REPORT

DSG2 Mutations Contribute to Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

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Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a disorder characterized by fibrofatty replacement of cardiac myocytes that typically manifests in the right ventricle. It is inherited as an autosomal dominant disease with reduced penetrance, although autosomal recessive forms of the disease also occur. We identified four probands with ARVD/C caused by mutations in *DSG2,* which encodes desmoglein-2, a component of the cardiac desmosome. No association between mutations in this gene and human disease has been reported elsewhere. One of these probands has compound-heterozygous mutations in *DSG2,* and the remaining three have isolated heterozygous missense mutations, each disrupting known functional components of desmoglein-2. We report that mutations in *DSG2* contribute to the development of ARVD/C.

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C [MIM #107970]) is a heritable form of cardiomyopathy characterized by right-ventricular dysfunction and life-threatening ventricular arrhythmias. The diagnosis is made on the basis of criteria proposed by an expert consensus panel in 1994.[1] Both dominant and recessive forms of inheritance occur.[2,3] Mutations in genes encoding several components of the cardiac desmosome have been associated with ARVD/C. This was first recognized in the autosomal recessive condition Naxos syndrome (MIM #601214), in which affected individuals develop right-ventricular cardiomyopathy, palmoplantar keratoderma, and woolly hair due to homozygous mutations in the gene encoding junctional plakoglobin (*JUP*).[3,4] Similarly, recessive mutations in *DSP* encoding desmoplakin have been described in Carvajal syndrome (MIM #605676), which consists of palmoplantar keratoderma, woolly hair, and arrhythmogenic cardiomyopathy.[5] Djabali and colleagues reported additional locus heterogeneity for Naxos syndrome and described exclusion of *DSP, JUP,* and several other components of the desmosome in two families with Naxos syndrome.[6]

Dominantly inherited ARVD/C in a single family was first shown to be caused by desmoplakin (*DSP*) mutations that are predicted to disrupt binding of desmoplakin to plakoglobin.[2] More recently, mutations in *DSP* were reported in four families with ARVD/C and a separate family segregating arrhythmogenic left ventricular cardiomyopathy.[7,8] On the basis of impaired cardiac development in mice with deletions for *Pkp2,* which encode plakophilin-2,[9] as well as involvement of other desmosomal elements in ARVD/C, Gerull and colleagues screened 120 probands with ARVD/C for mutations in *PKP2*.[10] Remarkably, they found that 32 of these individuals harbored heterozygous mutations in this gene, for a 27% prevalence among patients with ARVD/C. We subsequently confirmed high prevalence of *PKP2* mutations in a separate large cohort of patients with ARVD/C and reported that those with *PKP2* mutations present with arrhythmia earlier than do patients with ARVD/C who do not have the *PKP2* mutation.[11]

Other genes encoding nondesmosomal proteins have been implicated in ARVD/C. Mutations in *RYR2,* which encodes the cardiac ryanodine receptor, have been described in ARVD2, a subtype in which ventricular arrhythmias are particularly effort induced and structural right-ventricular involvement may be concealed.[12,13] In addition, mutations in *RYR2* result in catecholaminergic polymorphic ventricular tachycardia.[14] Beffagna and colleagues recently described mutations in the 5′ and 3′ UTRs of the gene encoding transforming growth factor β3 (*TGFB3*) in association with ARVD/C.[15] Transient transfection with luciferase reporter constructs harboring these alterations in the 5′ and 3′ UTRs suggests increased *TGFB3* mRNA abundance, which implicates this cytokine in the pathogenesis of ARVD/C.

The desmogleins are desmosomal cadherins and, together with the desmocollins, form the two essential transmembrane components of the desmosome.[16] Members of the desmoglein family (*DSG1–4*) each have four extracellular cadherin domains and a transmembrane domain. *DSG2* is expressed in many tissues, including the myocardium.[17] Because of the association between mutations in three components of the cardiac desmosome and

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ARVD/C, we analyzed probands with this disorder for mutations in *DSG2,* which encodes desmoglein-2.

Thirty-three cases of ARVD/C were identified in which no mutation was present in *PKP2* or *DSP,* genes previously associated with the classic form of ARVD/C. Written informed consent for genetic analysis was obtained from all participating individuals after approval of this protocol by the Johns Hopkins Institutional Review Board. Amplification and sequencing of the exonic and adjacent intronic sequence for the entire *DSG2* gene was performed (see table A1 for primer sequences). Four individuals with ARVD/C were identified with mutations in *DSG2* (table 1 and fig. 1). Each mutation disrupts a highly conserved amino acid within a functional domain of desmoglein-2 (fig. 2). Each mutation is absent in a control population of at least 110 ethnically matched individuals (220 control chromosomes).

