogenic cardiomyophaty. SCD: sudden cardiac death.
Data are expressed as N° (%) or mean ± standard deviation (SD), as appropriate.

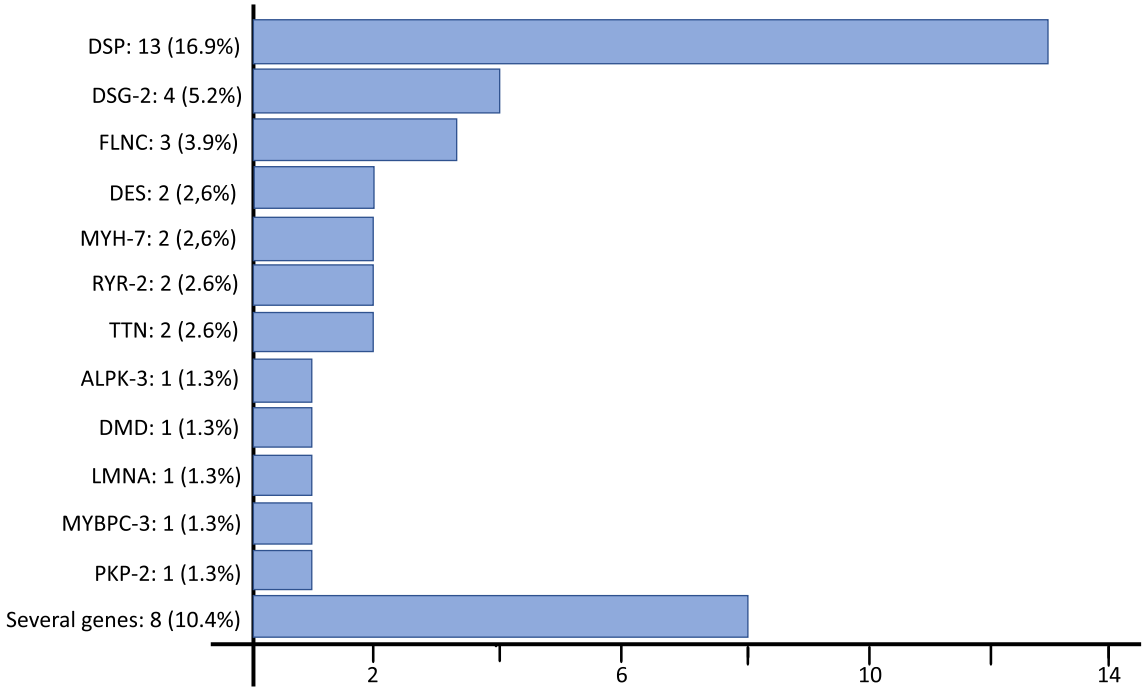

Fig. 1. Results of the genetic test. ALPK-3: alpha kinase-3; DES: desmin; DMD: dystrophin; DSG2: desmoglein-2; DSP: desmoplakin; FLNC: filamin-C; LMNA: lamina; MYBPC3: myosin-binding protein-C3; MYH7: myosin-7; PKP2: plakofilin-2; RYR2: ryanodine-2; TTN: titin. The data is expressed as N° (%).

Table 2
Phenotypic findings based on the result of the genetic test.

