

ORIGINAL ARTICLE

Clinical Findings and Diagnostic Yield of Arrhythmogenic Cardiomyopathy Through Genomic Screening of Pathogenic or Likely Pathogenic Desmosome Gene Variants

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BACKGROUND: Genomic screening holds great promise for presymptomatic identification of hidden disease, and prevention of dramatic events, including sudden cardiac death associated with arrhythmogenic cardiomyopathy (ACM). Herein, we present findings from clinical follow-up of carriers of ACM-associated pathogenic/likely pathogenic desmosome variants ascertained through genomic screening.

METHODS: Of 64 548 eligible participants in Geisinger MyCode Genomic Screening and Counseling program (2015–present), 92 individuals (0.14%) identified with pathogenic/likely pathogenic desmosome variants by clinical laboratory testing were referred for evaluation. We reviewed preresult medical history, patient-reported family history, and diagnostic testing results to assess both arrhythmogenic right ventricular cardiomyopathy and left-dominant ACM.

RESULTS: One carrier had a prior diagnosis of dilated cardiomyopathy with arrhythmia; no other related diagnoses or diagnostic family history criteria were reported. Fifty-nine carriers (64%) had diagnostic testing in follow-up. Excluding the variant, 21/59 carriers satisfied at least one arrhythmogenic right ventricular cardiomyopathy task force criterion, 11 (52%) of whom harbored *DSP* variants, but only 5 exhibited multiple criteria. Six (10%) carriers demonstrated evidence of left-dominant ACM, including high rates of atypical late gadolinium enhancement by magnetic resonance imaging and nonsustained ventricular tachycardia. Two individuals received new cardiomyopathy diagnoses and received defibrillators for primary prevention.

CONCLUSIONS: Genomic screening for pathogenic/likely pathogenic variants in desmosome genes can uncover both left- and right-dominant ACM. Findings of overt cardiomyopathy were limited but were most common in *DSP*-variant carriers and notably absent in *PKP2*-variant carriers. Consideration of the pathogenic/likely pathogenic variant as a major criterion for diagnosis is inappropriate in the setting of genomic screening.

Key Words: arrhythmogenic right ventricular cardiomyopathy ■ desmosome ■ genetic screening ■ genomics ■ sudden cardiac death

An important aspiration of genomic medicine, as a cornerstone of the vision for precision medicine, is genetically informed, individualized risk stratification enabling early action for disease prevention or

mitigation.^{1,2} The potential benefit of such foresight is perhaps most profound for heritable diseases characterized by a quiescent phase culminating in a dramatic or fatal presentation that is potentially avoidable via earlier

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Nonstandard Abbreviations and Acronyms

ACM	arrhythmogenic cardiomyopathy
ARVC	arrhythmogenic right ventricular cardiomyopathy
CMR	cardiac magnetic resonance
DSC2	desmocollin 2
DSG2	desmoglein 2
DSP	desmoplakin
EHR	electronic health record
LGE	late gadolinium enhancement
LP	likely pathogenic
LVEF	left ventricular ejection fraction
P	pathogenic
PKP2	plakophilin 2
RYR2	ryanodine receptor 2
SCD	sudden cardiac death
TFC	2010 Task force criteria

detection and intervention. This premise underlies the current recommendations from the American College of Medical Genetics and Genomics for reporting secondary findings from clinical sequencing for specific genes and conditions, such as arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC).³ ARVC—a specific form of arrhythmogenic cardiomyopathy (ACM)⁴ frequently linked with variants in desmosome genes—is associated with potentially deadly arrhythmias, with sudden cardiac death (SCD) reported as the presenting symptom in up to 23% of index cases,⁵ particularly in young adults.^{6,7} Early risk stratification based on genomic findings is, therefore, a promising potential paradigm for prevention of SCD in this setting through medical intervention or other means of mitigation.

Early efforts exploring the feasibility of this genomics-first paradigm to ACM diagnosis have identified significant potential challenges. One study estimated disease penetrance in the absence of symptoms or family history at ≈6%⁸—based in part on the population prevalence of loss-of-function desmosome variants (0.25%), which have the strongest association with ACM.⁹ Consistent with these low penetrance estimates, we have previously reviewed electronic health records (EHR) of desmosome-variant carriers bioinformatically identified through our institutional DNA sequenced biobank (MyCode) and have found generally weak or absent disease associations.^{8,10} These studies have been limited, however, by reliance on retrospective EHR data. This limitation is particularly important given both the complexity of ARVC/ACM diagnostic criteria^{11,12} and the inability to assess disease status for patients without sufficient EHR data, especially those with no prior indication for cardiac evaluation.

Through MyCode, many of these variant carriers have been notified of pathogenic (P) or likely pathogenic (LP) variants confirmed through a College of American Pathologists–accredited/Clinical Laboratory Improvement Amendments–certified laboratory and referred for genetic counseling and diagnostic evaluation, often by cardiologists with expertise in this area. Such follow-up allows for more detailed phenotypic assessment than prior studies, inclusive of detailed family history collection and disease-specific testing in many instances. Hence, we herein report clinical findings from the first 92 patients identified with P/LP desmosome variants. Our hypothesis was that appropriate clinical evaluation of desmosome-variant carriers would uncover otherwise masked or sub-clinical disease.

METHODS

A full description of the methods used in this study is available in the [Data Supplement](#). Institutional review board approval was obtained for this study; all individuals previously provided informed consent to participate in the MyCode Community Health Initiative (MyCode). The data that support the findings of this study will not be made available.^{13–18}

RESULTS

Patient and Variant Details

At the time of this analysis, 64 548 participants were consented in the Geisinger MyCode project and eligible for genomic screening. From this cohort, 92 individuals (0.14%) from 85 distinct families were identified with a clinical laboratory-confirmed P/LP variant in desmoplakin (*DSP*; n=35), plakophilin-2 (*PKP2*; n=24), desmocollin-2 (*DSC2*; n=24), or desmoglein-2 (*DSG2*; n=9); Figure 1. No patient was aware of his/her genetic variant before the result disclosure. The median (interquartile range) age at the time of result disclosure was 56 (38–65) years and 73% were female (Table 1). Collectively, 29 patients' variants were classified as pathogenic and 63 were classified as LP. Postdisclosure, one LP variant was reclassified to uncertain significance, and 2 LP variants were reclassified to pathogenic. Details of observed variants are provided in Table 2; we note that all reported variants are putatively truncating (null), which have strong or very strong evidence for pathogenicity by current standards and guidelines.

