Original Articles

Desmoglein-2 and Desmocollin-2 Mutations in Dutch Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Patients
Results From a Multicenter Study

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Background—This study aimed to evaluate the prevalence and type of mutations in the major desmosomal genes, Plakophilin-2 (PKP2), Desmoglein-2 (DSG2), and Desmocollin-2 (DSC2), in arrhythmogenic right ventricular dysplasia/cardiomypathy (ARVD/C) patients. We also aimed to distinguish relevant clinical and ECG parameters.

Methods and Results—Clinical evaluation was performed according to the Task Force Criteria (TFC). We analyzed the genes in (a) 57 patients who fulfilled the ARVD/C TFC (TFC+), (b) 28 patients with probable ARVD/C (1 major and 1 minor, or 3 minor criteria), and (c) 31 patients with 2 minor or 1 major criteria. In the TFC+ ARVD/C group, 23 patients (40%) had PKP2 mutations, 4 (7%) had DSG2 mutations, and 1 patient (2%) carried a mutation in DSC2, whereas 1 patient (2%) had a mutation in both DSG2 and DSC2. Among the DSG2 and DSC2 mutation-positive TFC+ ARVD/C probands, 2 carried compound heterozygous mutations and 1 had digenic mutations. In probable ARVD/C patients and those with 2 minor or 1 major criteria for ARVD/C, mutations were less frequent and they were all heterozygous. Negative T waves in the precordial leads were observed more (P<0.002) among mutation carriers than noncarriers and in particular in PKP2 mutation carriers.

Conclusions—Mutations in DSG2 and DSC2 are together less prevalent (10%) than PKP2 mutations (40%) in Dutch TFC+ ARVD/C patients. Interestingly, biallelic or digenic DSC2 and/or DSG2 mutations are frequently identified in TFC+ ARVD/C patients, suggesting that a single mutation is less likely to cause a full-blown ARVD/C phenotype. Negative T waves on ECG were prevalent among mutation carriers (P<0.002). (Circ Cardiovasc Genet. 2009;2:418-427.)

Key Words: arrhythmia ■ cardiomyopathy ■ desmosomes ■ genetics

Arrhythmogenic right ventricular dysplasia/cardiomypathy (ARVD/C) is a familial disease characterized by progressive fibrofatty replacement of the right ventricular (RV) myocardium.1 The main histologic feature is progressive loss of RV myocardium, which is replaced with adipose and fibrous tissue. These changes may be localized and in the early stages are often confined to the so-called triangle of dysplasia: the inflow, outflow, and apical regions of the RV.1 Aneurysm formation is typical. Diffuse myocardial involvement leads to global RV dilation. Left ventricular involvement occurs with disease progression and was present on histology in >75% of cases in a multicenter pathological study.2

ARVD/C is a genetically heterogeneous disease and is most commonly inherited as an autosomal-dominant trait with incomplete penetrance and variable expression. Its

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clinical picture is mainly characterized by the occurrence of ventricular arrhythmias and related consequences. Estimates of the prevalence of ARVD/C in the general population range from 1 in 2000 to 1 in 5000; it affects men more frequently than women, with an approximate gender ratio of 3:1. A familial background has been demonstrated in 30% to 50% of ARVD/C cases, and the majority of disease-causing mutations have so far been identified in genes encoding proteins of specialized adhesive junctions between cells, also known as desmosomes. Mutations in the PKP2 gene encoding Plakophilin-2 are the most prevalent and were identified in up to 43% of unrelated ARVD/C index patients. Dominant mutations in genes encoding Desmoglein-2 (DSG2) and Desmocollin-2 (DSC2) have been reported in up to 12% and 5% of ARVD/C patients, respectively. Rarely, dominant mutations in the Plakoglobin (JUP), Desmplakin (DSP), and TMEM43 genes have been reported in patients with ARVD/C, with recessive mutations in JUP and DSP being causal for the cardiocutaneous diseases, Naxos disease and Carvajal syndrome, respectively.