Variable	Total (n = 77)	Negative Genetics (n = 36)	Positive Genetics (n = 41)	*p*
T-wave inversion V4-V6, I, aVL	36 (46.8 %)	19 (52.8 %)	17 (41.5 %)	0.321
CMR findings				
Presence of fibrosis in LV	77 (100 %)	36 (100 %)	41 (100 %)	
Number of LV segments affected by fibrosis	10.0 (SD 5.2)	8.7 (SD 4.6)	11.0 (SD 5.4)	0.043
Fibrosis location				
Anterolateral wall	68 (88.3 %)	30 (83.3 %)	38 (92.7 %)	0.203
Inferolateral wall	72 (93.5 %)	34 (94.4 %)	38 (92.7 %)	0.758
Anterior wall	49 (63.6 %)	20 (55.6 %)	29 (70.7 %)	0.167
Inferior wall	67 (87.0 %)	31 (86.1 %)	36 (87.8 %)	0.825
IVS	45 (58.4 %)	18 (50.0 %)	27 (65.9 %)	0.159
Presence of fatty infiltration in LV	67 (87.0 %)	33 (91.7 %)	34 (82.9 %)	0.254
Number of LV segments with fatty infiltration	6.7 (SD 4.9)	5.8 (SD 4.1)	7.4 (SD 5.4)	0.144
Fatty infiltration location				
Anterolateral wall	58 (75.3 %)	25 (69.4 %)	33 (80.5 %)	0.262
Inferolateral wall	61 (79.2 %)	30 (83.3 %)	31 (75.6 %)	0.405
Anterior wall	38 (49.4 %)	16 (44.4 %)	22 (53.7 %)	0.420
Inferior wall	52 (67.5 %)	23 (63.9 %)	29 (70.7 %)	0.522
IVS	20 (26.0 %)	6 (16.7 %)	14 (34.1 %)	0.081
LVEDV index (mL/m2)	104.3 (SD 38.2)	103.5 (SD 32.5)	105.0 (SD 43.0)	0.860
LV dilation	40 (51.9 %)	19 (52.8 %)	21 (51.2 %)	0.891
LV segmental contractility abnormalities	46 (59.7 %)	23 (63.9 %)	23 (56.1 %)	0.487
LVEF (%)	45.8 (SD 13.1)	47.8 (SD 11.4)	44.1 (SD 11.4)	0.187
LVEF severity				0.782
Normal (≥50 %)	31 (40.3 %)	16 (44.4 %)	15 (36.6 %)	
Midly depressed (41–49 %)	23 (29.9 %)	10 (27.8 %)	13 (31.7 %)	
Depressed (≤40 %)	23 (29.9 %)	10 (27.8 %)	13 (31.7 %)	
RV involvement	22 (28.6 %)	11 (30.6 %)	11 (26.8 %)	0.718
RVEDV index (mL/m2)	153.9 (SD 51.6)	163.0 (SD 53.4)	145.9 (SD 49.2)	0.152
RV dilation	17 (22.1 %)	9 (25.0 %)	8 (19.5 %)	0.562
RV sacculations	14 (18.2 %)	7 (19.4 %)	7 (17.1 %)	0.788
RVEF (%)	55.0 (SD 13.1)	54.8 (SD 13.4)	55.1 (SD 12.9)	0.928

CMR: cardiac magnetic resonance; IVS: interventricular septum; LV: left ventricle; LVEDV: left ventricular end diastolic volume; LVEF: left ventricular ejection fraction; RV: right ventricle; RVEDV: right ventricular end diastolic volume; RVEF: right ventricular ejection fraction.
The data is expressed as N° (%) or mean ± standard deviation (SD), as appropriate.

In all cases included in the study, the presence of fibrosis was detected in the LV. However, patients with a positive genetic result presented a greater number of segments with LGE, this result being statistically significant (p = 0.043). Inferior wall and lateral wall were the most affected in both groups, without significant differences in the location of the LGE according to the genetic result. No statistically significant association was observed between the location of LGE, and the different genetic variants detected in the genetic study.

Regarding the presence of fatty infiltration in the LV and the number of affected segments, there were no significant differences between the two groups (Table 2). The segments most affected by fatty infiltration were also the inferior wall and lateral wall. Regarding the fatty infiltration in the IVS, it was higher among the patients with a positive result in the genetic test, without reaching statistical significance (p = 0.081). When analysing the relationship between the location of fatty infiltration and genetics, we did not observe a significant association.