Personal Medical History and Family History

None of the carriers of a desmosome variant had an existing diagnosis of ARVC. One carrier of a *DSP* variant had a history of nonischemic, left ventricular noncompaction dilated cardiomyopathy with significant ventricular ectopy diagnosed before age 50. Another *DSP*-variant carrier had an existing diagnosis of pulmonary sarcoidosis

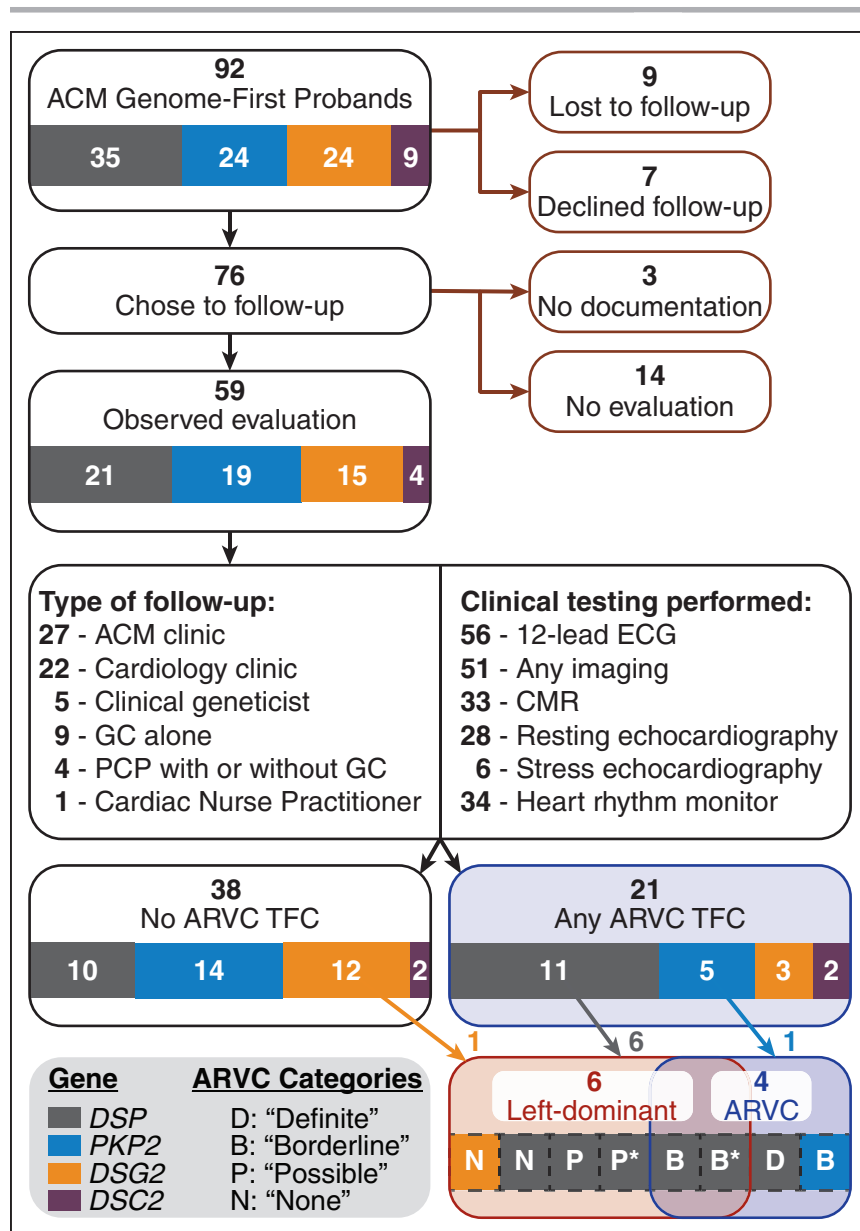


Figure 1. Summary of postdisclosure clinical course for desmosome-variant carriers identified genomics-first through MyCode.

ACM indicates arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; GC, genetic counselor; PCP, primary care provider; and TFC, task force criteria. *Denotes the 2 individuals with new cardiomyopathy diagnoses and implanted defibrillators.

with presumed cardiac involvement based on clinical and imaging criteria and noted ventricular ectopy. The clinical presentation in both of these patients is consistent with ACM based on current guidelines,⁴ although the contribution of the genetic variant to the cardiac findings in the setting of sarcoidosis is unclear.

The past medical history of the variant carriers, in aggregate, was similar to the 64 456 screening-eligible noncarriers from MyCode, inclusive of cardiomyopathy and heart failure diagnoses, and prescription of β -blocker and antiarrhythmic medications (Table 1). There was, however, a significantly higher proportion of pre-existing ventricular tachycardia diagnoses in the carrier group (7% versus 1%, $P=0.018$; Table 1). We note that the relatively high rates of some findings are consistent with the characteristics of MyCode as a health care-system-based population.

Family history details are summarized in Table 3. Individuals carrying the same variant and self-reporting as relatives were grouped as a family ($n=85$) for this analysis. No family history of ACM/ARVC, ventricular tachycardia, or ventricular fibrillation was reported. Sudden cardiac arrest/death was reported in 10 families (12%), but none was due to suspected ACM. Implantable cardioverter-defibrillator implantation was reported in 4 (5%) families and heart failure in 19 (22%). Besides the P/LP variant, no family history ARVC Task Force Criteria (TFC) were observed.

