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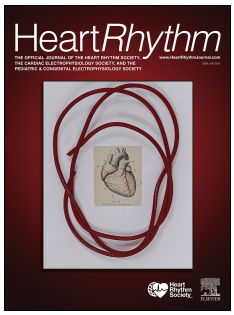

Clinical Features and Outcome of Arrhythmogenic Cardiomyopathy due to a Desmoglein-2 Founder Variant: A Multicenter Study

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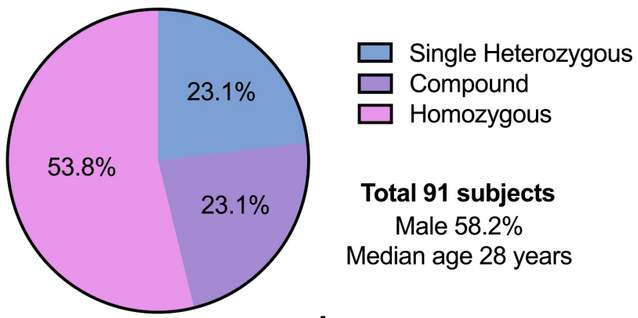
Clinical Features and Outcome of Arrhythmogenic Cardiomyopathy due to a Desmoglein-2 Founder Variant: A Multicenter Study

Objective and Study Design

Multicenter observation study in China

DSG2 c.T1592G (p.Phe531Cys)



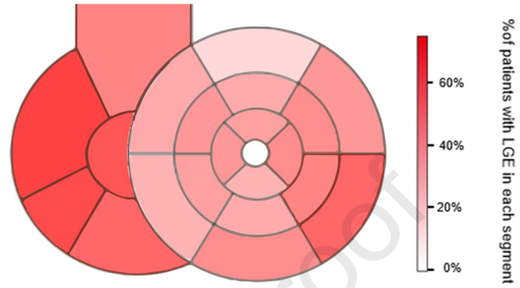
Total 91 subjects
Male 58.2%
Median age 28 years

Clinical feature and outcomes

- Clinical characteristics
- Malignant ventricular arrhythmia (MVA)
- Composite of heart transplantation (Htx) and cardiac death

Results and Conclusion

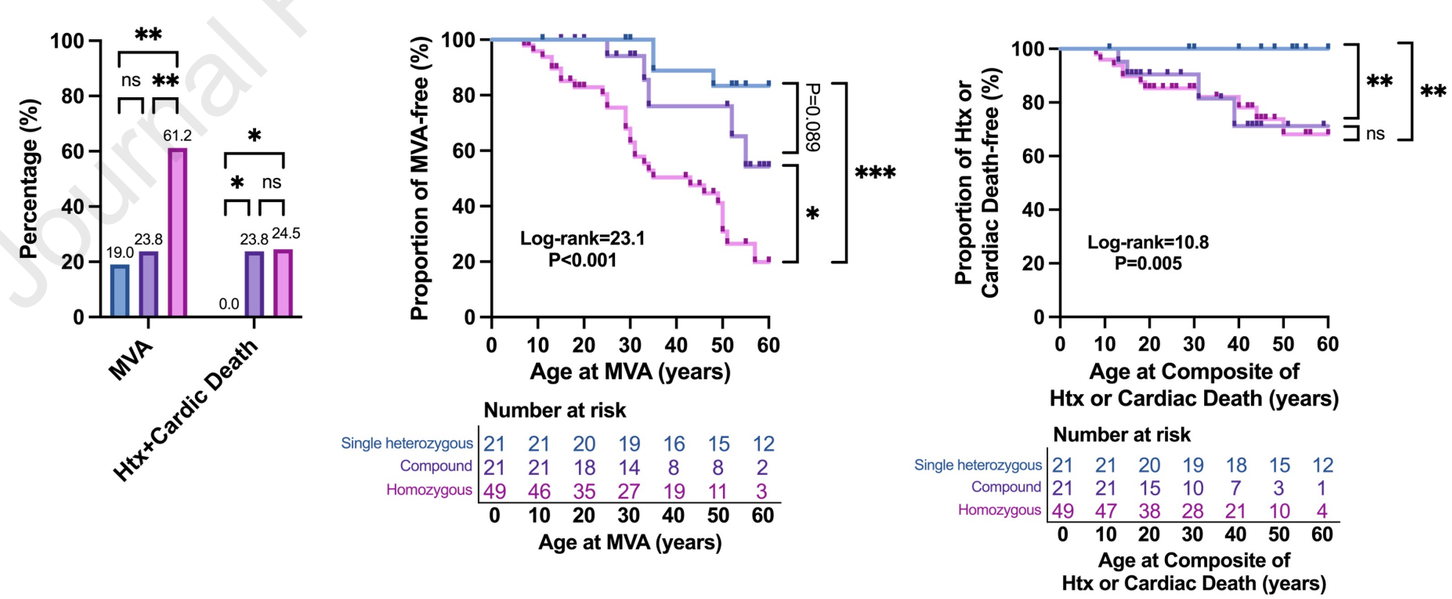
1 **The DSG2 c.T1592G (p.Phe531Cys) variant defines a distinct ARVC subset with high prevalence of biventricular involvement**