This study is an extension of our previous study in which we elucidated PKP2 mutations in our Dutch ARVD/C cohorts. Our goal now was to evaluate the prevalence of mutations in 3 cardiac desmosomal genes, PKP2, DSG2, and DSC2, and to study their impact on clinical phenotypes in the following 3 groups: (a) patients fulfilling the ARVD/C task force criteria (TFC+), (b) patients with probable ARVD/C (1 major and 1 minor, or 3 minor criteria), and (c) patients with either 2 minor or 1 major criteria for ARVD/C.

Genotype-phenotype analyses, of both clinical and ECG features, were also performed to identify potentially distinguishing features.

### Methods

#### Clinical Evaluation and Diagnostic Criteria

We evaluated 116 white, unrelated, index patients in 4 university hospitals in the Netherlands. A case history was taken from all patients, and they were physically examined and evaluated by 12-lead ECG, 24-hour Holter monitoring, exercise testing, and 2-dimensional transthoracic echocardiography. Diagnosis of ARVD/C was based on the diagnostic criteria of the Task Force of the European Society of Cardiology/International Society and Federation of Cardiology (Table 1). In cases of doubtful diagnosis, patients were discussed with experienced cardiologists from the 4 centers in a consensus meeting. The 116 index patients were subdivided into (a) 57 TFC+ patients, (b) 28 probable ARVD/C (who had 3 minor criteria, or 1 major and 1 minor criteria), and (c) 31 patients with 2 minor or 1 major criteria of ARVD/C (not including family history). Eight TFC+ patients from our previous study were excluded due to absence of DNA. Instead, 8 new TFC+ patients were included in this study (Table 2, marked “n”). The onset of disease manifestation was defined as the age at which initial symptoms most likely related to ARVD/C emerged, including paroxysmal tachycardia, prolonged syncope, and successful resuscitation.

#### Genetic Studies

Genomic DNA was extracted from whole blood or paraffin-embedded tissues according to the established protocol (Qiagen). Detailed procedures for screening the PKP2 gene were described elsewhere. DSG2 and DSC2 coding regions (exons 1 to 15 and exons 1 to 16, respectively) were screened for mutations. Primer sequences and PCR conditions are available on request. Mutational analysis of the amplimers was performed by denaturant high performance liquid chromatography (DHPLC) (Transgenic Wave) and denaturing gradient gel electrophoresis. PCR products with altered denaturant conditions were purified using QIAquick PCR purification kit (Qiagen) and were sequenced bidirectionally on an ABI 377 sequencer.

In this study, the pathogenic nature of the identified missense mutations were judged on the basis of 4 criteria (for an overview of criteria potentially useful for classifying variants see Goldgar et al26): (1) the differences in physicochemical properties of the amino acids involved in the respective substitutions; (2) the evolutionary conservation of the amino acids across several species; (3) the presence in an evolutionary conserved region; and (4) the localization within a functionally important domain (predicted or unpredicted). Missense mutations were considered pathogenic when the respective amino acid substitutions satisfied 2 or more of these criteria. Amino acid substitutions were considered as unclassified variants (UVs) when these satisfied none or only one of the criteria mentioned earlier and are not known as single nucleotide polymorphisms. In all cases, the reported mutations/variants were not identified in at least 150

### Table 1. TFC for the Diagnosis of ARVD/C

<table>
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<tr>
<th>Major</th>
<th>Minor</th>
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<tr>
<td>Global and/or regional dysfunction</td>
<td>Severe RV dilatation and reduction in systolic function with no (or only mild) LV impairment</td>
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<td>and structural alterations</td>
<td>Localized RV aneurysms</td>
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<td>Tissue characterization of walls</td>
<td>Severe segmental RV dilatation</td>
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<td>Repolarization abnormalities</td>
<td>Fibrofatty replacement of myocardium on EMB</td>
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<td>Depolarization abnormalities</td>
<td>Negative T-waves (V2 and V3); &gt;12 years of age in the absence of RBBB</td>
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<td>Arrhythmias</td>
<td>Late potentials on SA-ECG</td>
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<td>Family history</td>
<td>Sustained and nonsustained VT with LBBB morphology (on ECG, Holter, exercise testing)</td>
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Either 4 minor criteria, 2 major, or 1 major plus 2 minor criteria are sufficient to make a diagnosis of ARVD/C. EF indicates ejection fraction; EMB, endomyocardial biopsy; LV, left ventricular; SCD, sudden cardiac death; VT, ventricular tachycardia; RBBB, right bundle-branch block; LBBB, left bundle-branch block.
Table 2. Clinical Characteristics of the Probands With TFC+ ARVD/C Patients