Postdisclosure Course and Diagnostic Findings

The postdisclosure clinical course is summarized in Figure 1. Nine carriers were lost to follow-up at the time of result, while 7 carriers declined any follow-up based on the

Table 1. Demographics and Past Medical History of Desmosome-Variant Carriers Before the Genomic Result Disclosure vs Eligible Noncarriers From MyCode

Demographic/phenotype	Desmosome-variant carriers (n=92)	Noncarriers (n=64 456)	Adjusted <i>P</i> value
Age at result, y	56 (38–65)	60 (45–71)	0.044*
BMI, kg/m ²	32 (27–40)	30 (26–36)	0.18
Female	67 (73%)	41 393 (64%)	0.99
Pathogenic desmosome variant	29 (32%)
Likely pathogenic desmosome variant	63 (68%)†
Palpitations	19 (21%)	11 248 (17%)	0.99
Syncope	18 (20%)	12 173 (19%)	0.99
Chest pain	49 (53%)	31 871 (49%)	0.99
Hypertension	47 (51%)	32 046 (50%)	0.99
Atrial fibrillation	11 (12%)	5040 (8%)	0.58
Coronary artery disease	2 (2%)	4086 (6%)	0.58
Nonischemic cardiomyopathy	6 (7%)	4379 (7%)	0.99
Ischemic cardiomyopathy	2 (2%)	1911 (3%)	0.99
Heart failure	4 (4%)	2277 (4%)	0.99
Bundle branch block	2 (2%)	2221 (3%)	0.99
Prescribed beta blockers	29 (32%)	21 808 (34%)	0.99
Prescribed antiarrhythmic	2 (2%)	1898 (3%)	0.99
Ventricular fibrillation	0 (0%)	231 (0.4%)	0.99
Ventricular tachycardia	6 (7%)	744 (1%)	0.018*
Other arrhythmia	32 (35%)	19 009 (29%)	0.99
Cardiac arrest	6 (7%)	2251 (3%)	0.58

Values are median (interquartile range) or n (%). BMI indicates body mass index.

*Adjusted *P* values <0.05 were considered statistically significant. Noncarrier age at the time of analysis was used for comparison.

†One variant later downgraded to variant of uncertain significance.

disclosure. Of the 76 carriers who reported an intent to follow-up from the initial disclosure, 17 had either no observed diagnostic evaluation at least 6 months postdisclosure or followed-up externally to the Geisinger system. Hence, 59 carriers (64%) had at least some observed diagnostic evaluation based on the genomic finding (ie, 12-lead ECG, imaging, or ambulatory rhythm monitoring), and thus form the basis of our retrospective assessment. All 3 diagnostic evaluations were completed for 33 of these carriers (56%; Figure I in the [Data Supplement](#)). Demographics (age, sex, ethnicity, race) were not significantly different between the groups with or without observed follow-up.

All carriers, with 2 exceptions, completed a resting 12-lead ECG during follow-up. One additional patient's ECG was paced and, therefore, not scored. From the remaining 56, 4 carriers (7%) satisfied major ARVC repolarization criteria, while 8 (14%) had minor ARVC repolarization criteria. One of these 8 had T-wave inversions exclusively in leads V3–V6. Finally, 2 carriers (3%) had terminal activation delay (minor ARVC conduction criteria; Figure 2; Table 4).

Imaging studies were completed for 51 carriers (86%), inclusive of cardiac magnetic resonance (CMR) and echocardiography (resting or stress; Table II in the [Data Supplement](#)). Three carriers (5%) satisfied major imaging TFC (2 based on echocardiography and one based on CMR); no minor imaging criteria were observed (Figure 2). Of note, 15 carriers had global RV dysfunction/dilation without regional abnormalities. In addition, 10 carriers (17%) had findings of atypical LV late gadolinium enhancement (LGE), predominantly in the midwall or subepicardium of septal (10 carriers), inferior (4), inferolateral (3), anterolateral (2), or anterior (2) segments (Figure 3, Table 4). Four of these carriers had no evidence of arrhythmias or ECG criteria, although other nondiagnostic imaging abnormalities (mild LV or RV dysfunction, moderate RV dilation, mild septal thickening) were present in 3 of the 5. Finally, 5 individuals had reduced (<50%) LV ejection fraction (LVEF).

Ambulatory rhythm monitoring (Holter monitor or Zio Patch) was completed for 34 (58%) carriers. Episodes of nonsustained VT with left bundle branch morphology and superior axis (major ARVC arrhythmia criterion) were observed in 3 carriers (5%), while 6 carriers (10%) had >500 premature ventricular contractions in a 24-hour period (minor ARVC arrhythmia criterion; Figure 2, Table 4). In 4 other cases, episodes of nonsustained VT were observed with other/unknown morphology.

Diagnostic Results for ARVC

In total, 21 of the 59 unique carriers (36%) satisfied at least one of the ARVC TFC from the diagnostic evaluations above. As seen in Figure 2A, the majority of patients with diagnostic criteria had variants in *DSP* (11/21; 52%), particularly arrhythmia and imaging findings. Conversely, few criteria were noted for *DSG2*- (3/15; 20%) or *DSC2*- (2/4, 50%) variant carriers, and all were minor criteria. *PKP2*-carriers also had few criteria (5/19; 26%). Comparing these gene-specific rates showed no statistical differences.

The translation of these observed criteria into an ARVC diagnosis is dependent on the choice of how to incorporate the P/LP variant—a major criterion according to the 2010 TFC—as demonstrated in Figure 4. Strict inclusion of the variant as a major criterion yielded a high degree of purported diagnoses for ARVC, with 10/59 individuals (17%) qualifying for definite diagnosis, 11 (19%) satisfying criteria for a borderline diagnosis, and the remaining 38 (64%) having at least a possible diagnosis based on the variant alone. However, recognizing that a variant-based ascertainment may require a different diagnostic weighting for the variant than in the traditional symptoms-based or family history-based presentation, we additionally considered alternative weighting options. At the opposite extreme, not counting the variant toward diagnostic criteria yielded one individual

Table 2. Observed Pathogenic or Likely Pathogenic Variants (N=58) in Desmosome Genes Identified From Genomic Screening and Clinical Confirmation Within MyCode