Two of these individuals have mutations in the furin-cleavage site of the desmoglein-2 proprotein. Individual A.III-1 has a G→A transition at nt 134, which results in the substitution of a conserved arginine with glutamine (R45Q). Individual B.II-1 has a G→A transition at nt 143, which results in the substitution of a conserved arginine with histidine (R48H). These arginines occur as the first and fourth amino acids within the R-X-K-R furin-cleavage motif (fig. 2). ClustalW alignment demonstrates that these arginines are absolutely conserved in all species and subtypes of desmoglein, as is the lysine residue.

Newly synthesized desmogleins are initially inactive because of an NH_2-terminal propeptide sequence, which is then posttranslationally cleaved by subtilisin-like proprotein convertases (PCs), to create mature, active proteins. These endoproteases cleave C-terminal to the recognition motif Arg-X-Lys-Arg (RXKR), which is highly conserved throughout all cadherin molecules. Coexpression of the PC furin with human desmoglein-1 or desmoglein-3 proproteins results in efficient propeptide processing.[19] Mutation of the tetrapeptide recognition site or selective inhibition of PCs prevents endoproteolytic processing of cadherin propeptides and abrogates their adhesive function.[20,21] Therefore, we predict that the R45Q and R48H mutations abolish furin cleavage of pro-desmoglein-2, thereby disrupting production of mature, functional protein.

Individual C.II-1 has a mutation (C506Y) in the extracellular anchor (EA) domain, immediately distal to the fourth extracellular cadherin (EC) domain, which ends at residue 502. Cysteine→tyrosine substitution confers loss of a sulfur residue that likely participates in disulfide bonding in the nonreducing extracellular environment. This cysteine is conserved in all species of desmoglein-2 (fig. 2).

Individual D.II-4 has a mutation (G811C) in the intracellular cadherin-typical sequence (ICS) of desmoglein-2. This region is responsible for binding desmoglein-2 to plakoglobin, as determined elsewhere by mutagenesis analyses of residues 794–824.[22–24] All species and subtypes of desmogleins have glycine at this position (fig. 2).

In addition to the R48H mutation in the furin-cleavage domain, individual B.II-1 has a G→A transition at np 915 that results in a premature termination codon (PTC) in exon 8 (W305X). His 77-year-old unaffected mother (individual B.I-4) shares the W305X mutation but does not have the R48H mutation. She underwent screening echocardiography, electrocardiography (ECG), exercise stress testing, and several 24-h ambulatory Holter monitors. Results were notable for normal right and left ventricular size and function, normal ECG depolarization and repolarization, atrial fibrillation, and lack of significant ventricular arrhythmias. Because of the absence of any features of ARVD/C, endomyocardial biopsy was not performed. The proband's father (individual B.I-3) died—at age 74 years from diabetes mellitus and sepsis—prior to providing a DNA sample or consent for analysis. The father's surviving siblings (individuals B.I-1 and B.I-2) do not have the R48H mutation. Although the proband may have inherited this mutation from his father, the mutation may also be a de novo mutation. RT-PCR analysis, with use of mRNA derived from the proband's lymphocytes, indicates that the R48H mutation occurs on the paternal allele (fig. 3).

Three of the four probands have single, heterozygous missense mutations in *DSG2*. A fourth proband (B.II-1) has both a missense mutation on one allele of *DSG2* and

Table 1. *DSG2* Mutations

Proband	Exon	Nucleotide	Amino Acid	ARVD/C Criteria[a]
A.III-1	3	134G→A	R45Q	Structural or functional right ventricular abnormality*, histopathologic right ventricular fibrofatty replacement*, ECG repolarization abnormality†, and diagnostic arrhythmias†
B.II-1	3	143 G→A	R48H	Structural or functional right ventricular abnormality*, ECG depolarization abnormality*, ECG repolarization abnormality†, and diagnostic arrhythmias†
B.II-1	8	915 G→A	W305X	
C.II-1	11	1517 G→A	C506Y	Structural or functional right ventricular abnormality†, ECG repolarization abnormality†, ECG depolarization abnormality†, and diagnostic arrhythmias†
D.II-4	15	2431 G→T	G811C	Family history*, ECG repolarization abnormality†, and structural or functional right ventricular abnormality†

[a] An asterisk (*) indicates that a major criterion is filled in the category; a dagger (†) indicates that a minor criterion is filled in the category.