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<th>Age Initial Presentation</th>
<th>Structural Alteration</th>
<th>Tissue Characterization</th>
<th>Repolarization Abnormalities</th>
<th>Depolarization/Conduction Abnormalities</th>
<th>Arrhythmias</th>
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(Continued)
Nineteen patients (11 men, 8 women) had 1 major and 1 minor ARVD/C criteria; remaining 9 patients (4 men, 5 women) had 3 minor features of ARVD/C.

Thirty-one patients had one major (n = 15) or 2 minor criteria (n = 16). Those with 1 major criterion either had an ε wave (n = 8), sufficient structural alterations on echocardiography to fulfill a major criterion (n = 2) or abnormal tissue characterization (n = 2). The majority (20 of 25) of persons with 2 minor criteria presented with left bundle branch block ventricular tachycardias or ventricular extrasystoles with minor abnormalities on imaging. Two individuals presented with ventricular extrasystoles and late potentials on signal-averaged ECG, 2 presented with ventricular extrasystoles and a positive family history for premature sudden death and one had left bundle branch block ventricular tachycardias with negative T-waves in leads V1–V3.

The average age of first clinical presentation was 33 years in PKP2, 36 years in DSG2, 42 years in DSC2. 14 years for combined DSC2/DSG2 mutation carriers, and 37 years for nonmutation carriers (range, 14 to 68 years); these ages did not differ significantly between men and women.

**Results**

**Genetic Studies**

We screened the PKP2, DSG2, and DSC2 genes in 116 patients and performed haplotype analyses in patients with identical mutations. Results are shown in Figure 1A through 1C, and also in Tables 2 and 3 and supplemental Table 1. Mutations marked with asterisks in Figure 1A were reported in previous studies. 12,17

**Haplotype Analyses**

Haplotype analyses were performed in patients with identical mutations using 8 microsatellite repeat markers within a region of 10 Mb encompassing the entire genomic region of the DSG2 gene. Positioning of the markers related to the human sequence was based on NCBI Build 35 version 1 (supplemental Table I). Primers used for the amplification of these markers are available in NCBI database.

In patient B, additional family members were available for haplotype analyses. This enabled the complete reconstruction of the haplotype and verification of the phase.

**Statistical Analysis**

Clinical characteristics in the patients with a PKP2, DSG2, or DSC2 mutation/UV were compared using Fisher exact test. Values of P < 0.05 were considered significant. All data were analyzed with the Statistical Package for Social Sciences (SPSS 15.0, SPSS, Inc, Chicago, Ill).

**Clinical Evaluation**

Clinical data of the 57 TFC⁺ and 28 probable ARVD/C patients are shown in Tables 2 and 3, respectively.

The TFC⁺ group comprised of 40 male and 17 female patients. The age of first clinical presentation of the disease is broad, ranging between 12 years and 58 years, with 6 patients had their full blown phenotype before they reached 20 years (3 men and 3 women). In this group, 16 patients (13 men, 3 women) had 2 major criteria for ARVD/C, while 38 (25 men, 13 women) fulfilled 1 major and 2 minor criteria. The remaining 3 patients (2 men, 1 woman) in this group fulfilled 4 minor criteria of ARVD/C.

The probable ARVD/C group comprised of 15 male and 13 female patients. The age of first clinical presentation ranged between 17 years and 68 years, with 2 patients (1 man and 1 woman) had their disease before they reached 20 years. Nineteen patients (11 men, 8 women) had 1 major and 1 minor ARVD/C criteria; remaining 9 patients (4 men, 5 women) had 3 minor features of ARVD/C.