3.3. Events during follow-up

Follow-up of 100 % of the patients was carried out with a median of 3.24 years. During the follow-up period, the presence of events was recorded in 23 patients. We found 15 sustained ventricular arrhythmias (19.5 %), 3 sudden deaths (3.9 %), 4 aborted sudden deaths (5.2 %) and 1 heart transplant (1.3 %) (Table 3). In our series of patients, we observed that a positive result in the genetic test was not significantly associated with the occurrence of MACE during follow-up. When performing the analysis for each of the adverse events separately, no statistically significant differences were detected (p = 0.666). We also did not observe significant differences when we analyzed the relationship between MACE and the presence of a variant of uncertain significance versus pathogenic or probably pathogenic variants in the genetic test (*Supplementary* Table 2). Finally, no differences were found regarding the need for ICD implantation or the administration of appropriate therapies by the device.

4. Discussion

There is currently a growing interest in knowing how genetics affects the evolution of ACM. In our case, we focused on analysing the results of the genetic test and its role in the prognosis in patients diagnosed with LDAC or biventricular ACM. For this, we had a large sample of patients who were followed up over a long period from diagnosis. The main results of our study are the following. In the first place, in practically half of the cases we did not find any mutation responsible for the disease. Secondly, despite the existence of a high proportion of major cardiovascular adverse events during follow-up, we did not detect prognostic

Table 3
Association between the genetic test and follow-up events.

Variable	Total (n = 77)	Negative Genetics (n = 36)	Positive Genetics (n = 41)	*p*
Major adverse cardiovascular events	23 (29.9 %)	11 (30.6 %)	12 (29.3 %)	0.902
Sustained ventricular arrthythmias	15 (19.5 %)	7 (19.4 %)	8 (19.5 %)	0.666
Definitive sudden cardiac death	3 (3.9 %)	1 (2.8 %)	2 (4.9 %)	0.666
Aborted sudden cardiac death	4 (5.2 %)	3 (8.3 %)	1 (2.4 %)	0.666
Heart transplant	1 (1.3 %)	0 (0.0 %)	1 (2.4 %)	0.666
Need for an implantable cardioverter-defibrillator	35 (45.5 %)	15 (41.7 %)	20 (48.8 %)	0.532
Arrhythmias treated by implantable cardioverter-defibrillator	13 (16.9 %)	4 (26.7 %)	9 (47.4 %)	0.217

The data is expressed as N° (%).

differences in relation to the presence of a positive genetic test. Finally, there were no relevant phenotypic differences between patients with positive or negative genetics.

ACM requires for its diagnosis the fulfilment of a series of criteria that are constantly evolving. Until recently, we only had the 2010 International Task Force Criteria [13], which reliably detect the classic right variant but do not take into account patterns with LV involvement. The document recently developed by the group led by Padua et al [6] provides an update to allow the diagnosis of all ACM phenotypes, giving CMR a key role. Even with current advances, there are sometimes difficulties in making the differential diagnosis of left-dominant forms, since they can be confused with other entities with similar phenotypes. This is the reason why the Padua criteria emphasise the importance of diagnostic specificity of patterns with exclusively left involvement, requiring the demonstration of a genetic variant for diagnosis. However, this point has been widely criticised by different authors [9]. In our case, we had a relatively large series of patients diagnosed with LDAC and biventricular variants from 2010 to 2020, all of whom met the diagnostic criteria described by Sen-Chowdhry. However, in half of them no related genetic variant was identified. A relevant observation is also the absence of differences observed in terms of the results of the genetic test in the occurrence of major adverse cardiovascular events, including sustained ventricular arrhythmias, sudden death, and the need for heart transplantation (Fig. 2).