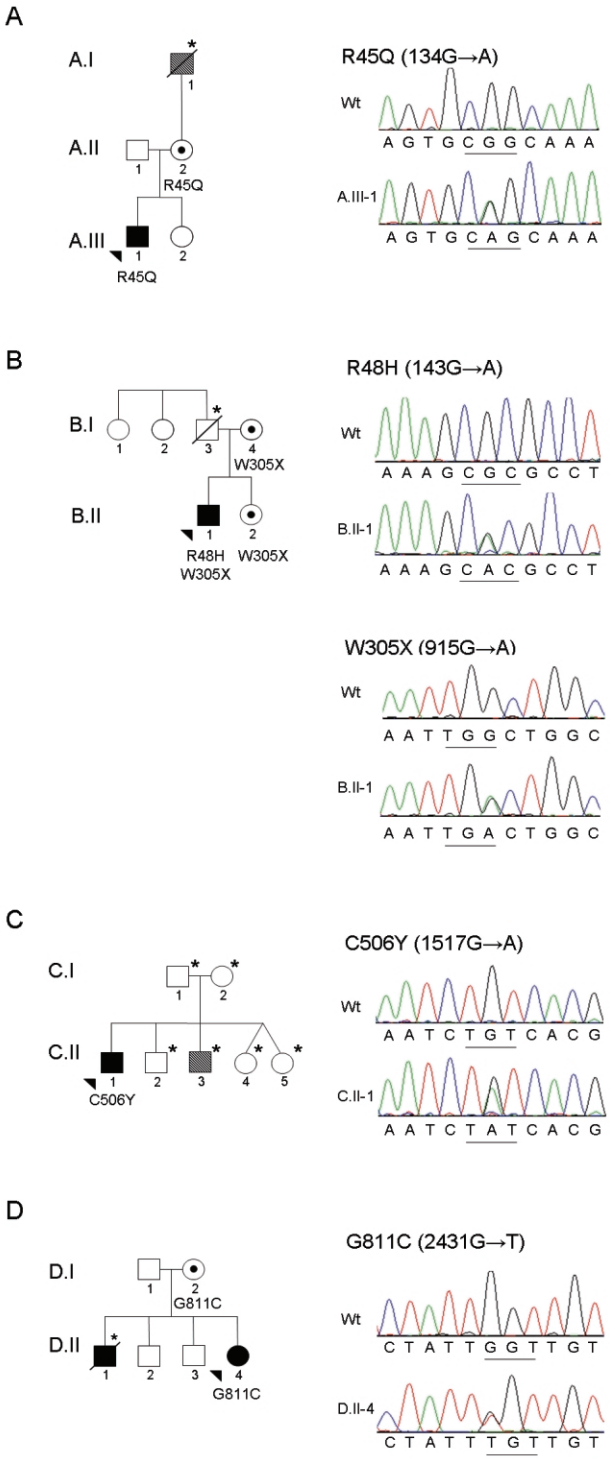

Figure 1. Pedigrees and chromatograms demonstrating mutations in *DSG2* for four probands with ARVD/C. In each pair of chromatograms, the top panel is from an unaffected control and the bottom panel is from the affected individual. *A,* Family A: individual A.III-1 with heterozygous R45Q (134G→A) mutation. *B,* Family B: individual B.II-1 with heterozygous R48H (143G→A) mutation and heterozygous W305X (915G→A) mutation. *C,* Family C: individual C.II-1 with heterozygous C506Y (1517G→A) mutation. *D,* Family D: individual D.II-4 with heterozygous G811C (2431G→T) mutation. Sequence analyses were performed bidirectionally with an ABI 3730 DNA Analyzer (Applied Biosystems). Chromatograms were analyzed using Sequencher 4.1 software for mutational analysis and with MacVector 7.2.2 software for ClustalW alignment. For pedigrees, squares represent males, circles represent females, blackened symbols indicate affected status, unblackened symbols indicate unaffected status, striped symbols indicate subdiagnostic features of ARVD/C, arrowheads indicate probands, dots indicate mutation carrier(s), and an asterisk (*) indicates that no DNA was available for sequencing.

