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Brief report

# Left Dominant Arrhythmogenic Cardiomyopathy Caused by a Novel Nonsense Mutation in Desmoplakin

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ABSTRACT

Left dominant arrhythmogenic cardiomyopathy (LDAC) exhibits characteristic phenotypic and genetic features which were found in the five Spanish family members described in this study. Triggered by a cold, a young man presented with a ventricular tachycardia of left ventricular origin and left ventricular late gadolinium enhancement. His resting ECG showed low potentials, delayed ventricular depolarization (inferior and V4-V6 leads) and atrioventricular conduction disturbances. His endomyocardial biopsy revealed myocyte loss with interstitial fibrosis. Despite the initial diagnosis of myocarditis, familial screening was pivotal in confirming the diagnosis of LDAC. A novel nonsense mutation in the desmoplakin gene (Q1866X) and the truncated protein which it produces were observed in skin samples.



## Miocardiopatía arritmogénica con afectación predominante del ventrículo izquierdo por una mutación nueva «sin sentido» en desmoplaquina

*Palabras clave:*
Miocardiopatía arritmogénica izquierda
Desmoplaquina
Cardiorresonancia

RESUMEN

La miocardiopatía arritmogénica predominantemente izquierda (MCAI) presenta características fenotípicas y genotípicas reflejadas en la familia española de cinco miembros que aquí describimos. Durante un catarro, un joven presentó una taquicardia ventricular con origen ventricular izquierdo y realce tardío en dicha localización. Su ECG basal mostró bajos voltajes, retraso en la activación terminal del QRS (cara inferior y V4-V6) y trastorno de la conducción auriculoventricular. Su biopsia endomiocárdica evidenció pérdida miocitaria y fibrosis. Aunque inicialmente fue catalogado de miocarditis, la evaluación familiar fue decisiva para sospechar una MCAI. El estudio genético identificó una mutación nueva en desmoplaquina tipo «sin sentido» (Q1866X) congruente con la presencia de una desmoplaquina truncada en muestras de piel de los afectados.



## INTRODUCTION

Arrhythmogenic cardiomyopathy (ACM) shows a prevalence of 1:5,000.[1] Forty percent of cases are associated with mutations, the majority being found in genes encoding desmosomal proteins, which normally exhibit autosomal dominant inheritance[1,2] and variable penetrance. The remaining 60% are estimated to be linked to genes which have not yet been identified or to acquired causes.[3]

Desmosomes are responsible for ensuring cellular adhesion and are found in great numbers in tissues subjected to constant mechanical strain, such as the skin and the myocardium. The inclusion of defective proteins in the desmosomes of patients with ACM reduces their adhesive properties and encourages myocyte loss, replacement with fibro-fatty tissue and inflammation. These factors provide the anatomical substrate to generate ventricular tachyarrhythmias and sudden death.[3]

Originally described in the right ventricle (RV), a broader definition of ACM now also includes forms which primarily affect the left ventricle (LV) and are known as arrhythmogenic left ventricular cardiomyopathies (ALVC).[4-6]

We present the case of a Spanish family that was studied following an episode of sustained monomorphic ventricular tachycardia (SMVT) in the proband. The cardiological and genetic protocol diagnosed ALVC in the proband and a family member, and identified 2 other family members as genetic carriers and another subject as healthy. We will emphasize the characteristic features of this cardiomyopathy to make it easier to recognize and to add to databases with genotype-phenotype correlations.

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## METHODS

### Patients

The proband, who was 36 years of age (Fig. 1, II:1) and was seen as an outpatient, complained of atypical chest pain; an effort test, performed in accordance with the Bruce protocol, proved negative. His cardiovascular magnetic resonance (CMR) results suggested myocarditis, owing to late gadolinium enhancement (LGE) in the LV. He was admitted 1 year later with a cold and symptoms of dyspnea, syncope, and poorly tolerated SMVT, with morphology findings indicating right bundle-branch and superior axis block, which was cardioverted. The ECG showed low potentials, delayed ventricular depolarization (inferior and V4-V6 leads, and also occasionally V1-V3 leads) and atrioventricular conduction disturbances (Fig. 2). The CMR coincided with the former findings, with evidence of slight LV systolic dysfunction. Wavy contours in the 64-slice multi-detector computed tomography (MDCT) images indicated myocardial infiltration by fatty deposits/epicardial fibrosis (Fig. 3). An endomyocardial biopsy (EMB) revealed interstitial fibrosis and myocyte loss <30% with no fatty infiltration. The patient was fitted with a defibrillator and discharged.

Although in this clinical study the proband did not meet ACM criteria,[7] the fact that ALVC was suspected led us to evaluate the patient's family (his parents and two sisters) using standard ECG, echocardiography, effort test, 24-h Holter ECG, CMR, and general biochemical tests.