The genetic aetiology of LDAC is known [8], and the genetic test is important for diagnosis, besides the fact that it allows the study of family members and enables stricter follow-up of those affected [13]. However, the role of genetics in the pathogenesis of ACM should not be simplified as a linear cause–effect relationship in which a certain phenotype corresponds to a particular genetic variant. For this reason, different factors that may influence expression of the disease, whether genetic or environmental, must be taken into account [10,14]. Furthermore, in all hereditary heart diseases there is a high proportion of patients in whom the genetics are negative' [8], probably explained by the existence of still unknown variants responsible for the disease. In recent years there have been major technological advances in the development of CMR, which in our case was key in providing very reliable data for tissue characterisation, which is why it has become a fundamental imaging test for the diagnosis of LDAC and biventricular variants [7]. For this reason, although genetics is important as it increases diagnostic specificity, the detection of a genetic variant should not be imposed as an essential criterion for making the diagnosis of LDAC. If we strictly followed the Padua criteria, almost half of the patients did not present any variant detected in the genetic test and would not have been diagnosed with ACM, with the future consequences that may entail leaving these patients without an adequate diagnosis and treatment. Thus, we consider that a negative genetic test is not an exclusion criterion for diagnosis in those patients in whom the clinical context and the findings provided by imaging techniques, especially CMR, strongly suggest LDAC or biventricular variants.

Regarding the secondary objective of the study, we found a significant difference in the number of segments affected by fibrosis, which was higher in those patients with a positive genetic result. In contrast, this was not accompanied by the appearance of more adverse events or by a greater need for ICD or administration of appropriate therapies. On the other hand, the detection of a genetic variant was not associated with the presence of RV or LV dysfunction or dilatation, nor with the presence and severity of LV fatty infiltration. These results suggest that, although the overall prognosis of these patients was poor due to the high incidence of sudden death and ventricular arrhythmias [3], the detection of a genetic variant causing LDAC did not imply a worse evolution of the disease in our population.

The most frequently affected LV wall in LDAC is the inferolateral. The IVS is also compromised in up to 50 % of cases, being an exceptional finding in the classic right variant' [3]. In recent studies of genotype–-phenotype correlation, no association has been found between the involvement of IVS and genetics [8]. Among our results, the greater presence of fatty infiltration and fibrosis in the IVS among patients with a positive result in the genetic test is striking. However, we did not observe a significant relationship with the different genetic variants detected. We believe that this finding would be of interest for future research to try to elucidate this association.

There are several studies that have linked the practice of sports with a higher incidence of sudden death and greater progression of the disease [7,14,15,16,17]. The male sex has also been associated with a greater occurrence of adverse events and a worse prognosis, during follow-up [7,17,18]. In trying to explain these associations, the greater frequency of high-intensity sports practice among men and hormonal influence have been linked as possible causes [15]. In our study, we found a greater number of male patients with negative genetics compared to the female gender. This finding could be related to what has previously been commented, although more data would be needed to