**Results**

**Table 2. Continued**

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Mutations identified in the PKP2, DSG2 and DSC2 are indicated. UVs are shown in italics. M indicates male; F, female; LBBVT, left bundle-branch block ventricular tachycardia; VES, ventricular extrasystoles; +, a major criterion; +, minor criterion.

The probable ARVD/C group comprised of 15 male and 13 female patients. The age of first clinical presentation ranged between 17 years and 68 years, with 2 patients (1 man and 1 woman) had their disease before they reached 20 years. Nineteen patients (11 men, 8 women) had 1 major and 1 minor ARVD/C criteria; remaining 9 patients (4 men, 5 women) had 3 minor features of ARVD/C. Thirty-one patients had one major (n = 6) or 2 minor criteria (n = 25). Those with 1 major criterion either had an ε wave (n = 2), sufficient structural alterations on echocardiography to fulfill a major criterion (n = 2) or abnormal tissue characterization (n = 2). The majority (20 of 25) of persons with 2 minor criteria presented with left bundle branch block ventricular tachycardias or ventricular extrasystoles with minor abnormalities on imaging. Two individuals presented with ventricular extrasystoles and late potentials on signal-averaged ECG, 2 presented with ventricular extrasystoles and a positive family history for premature sudden death and one had left bundle branch block ventricular tachycardias with negative T-waves in leads V1–V3.

The average age of first clinical presentation was 33 years in PKP2, 36 years in DSG2, 42 years in DSC2. 14 years for combined DSC2/DSG2 mutation carriers, and 37 years for nonmutation carriers (range, 14 to 68 years); these ages did not differ significantly between men and women.

**Haplotype Analyses**

Haplotype analyses were performed in patients with identical mutations using 8 microsatellite repeat markers within a region of 10 Mb encompassing the entire genomic region of the DSG2 gene. Positioning of the markers related to the human sequence was based on NCBI Build 35 version 1 (supplemental Table I). Primers used for the amplification of these markers are available in NCBI database.

In patient B, additional family members were available for haplotype analyses. This enabled the complete reconstruction of the haplotype and verification of the phase.

**Statistical Analysis**

Clinical characteristics in the patients with a PKP2, DSG2, or DSC2 mutation/UV were compared using Fisher exact test. Values of P < 0.05 were considered significant. All data were analyzed with the Statistical Package for Social Sciences (SPSS 15.0, SPSS, Inc, Chicago, Ill).
Patient 39 (woman) and 52 (man) had an identical mutation p.Arg46Gln in DSG2 (Table 2). Haplotype analyses revealed an identical haplotype (supplemental Table I). In addition, they carried p.Val158Gly (DSG2) on the same allele, which has been described as a mutation in a UK study. In our study, we also found this p.Val158Gly in our control population, and similar results were recently reported by Posch et al, and thus we should consider p.Val158Gly as a nonsynonymous SNP.

Patient 24, a 56-year-old man, was the only patient in this group who had a heterozygous mutation p.Ile603Thr only in DSC2 (Table 2 and Figure 1B). Patient 40 carried a heterozygous p.Val392Ile mutation in DSG2 and a heterozygous p.Leu732Val mutation in the DSC2 gene (Figure 1A and 1B, Table 2). We could not identify any mutations in any of these 3 genes in 28 (49%) TFC/H11001 patients (Figure 1C). A schematic representation of the mutation yield from the PKP2, DSG2, and DSC2 screening is shown in Figure 1C.

Table 3. Clinical Characteristics of the Probable ARVD/C Patients

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<th>Tissue Characterization</th>
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Mutations identified in the PKP2, DSG2 and DSC2 are indicated. UVs are shown in italics. M indicates male; F, female; LBBVT, left bundle branch ventricular tachycardia; VES, ventricular extrasystoles; +, a major criterion; +, minor criterion.