Having completed the family assessment, we screened the proband for mutations, conducting a family-based genetic cascade screening. A skin biopsy of the ALVC patients (II:1 and II:2) was then taken to analyze the pattern of desmoplakin expression in comparison with that of a control subject.

### Genetic Study

DNA was extracted from peripheral blood leukocytes. The five main desmosomic genes (plakoglobin, plakophylin-2, desmoglein-2, desmocollin-2 and desmoplakin) were sequenced in both directions (ABI Prism 3100 sequencer, Applied Biosystems) in the proband. Once the mutation was identified, the affected exon was selectively sequenced in the family members and 200 control chromosomes.

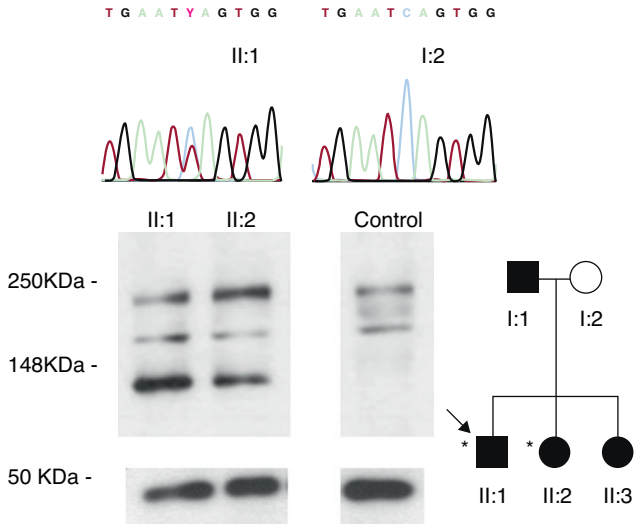


**Figure 1.** Family members included in the study (circles: females; squares: males; *left dominant arrhythmogenic cardiomyopathy phenotype). The chromatograms of the Q1866X mutation carriers (black symbols) and healthy subjects (white symbols) and their skin desmoplakin expression pattern are shown.

### Tissue Analysis

Desmoplakin expression in the affected subjects and a healthy control was analyzed by immunotransference in processed skin biopsies, as has been previously described,[6] using Novex 4%-12% gel, Tris-Glycine 1 mm gel (Invitrogen) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as the loading control. The primary antibodies were NW161 (*desmoplakin N-terminal specific antibody*, donated by Dr. Kathleen Green, Northwestern University, Evanston, Illinois, United States) and GAPDH rabbit mAb (14C10) (IZASA), and the secondary antibodies were sheep anti-mouse IgG-HRP (Amersham Bioscience) and rabbit anti-donkey IgG-HRP (Amersham Bioscience).

The protocol had previously been authorized by the ethics committee of our hospital and each subject signed an informed consent form.

## RESULTS

### Proband

The genetic study identified a new variant of the desmoplakin gene (c. 5596C>T, Q1866X) (Fig. 1), which was absent in controls and led to a stop codon in the translation in the central rod domain of the protein. Immunotransference detected a truncated form of desmoplakin in the proband's skin biopsy (Fig. 1).

### Family Study

There was no family history worthy of mention. The cardiological protocol performed on the parents and one sister of the proband was normal (Table 1). However, his other sister had an ALVC phenotype (II:2) with ECG, CMR and MSCT results similar to those of the proband (Figs. 2 and 3). An electrophysiological study in the RV revealed the presence of fragmented potentials and SMVT (with left bundle-branch and inferior axis block), which was readily induced. Her skin desmoplakin expression pattern coincided with that of the proband (Fig. 1). Following these results, she was fitted with a defibrillator. The Q1866X desmoplakin mutation, which was absent in the mother of the proband (I:2), was found in the sister with an ALVC phenotype (II:2), and in 2 genetic carriers with a normal cardiological profile: another sister (II:3) and the father (I:1). When genetic results were included, the 2 patients who were affected (II:1 and II:2) met the new ACM criteria.[8]

## DISCUSSION

This study highlights the importance of multidisciplinary analysis when families suspected of being affected by ACM are evaluated. It also describes a novel mutation in the desmoplakin gene, indicating the molecular mechanism which is most likely to be implicated.

The ECG of LV ACM revealed flattened/inverted (infero-)lateral repolarization.[4-6,8] Our patients also had low potentials, as well as delayed ventricular depolarization (inferior leads) and atrioventricular conduction. These novel findings, which have not been included in other articles[4-6] or in the new criteria,[8] came to light in a case of Carvajal disease[9] and could be useful in confirming suspected ALVC. The electrocardiographic localization of these