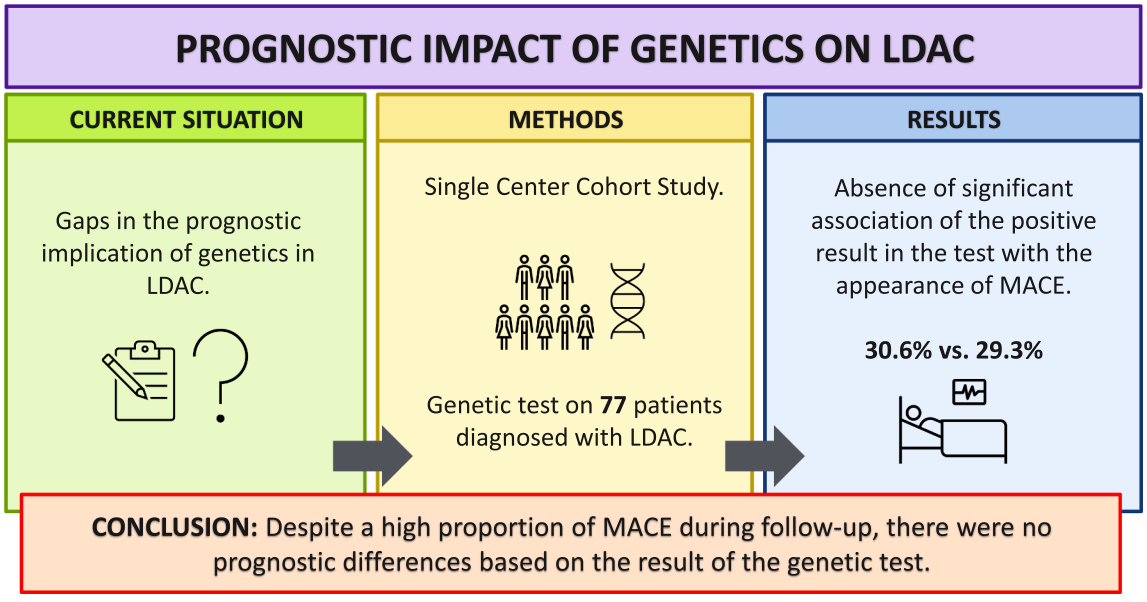

Fig. 2. Central figure. LDAC: left dominant arrhythmogenic cardiomyopathy; MACE: major adverse cardiovascular events.

confirm these results.

Although it can be detected in the entire spectrum of ACM patterns, mutation in desmosomal genes is more common in the classic variant with predominant RV involvement, the most frequently affected gene being plakophilin-2 [18,19]. In contrast, in the left and biventricular variants, mutation in non-desmosomal genes is found more frequently. In genotype–phenotype correlation studies, a higher detection of genetic variants in the desmoplakin gene has been shown in patients with predominantly LV involvement, followed by phospholamban and filamin C [3,17]. In our series, we observed a similar proportion between variants in desmosomal and non-desmosomal genes, with desmoplakin being the most affected gene, consistent with what has been reported in the series of patients with LDAC.

4.1. Limitations

As our hospital is a referral centre in CMR, we have a relatively large series of patients. Despite this, in absolute terms the number of patients we included is small, which could affect the results of our study.

On the other hand, we initially included 105 patients diagnosed with LDAC or biventricular ACM in our database, although we only have the results of the genetic study in 77 of them. The reason why it was not performed on all patients is probably because inclusion began in 2010 (more than 10 years ago), and genetic study requests were not so frequent at that time. In addition, since these are old studies, it is possible that they did not include new genetic variants that have subsequently been discovered and that have recently been incorporated into arrhythmogenic cardiomyopathy panels.

The diagnosis of LDAC or biventricular ACM in our case is largely based on CMR findings, so there is the possibility that a patient with a similar phenotype was included, such as dilated cardiomyopathy or recurrent myocarditis. To reduce this error, an exhaustive review of the medical records of all the cases was carried out to verify if they met the clinical, echocardiographic and electrocardiographic criteria of LDAC according to Sen-Chowdhry, and to eliminate the cases that raised diagnostic doubt.

5. Conclusions

In a large series of patients diagnosed with LDAC and biventricular ACM, the genetic test was positive in only 53.2 % of the sample, with the desmoplakin gene being the most affected. We observed a high proportion of patients with major adverse cardiovascular events during follow-up, the most common being ventricular arrhythmias. However, the detection of a genetic variant was not associated in our study with a worse prognosis of the disease; nor were significant differences observed based on the genetic test in the phenotypic variables analysed.

Authors contribution

All the authors contributed to the study conception and design. LGC and JMMT contributed to the acquisition of data. LGC, AGG, JMRN and JMMT had the lead in preparing the manuscript. AGG, JMRN and EFR critically revised the manuscript. AGF and EFR were involved in the clinical management of the patient. All authors read and approved the final manuscript.

7. Authors agreement

All authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

CRediT authorship contribution statement

Laura García-Cano: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **José Miguel Martín-Torres:** . **Amaya García-Fernández:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Data curation, Conceptualization. **Eloísa Feliu-Rey:** Writing – review & editing, Resources, Methodology, Investigation, Data curation, Conceptualization. **Juan Gabriel Martínez-Martínez:** . **Juan Miguel Ruiz-Nodar:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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