TFC—Group

Probable ARVD/C Patients

In the patients with probable ARVD/C (n=28), we detected one heterozygous truncating mutation, c.397C>T (p.Gln133X), in PKP2 (patient 63; Table 3). Patient 59 had a heterozygous UV, p.Leu15Gln, in DSG2 (Figure 1A and Table 3). Leu15 in DSG2 is not very well conserved across diverse species, but it is located in a functionally important signal sequence domain. Patient 64 carried a heterozygous mutation, p.Asp350Tyr, and patient 75 carried an UV, p.Pro289Ser, in DSC2 (Figure 1B and Table 3). We were able to study the segregation of the mutation in the family of patient 64: it was also found in a brother and a sister, with a positive signal-averaged ECG as a sole manifestation, at ages 48 and 47 years, respectively (Figure 2).

Patients With 1 Major or 2 Minor Criteria for ARVD/C

In this TFC-group of patients (n=31) who had only 1 major or 2 minor criteria of ARVD/C, we detected 2 UVs in PKP2:
Figure 1. A, Schematic representation of the DSG2 mutations and UVs. Most mutations, except 3 (indicated by *), are previously unreported.12,17 **Mutation was detected in 2 unrelated patients/families and was also reported previously. UVs are shown in italics. B, Schematic representation of the DSC2 mutations and UVs. UVs are shown in italics. C, Graphical representation of PKP2, DSG2, and DSC2 gene screening in the ARVD/C, probable ARVD/C, and patients with 1 major or 2 minor criteria of ARVD/C. Filled bars represent PKP2 mutation carriers, slashed bars represent DSG2 mutation carriers, dotted bars represent DSC2 mutation carriers, vertical-lined bars represent patients carrying mutations in both DSG2 and DSC2, and unfilled bars represent patients without mutations in one of the 3 genes. The x axis represents the analyzed genes, and the y axis represents the percentages of mutations identified in each group. The number of mutation carriers or nonmutation carriers in the respective genes are shown on top of each bar.
The DSG2 mutations identified in our study, p.Val392Ile, p.Leu732Val, and one UV, p.Pro289Ser (Figure 1B). The latter UV was identified in patient A with left bundle branch block ventricular tachycardias and mild global right ventricular dilatation. This UV was also identified in her unaffected father (Figure 2).

The patient with p.Val392Ile amino-acid change in DSG2 was a woman (patient B, Figure 2). She had negative T waves at leads V4–6, a low voltage ECG and was diagnosed with dilated cardiomyopathy at the age of 47 years, after she experienced an out-of-hospital cardiac arrest due to ventricular fibrillation. She died with RV failure at 56 years and tachycardias and mild global right ventricular dilatation. This UV was also identified in her unaffected father (Figure 2).

The identical mutation was also found in patient 40 (Table II:1). Haplotype analysis revealed a partially identical haplotype DSG2 near-syncope. He was also found to carry this p.Val392Ile mutation in DSG2 was diagnosed post mortem in paraffin-embedded tissue material. Her sister (the dead sister’s son; Figure 2) showed negative T-waves in leads V4–V6 and was diagnosed with dilated cardiomyopathy at the age of 49 years after experiencing a near-syncope. He was also found to carry this p.Val392Ile DSG2 mutation. These data suggest a left-dominant arrhythmogenic cardiomyopathy.

This identical mutation was also found in patient 40 (Table 2). Haplotype analysis revealed a partially identical haplotype around DSG2 (supplemental Table I).

Mutation Characteristics
The DSG2 mutations identified in our study, p.Val392Ile, p.Val56Met, and p.Arg46Gln, were previously reported in studies from the United States, United Kingdom, and Germany.28 We identified 4 novel DSG2 mutations: p.Ile73Val, p.Val149Phe, p.Pro205Leu, and p.Asp297Asn (Figure 1A). In addition, we detected 3 novel UVs in DSG2 (p.Leu15Gln, p.Asn1067Asp and p.Gly1083Ser; Figure 1A). In DSC2, we identified 3 novel mutations, p.Asp350Tyr, p.Ile603Thr, p.Leu732Val, and one UV, p.Pro289Ser (Figure 1B). The mutation yield in various groups of patients is shown in Figure 1C.

The DSG2 and DSC2 mutations, we identified are all missense mutations (Figure 1A and 1B and Tables 2 and 3), in contrast to PKP2 mutations, which are mostly truncating/frameshift mutations.5 In this study, 3 patients (patient 25 and 41, TFC+ group; and 1 patient with 2 minor criteria) among the DSG2 mutation carriers were familial cases. The DSC2 mutation carriers were all sporadic, with no family history pertaining to ARVD/C.