Gene	Transcript	cDNA change	Protein change	Pathogenicity	Variant carriers	Distinct families
All variants				17 P; 41 LP	92	85
DSG2	NM_001943.3	c.45+1G>A		LP	1	1
		c.73_77delCACTT	p.His25ThrsX8	LP	1	1
		c.523+1_523+2delGT		LP	9	8
		c.523+2T>C		P/LP*	2	2
		c.829_840del12	p.Leu277_Met280del	LP	7	7
		c.1880-2A>G		P	1	1
		c.2533delA	p.Ile845X	P	1	1
		c.2761_2764dupGCTA	p.Thr922SerfsX6	P	1	1
		c.2923delG	p.Val975X	P	1	1
DSG2 totals				4 P; 5 LP	24	23
DSP	NM_004415.2	c.226C>T	p.Gln76X	LP	1	1
		c.273delT	p.Glu92AsnfsX2	LP	1	1
		c.329_330delGTinsAA	p.Cys110X	P	1	1
		c.478C>T	p.Arg160X	LP	1	1
		c.699G>A	p.Trp233X	P/LP*	3	2
		c.919C>T	p.Gln307X	LP	1	1
		c.1141-2A>T		LP	3	3
		c.1693delA		LP	1	1
		c.2436+2T>C		LP	2	2
		c.2802_2803delCA	p.His934GlnfsX2	LP	1	1
		c.3133C>T	p.Arg1045X	LP	1	1
		c.4026G>A	p.Trp1342X	LP	1	1
		c.4037_4041delATGAA	p.Asn1346ThrsX3	P/LP*	2	1
		c.4198C>T	p.Arg1400X	P	1	1
		c.4397dupA	p.Gln1467AlafsX4	LP	1	1
		c.4882_4886delinsTTCT	p.Arg1628PhefsX17	LP	1	1
		c.4999C>T	p.Gln1667X	P/LP*	3	3
		c.5327_5330delAGAG	p.Glu1776GlyfsX4	LP	1	1
		c.6466dupA	p.Arg2156LysfsX9	P	1	1
		c.6583_6584delCA	p.His2195TyrfsX26	P	1	1
		c.7075del	p.Ile2359SerfsX10	LPT†	1	1
		c.7129dupA	p.Ile2377AsnfsX3	LP	1	1
		c.7469delA	p.Tyr2490LeufsX17	LP	3	1
c.7656_7657dupCA	p.Ser2553ThrsX9	LP	1	1		
c.7874_7875del	p.Thr2625ArgfsX18	LPT†	1	1		
DSP totals				4 P; 21 LP	35	31
PKP2	NM_004572.3	c.235C>T	p.Arg79X	P	3	3
		c.337-2A>T		LP	1	1
		c.499C>T	p.Gln167X	P	1	1
		c.533dupT	p.His179AlafsX37	LP	1	1
		c.968_971delinsGCT	p.Gln323ArgfsX29	LP	1	1
		c.968_975dupAGGCGGCC	p.Ala326ArgfsX29	LP	1	1
		c.1034+1delG		LP	1	1
		c.1035-1G>A		LP	1	1
		c.1237C>T	p.Arg413X	P	1	1
		c.1677dupT	p.Gly560TrpfsX12	P	1	1

(Continued)

Table 2. Continued

Gene	Transcript	cDNA change	Protein change	Pathogenicity	Variant carriers	Distinct families
		c.1677_1678insT	p.Gly560TrpfsX12	LP	1	1
		c.1840delC	p.Leu614SerfsX42	LP	1	1
		c.1912C>T	p.Gln638X	P	1	1
		c.2146-1G>C		P/LP*	6	4
		c.2489+1G>A		P	3	3
<i>PKP2</i> totals				6 P; 9 LP	24	22
<i>DSC2</i>	NM_024422.3	c.123delC	p.Lys42AsnfsX2	LP	1	1
		c.631-2A>G		LP‡	1	1
		c.663T>A	p.Tyr221X	P	1	1
		c.880delC	p.Leu294TyrfsX10	LP	1	1
		c.1167G>A	p.Trp389X	LP	1	1
		c.2200C>T	p.Gln734X	P	1	1
		c.2250+1G>C		LP	1	1
		c.2431G>T	p.Gly811X	LP	1	1
		c.2463C>A	p.Tyr821X	P	1	1
<i>DSC2</i> totals				3 P; 6 LP	9	9

LP indicates likely pathogenic; and P, pathogenic.

*Different pathogenicity calls between clinical laboratories for the same variant (counted as LP for totals).

†Variant subsequently upgraded to pathogenic by Invitae.

‡Variant subsequently downgraded to uncertain significance by the partners laboratory for molecular medicine.

(2%) with a definite diagnosis, 3 (5%) borderline diagnoses, 6 (10%) possible diagnoses, and the remaining 49 (83%) with no diagnosis.

To date, one patient from this cohort has been diagnosed with ARVC (with bi-ventricular involvement)—one of the borderline diagnosis cases from the variant-exclusive summary above. This was a 57-year old male with a LP *DSP* variant (NM_004415.2:c.1141-2A>T), who met major imaging criteria by CMR (RV dyskinesia and RV end-diastolic volume, 117 mL/m²) and minor arrhythmia

criteria (1219 ventricular ectopies on 24-hour Holter monitor). Imaging also revealed a LVEF of 45% and regions of mid-myocardial and subepicardial LGE, including near transmural enhancement of the mid inferior wall of the LV. None of these findings was known before patient evaluation following the genomic result disclosure. He subsequently underwent a dual-chamber defibrillator implant for primary prevention of SCD.

The individual with the definite diagnosis from the variant-exclusive summary was a 38-year old male with a LP *DSP* variant (NM_004415.2:c.273delT, p.Glu92fs), who met major criteria for both imaging (RV akinesia and fractional area change, 14% by echocardiography) and repolarization (T-wave inversions V1–V4 in the absence of complete right bundle branch block). However, this case was diagnostically confounded by the presence of chronic thromboembolic pulmonary hypertension—to which these findings have been attributed—precluding a diagnosis of ARVC, although the potential contribution of the genetic variant to the development of these secondary cardiac findings is unclear.

Left-Dominant Phenotype

Left-dominant criteria findings (arrhythmia or LV structure/function abnormality) are summarized in Figure 2B. Of note, the arrhythmia criteria for this purpose were broadly inclusive of observed VT as well as past diagnostic history of cardiac arrhythmias (see Methods). Six carriers (10%) satisfied both criteria (5 with a variant in *DSP*, 1 in *DSG2*), including the 1 ARVC-diagnosed case from above (Figure 1). Of the other 5 carriers, 4 had a

Table 3. Self-Reported Family History From Unique Desmome-Variant-Carrying Families

Source of family history data	Individuals (n=92)	
Pedigree and EHR	66 (72%)	
EHR only	24 (26%)	
Pedigree only	2 (2%)	
Phenotype of interest	Unique families (n=85)	
	FDRs	Total
ACM/ARVC diagnosis	0	0
SCD or SCA	4 (5%)	10 (12%)
SCD <35 y of age	0	1 (1%)*
ICD	4 (5%)	4 (5%)
Heart failure (right or left)	10 (12%)	19 (22%)
VT or VF	0	0

Values are n (%). ACM indicates arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; EHR, electronic health record; FDRs, first-degree relatives; ICD, implantable cardioverter-defibrillator; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Third-degree relative, during sleep at age 14.