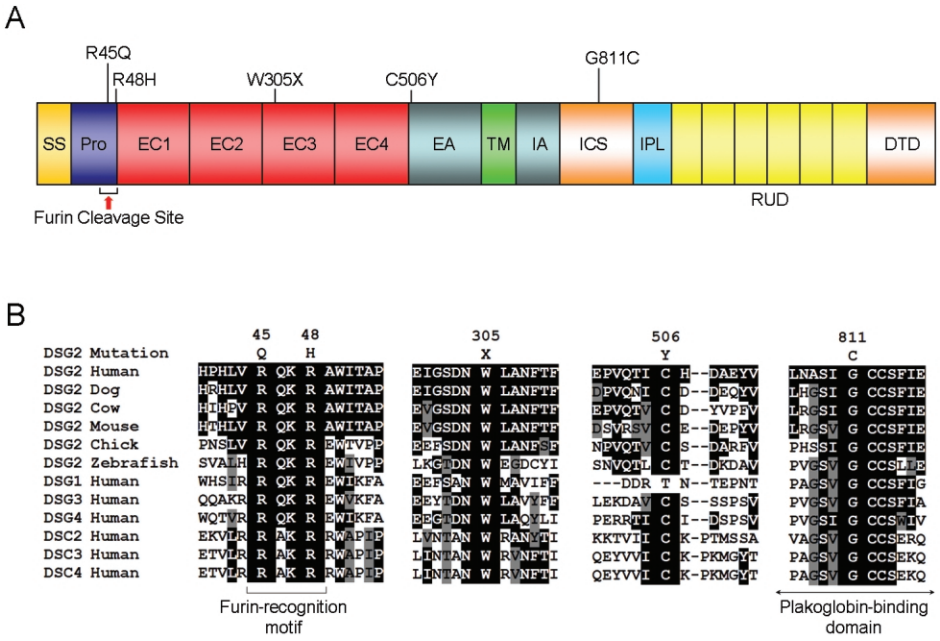

Figure 2. Location and conservation of mutated residues. *A,* Location of mutations along schematic representation of pre-pro-desmoglein-2. SS = signal peptide sequence; Pro = propeptide; TM = transmembrane domain; IA = intracellular anchor; IPL = intracellular proline-rich linker; RUD = repeated-unit domains; DTD = desmoglein-specific terminal domain (adapted from the work of Getsios et al.[18]). *B,* ClustalW sequence alignment of human *DSG2* to orthologues and to other human desmogleins (*DSG1, DSG3,* and *DSG4*) and desmocollins (*DSC2, DSC3,*and *DSC4*). Identical residues are shaded in black; conserved residues are shaded in gray. Mutations identified in the present study are shown at the top of each alignment. The furin-recognition motif and plakoglobin binding domain are indicated.

a nonsense mutation on the other. This raises the question of whether mutations in *DSG2* cause disease by a recessive or dominant mode of inheritance. If inheritance is recessive, the three singly heterozygous probands could harbor mutations on a second, as-yet-unidentified disease-causing gene. This could explain why individual B.I-4 shares the R45Q mutation but has no evidence of ARVD/C on cardiac magnetic resonance imaging, ECG, Holter monitoring, or signal-averaged ECG. Alternatively, these findings could result from dominant inheritance with low penetrance, as has been reported for other genetic forms of ARVD/C.[25] Complete loss of desmoglein-2 in mice results in early embryonic lethality.[26] The presence of compound heterozygous mutations in individual B.II-1 suggests either partial function or a functional redundancy in humans that is not present in mice.

Among these probands, none has woolly hair or keratoderma. As a child, after receiving penicillin, individual B.II-1 developed a disseminated cutaneous exanthem with extensive mucosal involvement, which was diagnosed as Stevens Johnson syndrome (SJS). Other than a severe postoperative wound infection, he has had no other cutaneous diseases. The occurrence of SJS in the proband with compound heterozygosity for mutations in desmoglein-2 suggests that this desmosomal protein may be involved in the pathogenesis of SJS. Several members of the desmoglein family have been associated with other diseases of the skin. Stanley et al. demonstrated that desmoglein-1 is the antigen target in pemphigus foliaceus, an autoimmune disorder affecting skin.[27] Similarly, desmoglein-3 and desmoglein-4 have been identified as antigen targets in pemphigus vulgaris.[28,29] Mutation in *DSG1* has also been described in the dominantly inherited skin disease striate palmoplantar keratoderma type I.[30] Mutations in *DSG4* result in localized autosomal recessive hypotrichosis.[29] Finally, cleavage of desmoglein-1 by staphylococcal exfoliative toxins has been shown to result in staphylococcal scalded skin syndrome by facilitating the spread of *Staphylococcus aureus* under the stratum corneum.[31]