Genotype-Phenotype Relationships/Phenotypic Characteristics
Figure 3A and 3B show examples of a classical ARVD/C ECG recorded from a male symptomatic patient in this study. Figure 4 shows a representative ARVD/C histopathology of myocardial tissue taken from patient 64. We have compared various pertinent phenotypic features (age of onset, cardiac structural alteration, ECG features, and ventricular extrasystoles) among the patients with defects in PKP2 (n=24), DSG2 (n=5), DSC2 (n=3), and both DSG2/DSC2 (n=1). Patients without a mutation in any of these 3 genes were also compared with the mutation carriers and TFC+ and probable ARVD/C patients were included in this analysis.

The presence of T wave inversions (negative T wave) in right precordial leads on 12-lead ECG in individuals with a mutation (PKP2, DSG2, and DSC2) was significantly higher than that of individuals without a mutation (P<0.002). Among the 33 mutation and UV carriers in these 3 genes, 30 patients had negative T waves in their right precordial ECG leads. This difference in T wave was more evident among the PKP2 mutation carriers.3 Disease onset was slightly earlier among the small group of DSG2 mutation carrier patients (including the one with an additional DSC2 mutation) compared to those with a PKP2 mutation in the TFC+ group (34 years versus 36 years; not significant), yet sample size is too small to make a definitive conclusion. No other significant differences in any other parameters could be established.

Discussion
In this multicenter Dutch study, we have systematically evaluated a large number of ARVD/C patients, both clinically and genetically. We have screened 3 cardiac desmosomal genes (PKP2, DSG2, and DSC2) in 116 patients, of whom 57 were TFC+. PKP2 mutations were most prevalent in TFC+ patients, who comprised just less than half of the ARVD/C patients (40%). Mutations in DSG2, DSC2, or both were found in 4, 1, and 1 of ARVD/C index patients, respectively (7%, 2%, and 2%); this frequency is similar to reports published from other countries.12,14,17 DSG2 mutations ranged...
between 3.5% and 17% in our probable ARVD/C patients and in those with 1 major or 2 minor criteria for ARVD/C. The DSC2 mutation frequencies in these groups were 7% and 0%, respectively. In approximately 50% of our TFC/H11001 ARVD/C patients, we identified no mutation in any of the 3 desmosomal genes screened, although large deletions or mutations in regulatory regions (promoter/intronic) cannot be excluded. Mutations in other genes related to ARVD/C are believed to be involved far less often and might add only a few more patients to our groups.4

In this study, we have identified compound heterozygous or homozygous mutations in DSG2 in 2 unrelated patients. In addition, a third patient carried mutations in both DSG2 and DSC2. Interestingly, all 3 patients fall in the full blown ARVD/C group (TFC+). Moreover, in 2 patients from the TFC+ group, p.Arg46Gln (DSG2) occurred with p.Val158Gly on the same allele. Haplotype analyses suggested a common founder. Previously, p.Val158Gly has been reported in 2 families as potentially pathogenic;16 however, we found p.Val158Gly in 1% of our control subjects, similar to the frequency reported by Posch et al.27 Thus, we cannot conclude at this stage whether the presence of this p.Val158Gly adds to the pathogenicity of the p.Arg46Gln mutation. Though previous studies detected compound heterozygous DSG2 mutations in 2 TFC+ ARVD/C patients,12,14 the majority of the mutation carriers were heterozygous for a DSG2 mutation, unlike our ARVD/C patients.12,14 But it should be noted that previous studies did not look for digenic mutations in their ARVD/C cohorts.5,7,9,10,12–16,19,20 This suggests that the heterozygous missense mutations in the genes encoding desmosomal cadherins (DSG2/DSC2) are associated with a less fulminant pheno-

**Figure 3.** ECGs from a male symptomatic patient at baseline (A) and during palpitations (B). At baseline, there is a sinus rhythm of 60 bpm, intermediate electric axis, normal conduction intervals, and normal repolarization with exception of the negative T-waves in the precordial leads V1–V4. B, ventricular tachycardia (250 bpm) with left bundle branch morphology and an intermediate electric axis suggesting its origin in the RV free wall.