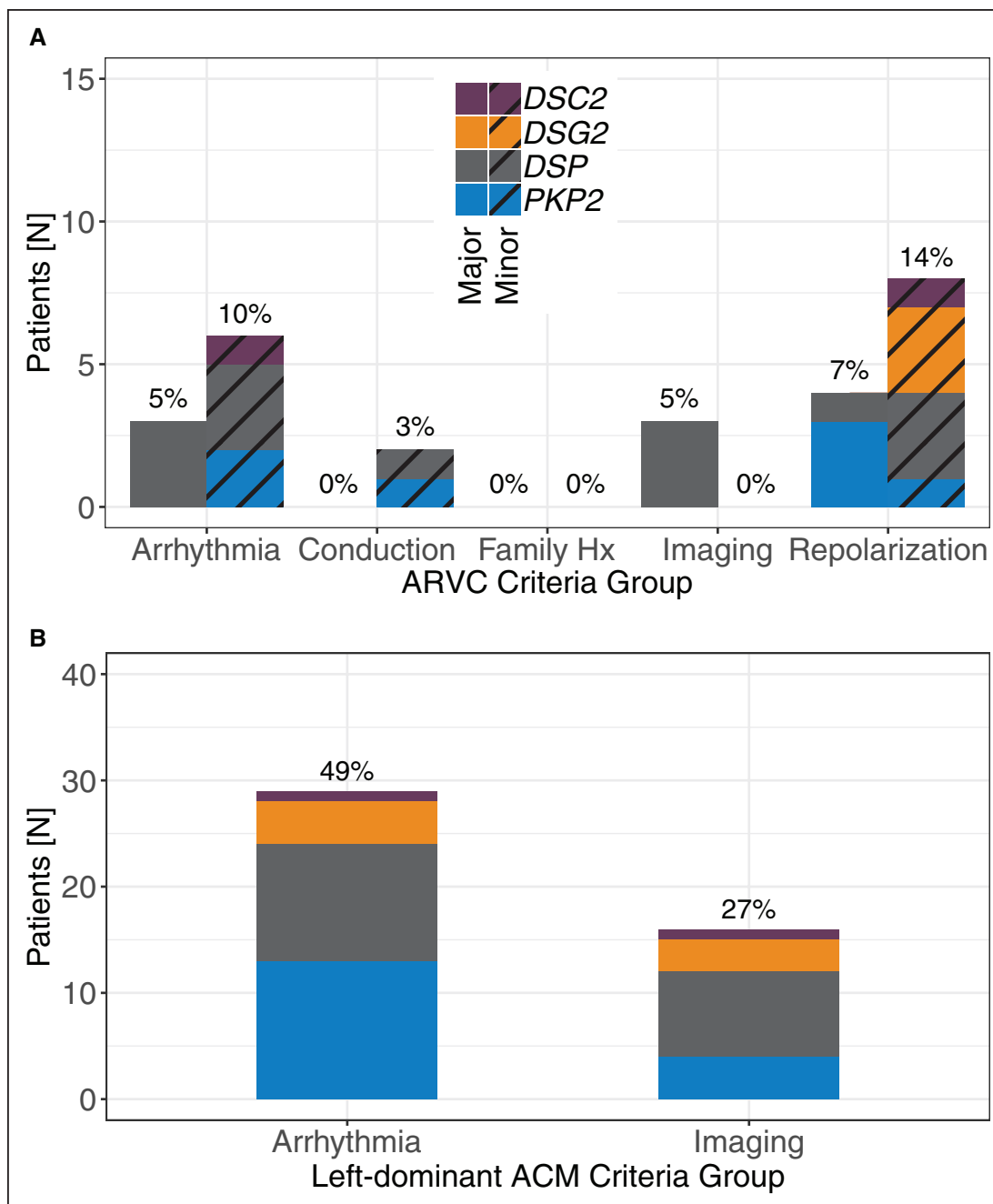


Figure 2. Number of patients (and percentage of 59 with follow-up) satisfying diagnostic criteria by group.

A, Diagnostic arrhythmogenic right ventricular cardiomyopathy (ARVC) task force criteria groups, separated by major and minor criteria. **B**, Left-dominant criteria groups. Imaging findings included reduced ejection fraction or atypical late gadolinium enhancement in the left ventricle. Of note, the majority of arrhythmia findings (15/29; 52%) were in carriers with only other cardiac arrhythmias. ACM indicates arrhythmogenic cardiomyopathy; and Hx, history.

postresult CMR, all of which revealed atypical LV LGE in mid-myocardial or subepicardial regions of the basal to mid-LV, including the septum. Reduced (<50%) LVEF was observed in 3 of 5. Regarding arrhythmia findings, there was no history of ventricular fibrillation or cardiac arrest, but 4 of the 5 had history of (predisclosure or postdisclosure) nonsustained ventricular tachycardia, and 3 had an existing diagnosis of cardiac arrhythmia (including atrial arrhythmias, Table 1 in the [Data Supplement](#)). Of note,

the existing ARVC TFC demonstrated poor sensitivity for identifying these patients with left-dominant phenotypes as only 2 of 6 cases had findings sufficient for a borderline diagnosis, with another 2 having possible diagnoses (Figure 1). Finally, though suggestive, the differences in observed criteria by gene were not statistically significant (eg, *DSP* [24%] versus *PKP2* [0%]; $P=0.25$).