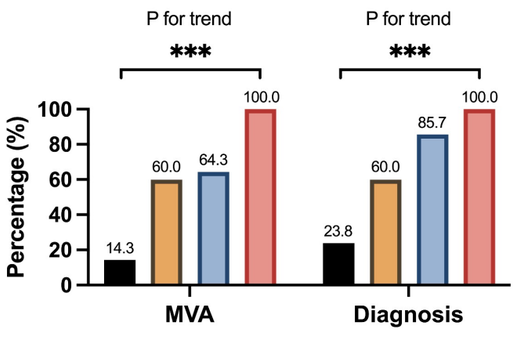
Among patients underwent contrast-enhanced cardiac magnetic resonance imaging, 75.9% exhibited biventricular late gadolinium enhancement.

2 **Variants of uncertain significance and intense exercise may serve as second-hit that promotes phenotypic penetrance and adverse prognosis.**

Clinical outcomes according to zygosity



Clinical outcomes according to intense exercise and zygosity



Intense exercise	Zygosity
No	Single Heterozygous + Compound
Yes	
No	Homozygous
Yes	

Clinical Features and Outcome of Arrhythmogenic Cardiomyopathy due to a Desmoglein-2 Founder Variant: A Multicenter Study

Short title: DSG2 Founder Variant-Associated ACM

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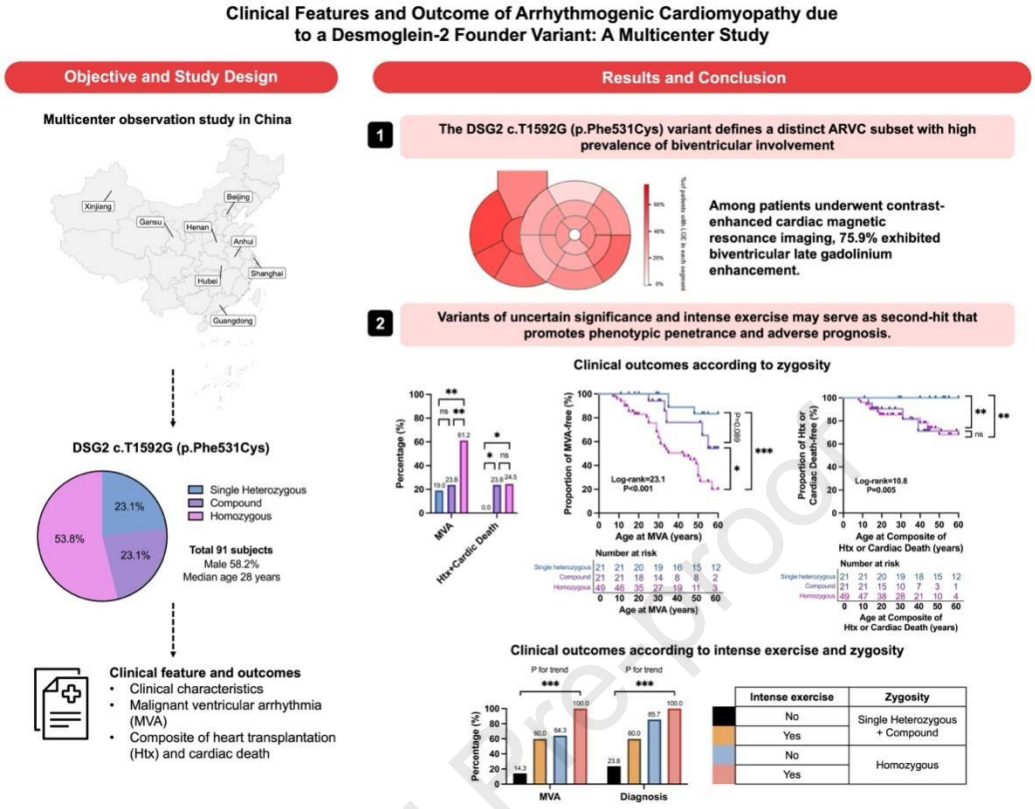
Central Figure



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Abstract

Background: Desmoglein-2 (DSG2)-associated cardiomyopathy represents a distinct subset of arrhythmogenic cardiomyopathy (ACM). A founder variant, NM_001943.5 (DSG2): c.T1592G (p.Phe531Cys), was identified with high frequency in China.