Results of clinical screening for ARVD/C and *DSG2* genetic testing on those family members who consented to these analyses are available in table A2. Incomplete penetrance is evident, as described in other forms of ARVD/C.[25] The absence of phenotypic manifestations of ARVD/C in the mother and sister of individual B.II-1, who share the single W305X mutation, could be due to incomplete penetrance, or this mutation may be insufficient to result in ARVD/C in isolation. Because the mutation creates a PTC, mutant transcripts are predicted to be rapidly degraded by the nonsense-mediated mRNA decay (NMD) pathway.[32] This would then suggest that haploinsufficiency for desmoglein-2 is not the mechanism for disease.

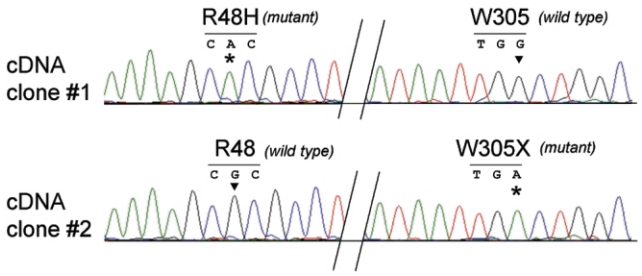

Figure 3. Compound heterozygous mutations in *DSG2* for individual B.II-1. Total RNA was isolated from Epstein-Barr virus–transformed lymphoblasts from individual B.II-1 (Trizol [Invitrogen]; RNeasy clean-up [Qiagen]), and cDNA was generated by reverse transcription (Superscript III 1st-strand cDNA synthesis kit [Invitrogen]). PCR products amplified with primers spanning the proband's two mutations were cloned into the pCR2.1 plasmid (TOPO-TA cloning kit [Invitrogen]), and several individual clones were sequenced using both M13 forward and reverse primers. Representative chromatograms from two clones are displayed, which demonstrate that the R48H and W305X mutations lie on different alleles.

Even if the mutant transcript escapes NMD, the resulting truncated protein lacks a transmembrane domain (aa 612–634) and would likely be secreted extracellularly, which would prevent a potentially deleterious dominant negative effect.[33] In this model, the phenotypic manifestations of heterozygous *DSG2* mutation carriers would be same as for those with compound heterozygous mutation, with one mutation causing a PTC prior to the transmembrane domain (TM). However, additional individuals harboring mutations that prevent transmembrane anchoring of desmoglein-2 are required for definitive conclusions regarding the role of haploinsufficiency.

The mechanism whereby mutations affecting components of the cardiac desmosome result in ARVD/C remains in question. Some have suggested that either a lack of desmosomal protein or incorporation of mutant protein will disrupt cell-cell adhesion, predisposing regions of greatest stretch to fibrofatty degeneration.[10,34] Others have invoked a pathogenic role for viral infection, perhaps worsened by a mutant cardiac desmosome.[35,36] Finally, alteration in cytokines such as transforming growth factor $\beta 3$ may also contribute to disease pathogenesis.[15]

In conclusion, we report that mutations in *DSG2* contribute to the development of ARVD/C in the absence of mutations in *PKP2* or *DSP*. This provides further evidence that disruption of the cardiac desmosome is important in the pathogenesis of this condition. Since sudden cardiac death is a prominent manifestation of ARVD/C, recognition of those at highest risk of developing the condition may be improved by genetic screening within affected families.