Upon follow-up, one patient with a *DSP* variant (NM_004415.2:c.699G>A, p.Trp233X) received new

Table 4. Imaging, ECG, and Arrhythmia Characteristics of Desmosome-Variant Carriers

Category	Count	Test-specific percentage	Percentage of 59 with any testing
Patients with echocardiography	28	...	47%
RV akinesia, dyskinesia, or aneurysm	2	7%	3%
RV FAC (33%<x≤40%)	14	50%	24%
RV FAC ≤33%	2	7%	3%
RVOT size (PSAX; 18≤x<21 mm/m ²)	1	4%	2%
RVOT size (PSAX) ≥21 mm/m ²	0	0%	0%
LVEF <50%	1	4%	2%
Patients with CMR	33	...	56%
RV akinesia, dyskinesia, or dyssynchrony	1	3%	2%
RVEF ≤45%	0	0%	0%
RV EDVI (90/100≤x<100/110 mL/m ² F/M)	1	3%	2%
RV EDVI ≥100/110 mL/m ² (F/M)	2	6%	3%
Atypical LGE (LV)	10	30%	17%
Septum	10	30%	17%
Inferior	3	9%	5%
Inferolateral	4	12%	7%
Anterolateral	2	6%	3%
Anterior	2	6%	3%
LVEF <50%	4	12%	7%
Patients with ECG	56	...	95%
TWI V1–V3 or beyond without complete RBBB	4	7%	7%
TWI V1–V2 without complete RBBB	6	11%	10%
TWI in V4, V5, or V6	1	2%	2%
TWI V1–V4 with complete RBBB	0	0%	0%
TWI V3–V6 only	1	2%	2%
QRS duration ≥120 ms	3	5%	5%
Complete RBBB	1	2%	2%
Complete LBBB	0	0%	0%
Nonspecific IVCD	2	4%	3%
Epsilon waves	0	0%	0%
PVCs present	2	4%	3%
RBBB morphology	1	2%	2%
LBBB morphology	1	2%	2%
Terminal activation delay	2	4%	3%
Brugada pattern	0	0%	0%
Hypertrophy	1	2%	2%
Patients with Holter/Zio	34	...	58%
NSVT (LBBB, superior axis)	3	9%	5%
NSVT (LBBB, inferior/unknown axis)	0	0%	0%
NSVT (unknown/other morphology)	4	12%	7%
>500 VEs in any 24 h period	6	18%	10%

CMR indicates cardiac magnetic resonance; EDVI, end-diastolic volume index; EF, ejection fraction; F/M, female/male; FAC, fractional area change; IVCD, inter-ventricular conduction delay; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; NSVT, nonsustained ventricular tachycardia; PSAX, parasternal short axis; PVC, premature ventricular complex; RBBB, right bundle branch block; RV, right ventricle; RVOT, RV outflow tract; TWI, T-wave inversion; and VE, ventricular extrasystole.

diagnoses of nonischemic dilated cardiomyopathy and heart failure in conjunction with this genomic finding. This was a 59-year old male with significant arrhythmia burden (nonsustained VT and >10 000 PVCs (burden of 12%; multi-focal) observed via prior 24-hour Holter monitor) and postdisclosure LVEF of 29%. He has since received an implantable cardioverter-defibrillator. The other 2 patients with reduced LVEF were the 2 *DSP*-variant carriers (NM_004415.2:c.7469delA, p.Tyr2490LeufsX17; NM_004415.2:c.3133C>T, p.Arg1045X) noted with preexisting ACM diagnoses (dilated cardiomyopathy/left ventricular noncompaction and sarcoidosis).

DISCUSSION

In this first retrospective evaluation of a clinical program aimed at follow-up of P/LP desmosome-variant carriers identified by genomic screening, we found that genomics-first ascertainment indeed resulted in new diagnoses of ACM. These diagnoses represented both ARVC—the primary phenotype expected with desmosome variants—and left-dominant ACM, a newer and still evolving disease entity. Moreover, we observed both new diagnoses of previously unrecognized cardiomyopathy, as well as refined classification of existing diagnoses. However, it is important to recognize that the overall diagnostic yield, particularly for ARVC, was low. Thus, a conservative approach to diagnosis and invasive intervention based on genomic screening is warranted.

Diagnostic Considerations for ARVC

Of the carriers with postdisclosure follow-up, 36% satisfied at least 1 of the 2010 ARVC TFC, independent of the genetic variant. However, the findings represented only isolated criteria (major or minor) for all but 5 carriers (8%) who met multiple criteria. A formal diagnosis of ARVC has so far been made in one of those 5 cases. We have previously observed that isolated TFC from secondary review of clinical testing are comparable in frequency between desmosome-variant carriers and noncarriers.^{8,10} It is, therefore, reasonable to expect that findings of isolated criteria through genomic result-directed testing are also unlikely to carry diagnostic significance. This understanding requires that genetic variants identified by population or secondary screening not be counted as a major criterion; otherwise, finding another isolated major or minor criterion yields a definite or borderline diagnosis, respectively, as illustrated by Figure 4. Instead, counting the variant only as a minor criterion, or not counting it at all, resulted in diagnostic outcomes that were better aligned with the clinical impression in this cohort—that most carriers did not have overt evidence of ACM. Continued surveillance, particularly of individuals with possible or borderline diagnoses, will provide further clarification on the most appropriate strategy in this regard.