**Figure 4.** Histology: high powered visualization of fibrolipomatosis surrounding atrophic cardiomyocytes and indicative of ARVD/C. The endomyocardial biopsy was taken from patient 59 who carries the heterozygous p.Asp350Tyr mutation in the DSC2 gene.
type. This is corroborated by the fact that we identified mutations in these genes predominantly in the probable ARVD/C patients or group of patients with 1 major or 2 minor criteria. However, this observation in small groups has to be confirmed in a larger series. Furthermore, we have only identified missense mutations in DSG2 and in DSC2 in our Dutch cohort, whereas 3 published reports reported mainly missense mutations, and some truncating mutations, in these 2 genes in their ARVD/C cohorts.12,14,17 Moreover, except for the family with the p.Val392Ile mutation, we found no significant predilection for left ventricle involvement among DSG2 mutation carriers in our study, as has been reported in a UK population by Syrris et al.17

Patient 40 (TFC+) and another unrelated patient, referred as patient B (not shown in the table) harbored the identical mutation p.Val392Ile in DSG2 with a partial identical haplotype, but their clinical presentation is quite variable. Patient 40 had full blown features of ARVD/C (TFC+; Table 2), while the patient B from the 2 minor or 1 major criteria group demonstrated a left-dominant arrhythmogenic cardiomyopathy. We think the difference in phenotype could be attributed to the fact that patient 40 (TFC+) harbored a second mutation, p.Leu732Val, in DSC2.

During this study, we also observed a frequent polymorphism, p.Glu713Lys (DSG2), equally prevalent among controls and the ARVD/C population (4%), which has also been described by Posch et al27 as an innocent SNP. However, suspicion about the pathogenicity of p.Val56Met (DSG2) should be verified as we did not detect p.Val56Met in controls in our study, in contrast to Posch et al.27

In DSC2, variant p.E896fsX5 was detected in 3 different families and in 4% of our control population. We therefore now consider this to be a nonpathogenic common variant in our population, although in a previous study it was considered pathogenic.16

As to the phenotype, we have observed predominance of negative T waves in V1–V3 among the mutation carriers, more specifically among the PKP2 mutation carriers. Turrini et al.29 while retrospectively studying ECG parameters in various groups of ARVD/C patients, found negative T waves in precordial leads as a predictor of sudden cardiac death.28 Another study from the various groups of ARVD/C patients, found negative T waves in precordial leads as a predictor of sudden cardiac death.28

ACKNOWLEDGMENTS

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Disclosures

None.

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**CLINICAL PERSPECTIVE**

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is most often an autosomal dominantly inherited cardiomyopathy with primarily right ventricular involvement. Clinical presentation of ARVD/C could be highly variable but is characterized mainly by ventricular arrhythmias, syncope, and sudden cardiac death. The condition is uncommon (estimated prevalence ranging from 1 in 2000 to 1 in 5000 in the general population), and the diagnosis is based on criteria proposed by a task force (TFC). In this multicenter study from The Netherlands, the investigators systematically evaluated a large number of ARVD/C patients; they screened 116 patients (57 were TFC+) for mutations in 3 cardiac desmosomal genes (PKP2, DSG2, and DSC2). Mutations in PKP2 gene were most prevalent in TFC+ patients; nearly half (40%) of the TFC+ ARVD/C patients harbored a mutation in the PKP2 gene. The investigators found DSG2 and DSC2 mutations in 10% of TFC+ patients. Mutations in DSG2 and DSC2 also were observed in 10% of probable ARVD/C patients. Intriguingly, compound heterozygous mutations and mutations in both DSG2 and DSC2 genes were exclusively detected in TFC+ patients, suggesting a dose effect of mutations correlating with disease severity, although larger studies are needed to confirm this observation.
Desmoglein-2 and Desmocollin-2 Mutations in Dutch Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Patients: Results From a Multicenter Study


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