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Appendix

Table A1. Oligonucleotide Primer Sequences

	Primer Sequence (5′→3′)	
Region	Sense	Antisense
Exon 1	ACCCAAGGACGTCACGGTCCC	CCAAGAGGATTTTCCGAAGCC
Exon 2	AGGAGTCAGTATGGATCCAGG	ATTCAGCACCTCGTCATGGAC
Exon 3	TAGACAATGAAGCCTCATAGG	CAATGATGCTGCATCTTCCGG
Exon 4	ATCACTTCTTAGGCTTTTGGC	
Exon 5		AGGAAAGCAGTTCTGAACTGC
Exon 6	CTAATGTGTTCTAATTGGTTGGACC	TTGGCTCACTGCAACTTCTGCC
Exon 7	TTCTGCAAAAGCTCTGACTGC	
Exon 8		GAATTTGAACCATAGTGTGACC
Exon 9	AGTTGGACTATTCAGTGCTGC	TTTGGGGAACTATAATGCTGG
Exon 10	TGACATGCAGTAAAGAGAGGG	CAAAGTGCTGGGATTACAGGC
Exon 11	AAACATCTTCATCAACCTCTGG	TTCCAGTGCATCTTTGTGAACG
Exon 12	CAGCAATGAAAGAACATTTGTGG	CAGTTGTTTCCCTATTCACCC
Exon 13	GTGAAGACAAGTCCAGGAAGG	CAAAGGCACATGAGTGAAATCC
Exon 14	AGCTTATACCTTCCTATGCCC	AGTCTCATTTGGATCCAAGGC
Exon 15	TTGTGTTTCCCTGATGGTTCC	CTGTAAGGCTCATGAAAAATCAGG
cDNA	TGCTTTAACGTTGGAAGTGG	TTGATGGGAATGGGTGTAGG

NOTE.—Intronic sense and antisense oligonucleotide primers used for sequencing the 15 exons of human *DSG2* are shown. Primers used to amplify the coding region containing both the R48H mutation and the W305X mutation are shown (cDNA). Reference human sequence was obtained from Ensembl.

Table A2. Clinical and Genetic Findings in Study Families

Subjects	*DSG2* Mutation	Age[a] (YEARS)	Family History[b]	Finding or Result: Right Ventricle Structure Abnormality	Depolarization Abnormality	Repolarization Abnormality	Arrhythmia	Histopathology	Criteria[c] (Major/ Minor)
Family A:									
I-1	Not tested	62*	Minor	Not screened	Not screened	Not screened	Not screened	Not screened	0/1
II-1	Not tested	46	Minor	None	None	None	None	Not screened	0/1
II-2	R45Q	46	Minor	None	None	None	None	Not screened	0/1
III-1	R45Q	19	Proband	Major	None	Minor	Minor	major	2/2
III-2	Not tested	16	Minor	None	None	None	None	Not screened	0/1
Family B:									
I-1	None	81	Minor	Not screened	Not screened	Not screened	Not screened	Not screened	NA
I-2	None	80	Minor	Not screened	Not screened	Not screened	Not screened	Not screened	NA
I-3	Not tested	74*	Minor	None	None	None	None	Not screened	0/1
I-4	W305X	77	Minor	None	None	None	None	Not screened	0/1
II-1	W305X R48H	42	Proband	Major	Major	Minor	Minor	Not screened	2/2
II-2	W305X	39	Minor	None	None	None	Not screened	Not screened	0/1
Family C:									
I-1	Not tested	73	Minor	None	None	None	None	Not screened	0/1
I-2	Not tested	69	Minor	None	None	None	None	Not screened	0/1
II-1	C506Y	45	Proband	None	Minor	Minor	Minor	Not screened	0/4
II-2	Not tested	44	Minor	None	None	None	None	Not screened	0/1
II-3	Not tested	43	Minor	Minor	None	None	None	Not screened	0/2
II-4	Not tested	39	Minor	None	None	None	None	Not screened	0/1
II-5	Not tested	39	Minor	None	None	None	None	Not screened	0/1
Family D:									
I-1	None	73	Major	None	None	None		Not screened	1/0
I-2	G811C	73	Major	Not screened	Not screened	Not screened	Not screened	Not screened	NA
II-1	Not tested	32*	Proband	On autopsy	Not screened	Not screened	Not screened	On autopsy	Autopsy[d]
II-2	None	45	Major	None	None	None	None	Normal	1/0
II-3	None	44	Major	None	None	None	None	Not screened	1/0
II-4	G811C	40	Major	Minor	None	Minor	None	Not screened	1/2

[a] An asterisk (*) indicates age at death.

[b] Minor = satisfies minor criterion in this category; major = satisfies major criterion in this category.

[c] To establish a diagnosis of ARVD/C, the subject must meet two major criteria, one major and two minor criteria, or four minor criteria in different categories. NA = not available.

[d] The diagnosis was established during postmortem autopsy rather than by use of the clinical criteria.

Web Resources

The URLs for data presented herein are as follows:

Ensembl, http://www.ensembl.org/Homo_sapiens/index.html
Johns Hopkins ARVD Program, http://www.arvd.com/
Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/Omim/ (for ARVD/C, Naxos syndrome, and Carvajal syndrome)

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