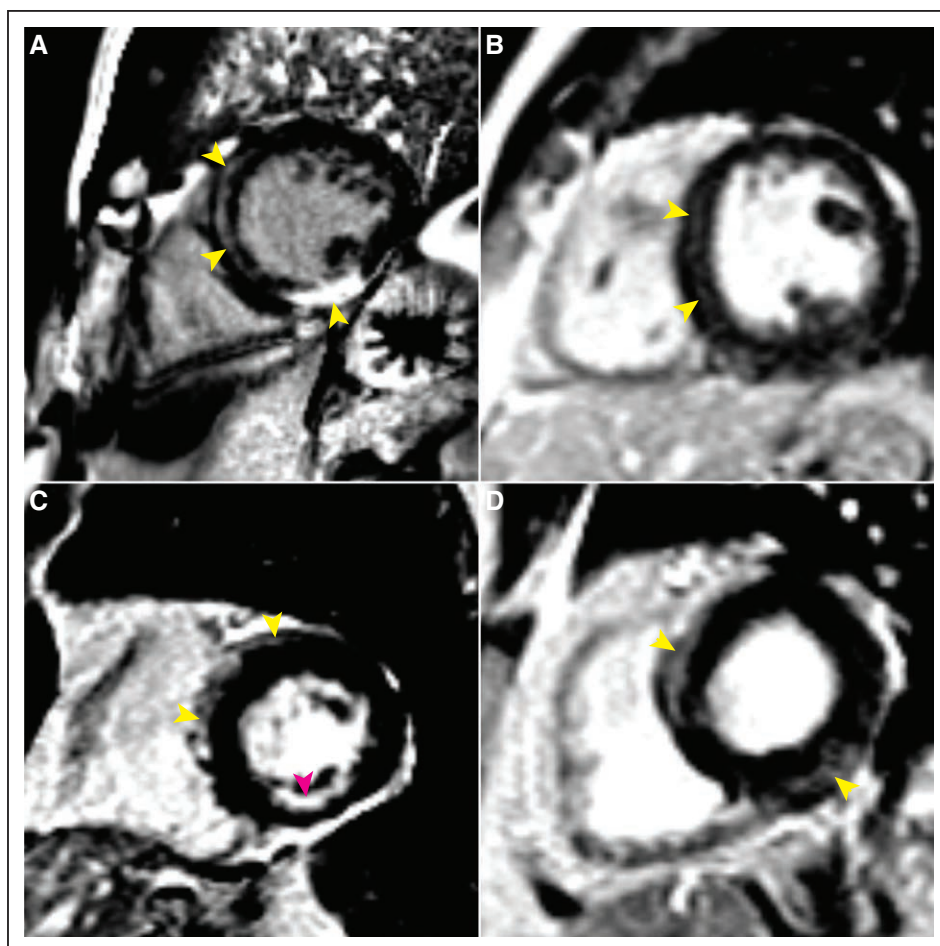


Figure 3. Features of atypical late gadolinium-enhanced (LGE) cardiac magnetic resonance imaging of 4 desmosome-variant carriers.

Yellow arrowheads denote atypical LGE locations in the left ventricle (LV). **A**, Marked atypical LV LGE in the 57 y-old male *DSP*-variant carrier subsequently diagnosed with arrhythmogenic right ventricular cardiomyopathy (ARVC). **B**, Septal midwall LGE in a 35 y-old male *PKP2*-variant carrier. **C**, Septal and anterior LGE in the subepicardium of a 72 y-old female *DSP*-variant carrier. Subendocardial enhancement in the inferior LV wall possibly due to prior infarct also visible (magenta arrowhead). **D**, Atypical midwall LGE in the basal to mid interventricular septum, as well as basal inferolateral segment in a 59 y-old female *DSP*-variant carrier.

This low yield of definitive ARVC is consistent with our prior work,^{8,10} even in the new context of informed clinical evaluation following the genomic result disclosure. However, this analysis adds support to these prior findings as, in addition to the exclusive focus on postresult clinical evaluations, we reported findings from a detailed family history analysis. These family histories were generally unremarkable given the lack of reported ACM/ARVC and low or expected rates of other nonspecific characteristics, such as heart failure and SCD; that is, no independent family history criteria suggestive of a diagnosis. These data, therefore, support prior conclusions, including previous theoretical estimates of genomics-first ARVC penetrance (6%).⁸

Left-Dominant ACM

The collection of postdisclosure diagnostic data, particularly CMR images with LGE, enabled an assessment of left-dominant ACM prevalence from genomics-first

ascertainment for the first time. In general, the findings were similar to ARVC in that only 10% of variant carriers met the specified criteria for possible left-dominant disease. However, the burden of overt disease was higher for the LV than the RV as 3 carriers had clinically recognized cardiomyopathy in conjunction with reduced LVEF, 2 of which preceded the variant disclosure.

The frequency of LGE—found in 30% of the carriers who underwent CMR evaluation—was another novel finding of this analysis. In 5 carriers, the LGE was accompanied by arrhythmia criteria satisfying the left-dominant phenotype definition, but similar LGE findings in the absence of noted arrhythmias were identified in 5 additional desmosome-variant carriers (10/59, 17% in total). In both situations, the diagnostic and prognostic significance of these findings remains largely unclear. However, a study of clinically acquired CMR data found that of 409 patients without ischemic disease, nonischemic LGE findings were present in only 19 (5%), suggesting a much higher frequency

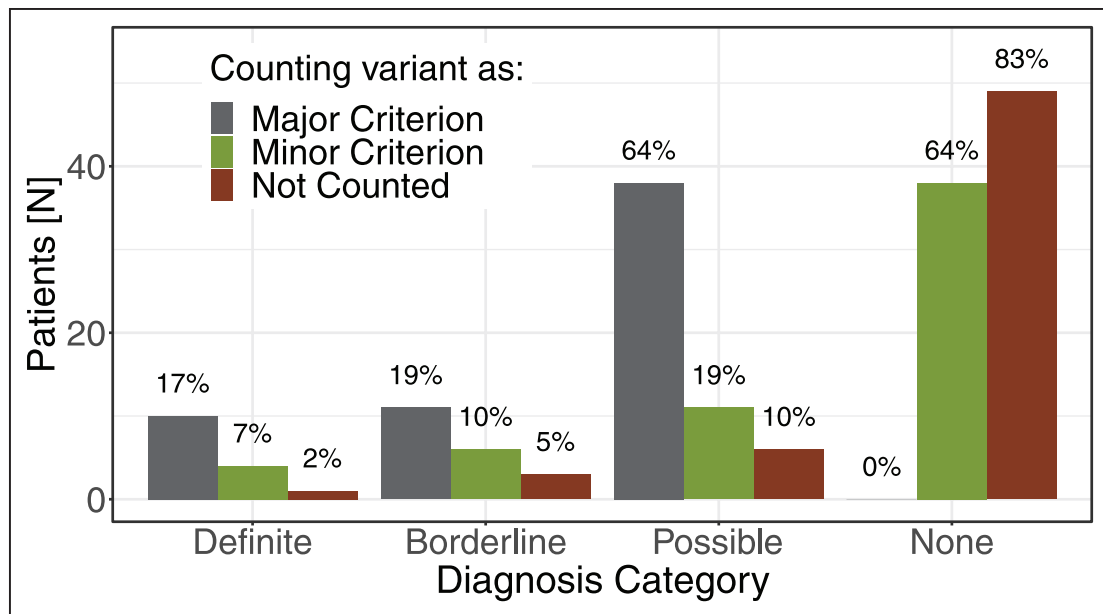


Figure 4. Distributions of arrhythmogenic right ventricular cardiomyopathy diagnostic categories according to the 2010 Task Force Criteria, modulated by the weight applied to the pathogenic/likely pathogenic variant.

in our cohort.¹⁹ Although LGE has historically not been included in diagnostic criteria for ARVC, more recent studies have provided evidence for its inclusion, presumably in combination with other criteria, particularly for left-dominant ACM.^{12,20–22} Longitudinal follow-up of these carriers will help clarify the prognostic significance of nonspecific imaging findings, including LGE and isolated global RV dilation/dysfunction. Our analysis also highlights the need for greater awareness and consensus guidelines for diagnosis of left-dominant disease.

Gene-Specific Observations

Our observed genotype-phenotype associations are noteworthy in 2 regards. First, none of the *PKP2*-variant carriers in this cohort had a demonstrable phenotype. As the most commonly affected gene in ARVC,²³ this specific lack of *PKP2* association is likely a main contributor to the low number of observed ARVC cases. The explanation for this result is unclear, but may relate to survival bias, or the influence of secondary modifying factors, such as exercise or lack thereof. The link between vigorous exercise/athletics and ARVC has the strongest supporting evidence in *PKP2*-variant carriers,^{24,25} and the median body mass index in our *PKP2*-variant carriers was 35 (32 for all desmosome-variant carriers), suggesting a lack of such activities based on this rate of obesity. Additionally, increasing evidence suggests a mediating role of other cellular proteins, such as the RYR2 (ryanodine receptor 2) and integrin β 1D,^{26,27} in the setting of *PKP2*/desmosome disruption leading to ARVC, so it is also possible that secondary genetic variation may be moderating penetrance in these individuals as well.

Conversely, the most notable phenotypes from our analysis were observed in *DSP*-variant carriers. These represented both the majority of the left-dominant ACM phenotypes and also perhaps explains the LV involvement in the patient with diagnosed ARVC. The tendency for LV involvement in association with *DSP* variants has been well documented,²⁸ and *DSP* is frequently cited as a risk gene both for dilated cardiomyopathy as well as ACM.^{4,29,30} Yet, the unique attributes of the *DSP*-specific phenotype are rapidly evolving, as exemplified by the recent work of Smith et al.²⁰ Findings in many of our *DSP*-variant carriers are largely consistent with this study, including a high prevalence of LGE, frequently without overt systolic dysfunction, frequent PVCs, and poor sensitivity of the ARVC TFC.²⁰ Our findings further underscore the need for a comprehensive bi-ventricular evaluation—inclusive of CMR with LGE—following genomics-first identification of *DSP* variants.

It is important to note, however, that while visually striking, the apparent differences in gene penetrance were not statistically significant in this analysis. It is most likely that the study was under-powered ($\approx 40\%$) to detect such differences ($\approx 25\%$) based on the sample sizes. Therefore, these specific findings should be interpreted with caution and warrant replication in future analyses.

Implications for Genomics-First Screening of Desmosome Genes

This study represents the first report of new ACM diagnoses following genomics-first ascertainment and is thus an important proof-of-concept. The value of genomic screening efforts for ACM-associated variants is also highlighted by the novel discovery of otherwise unknown disease, with

subsequent interventions in 2 cases (ie, defibrillator implantation) to prevent potentially severe outcomes. Moreover, with surveillance and follow-up of the other borderline or possible diagnoses for both phenotypes, the low diagnostic yield we observed may increase over time.

Additionally, the genomics-first identification of LV-dominant disease is an important finding of this work considering that American College of Medical Genetics and Genomics guidelines for screening desmosome genes focus exclusively on ARVC. Instead, these data demonstrate that the potential for either left- or right-dominant disease presentations in connection with these genes must be appreciated in the clinical assessment, particularly for carriers of *DSP* and *DSG2* variants.²⁸ Future revisions of the American College of Medical Genetics and Genomics secondary findings recommendations should, therefore, focus on associations with ACM instead of the more specific ARVC.

Finally, an important question to consider is whether desmosome variants should remain included in initiatives of genomic screening or disclosure of secondary findings. Having a high rate of apparent nonpenetrance is problematic, particularly given the costs associated with unnecessary diagnostic evaluations and the potential burden of anxiety associated with result disclosure. Yet, the potential benefits of uncovering unrecognized disease—which we have now shown to be possible—are substantial. Therefore, a critical focus of future study will be to develop additional criteria (eg, history of vigorous exercise/athletics) to improve the precision of risk assessment given the finding of a desmosome variant, potentially leveraging our developing understanding of gene-phenotype associations. Such refinements will guide development of risk management recommendations that help reduce the cost of population-level desmosome screening (both financial and psychological) and improve its effectiveness in the long-term.

Limitations

Due to heterogeneous clinical testing, some patients were incompletely evaluated, even within the subset of 59 carriers analyzed for diagnostic criteria. Therefore, phenotypes and diagnostic findings may be underestimated (Figure I in the [Data Supplement](#)). Efforts are ongoing to continue engaging and longitudinally evaluating this cohort with more standardized testing procedures to further refine these insights.

This cohort has a relatively high median age compared with typical disease onset,³¹ so as mentioned above, there is some degree of survival bias in this group. Our family history assessment provides some confidence that survival bias is not masking early SCD in these families. Yet, evaluation of phenotypes in younger individuals, for example, through ongoing cascade testing, may uncover additional disease, despite an unaffected proband.

The history of exercise/athletics in this cohort is as yet unknown, which very likely influences disease expressivity and progression.²⁴ Future work will better establish this connection in genome-first ascertainment.

Finally, it is also important to recognize that this experience is from a single healthcare system cohort, which is susceptible to other potential sources of ascertainment bias, including female predominance. Ultimately, replication in another cohort will be critical to confirm these findings.

Conclusions

Genomics-based identification of individuals at risk for ACM can uncover new evidence of disease as well as sub-clinical abnormalities. This represents an important proof-of-concept for a genomics-first approach to ACM, although the likelihood of newly discovered disease, at least in the short-term following result disclosure, appears relatively low. We observed an equal, if not greater likelihood of left-sided disease as right-sided disease, demonstrating the importance of bi-ventricular clinical follow-up of these genomic findings, although consensus guidelines for left-dominant ACM are needed to facilitate a formal diagnosis and provide greater awareness of that phenotype. Relatedly, *DSP*-variant carriers constituted the majority of patients observed with clinical criteria, particularly left ventricular disease, while only one *PKP2*-variant carrier had a demonstrable ARVC phenotype. Hence, the penetrance associated with *DSP* variants may be higher than *PKP2*, but future work is needed to confirm. Finally, the consideration of a P/LP variant as a major criterion for ARVC diagnosis is not appropriate in the setting of genomic screening; it should at most be regarded as a minor criterion.

ARTICLE INFORMATION

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Supplemental Materials

Online Methods

Online Tables I and II

Online Figure I

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