Objective: The study aimed to describe clinical features and outcomes of this founder variant.

Methods: Individuals with DSG2 c.T1592G (p.Phe531Cys) variants were recruited from 9 centers across China and categorized as single heterozygous, compound heterozygous (single variant plus rare variants of uncertain significance; abbreviated as compound) and homozygous. Clinical features and risk factors for malignant ventricular arrhythmias (MVA), end-stage heart failure (ESHF), and composite events of heart transplantation or cardiac death were analyzed.

Results: Ninety-one subjects were included: 21 (23.1%) single heterozygous, 21 (23.1%) compound, and 49 (53.8%) homozygous. Most of subjects (74.7%) showed right ventricular dilatation and nearly half (49.5%) had biventricular involvement. In patients with contrast-enhanced magnetic resonance imaging, 75.9% exhibited biventricular involvement. Compared with single heterozygous, compound and homozygous had younger age at onset, more T wave inversion, epsilon waves, and biventricular involvement (all pairwise $P<0.05$). Homozygous experienced significantly earlier MVA than compound ($P=0.013$), and single heterozygous ($P<0.001$), with a trend toward earlier MVA in compound compared with single heterozygous ($P=0.089$). Compound and homozygous exhibited significantly higher incidences of ESHF and composite events while single heterozygous remains event-free (all $P<0.05$).

Conclusion: DSG2 c.T1592G (p.Phe531Cys) founder variant defines a distinct ACM subset with high prevalence of biventricular involvement. Single heterozygous variant carriers held less severe phenotype and relatively favorable prognosis, while compound and homozygous held advanced phenotype and poorer prognosis.

104 **Keywords**: arrhythmogenic cardiomyopathy, desmoglein, clinical outcomes,
105 arrhythmia, heart failure.

106 **Abbreviation**

ACM	Arrhythmogenic cardiomyopathy
ARVC	Arrhythmogenic right ventricular cardiomyopathy
DSG2	Desmoglein 2
ESHF	End-stage heart failure
LGE	Late gadolinium enhancement
LV	Left ventricle
MVA	Malignant ventricular arrhythmia
NSVT	Non-sustained ventricular tachycardia
RV	Right ventricle
RVD	Right ventricular diameter

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Introduction

Arrhythmogenic cardiomyopathies (ACM) are inherited in most cases associated with ventricular arrhythmias (VA), and sudden cardiac death (SCD) [1,2]. The most classical form of ACM is arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC), characterized by fibrofatty replacement in myocardium [3], creating a vulnerable substrate for malignant ventricular arrhythmia (MVA). Emerging evidence indicates a strong genotype–phenotype correlation in ACM [3-6]. Desmoglein 2 (DSG2)-associated cardiomyopathy represents a distinct subset of ACM, with relatively high biventricular involvement and heart failure (HF) risk [7,8]. A recent large-scale clinical characterization of desmosomal cadherins variants demonstrated the importance of multiple pathogenic or likely pathogenic mutations in risk stratification. Individuals carrying multiple variants of DSG2/desmocollin 2 (DSC2) showed significantly higher penetrance, earlier onset, and worse clinical outcomes, compared with single variant carriers [7]. However, this study did not consider variants of uncertain significance (VUS).

NM_001943.5 (DSG2): c.T1592G (p.Phe531Cys) was identified as a founder variant for DSG2-associated ACM in East Asia and follows an autosomal recessive inheritance pattern. Homozygous carriers exhibit a higher rate of complete disease penetrance and a more severe phenotype, compared with heterozygous variant carriers [9]. Nevertheless, small sample sizes in existing studies hindered our understanding of this founder variant, creating a critical gap in detailed phenotyping and prognostic assessment. The present study aims to fill this gap, by describing clinical spectrum

and outcomes of this founder variant, elaborating potential impact of rare VUS, and analyzing risk factors for poor prognosis in a multicenter cohort.

Methods

Study cohort

This study used data from the ChinaCORE ACM registry (ChiCTR2500098971), and included individuals carrying DSG2 c.T1592G (p.Phe531Cys) variant from 9 centers in China [10]. Probands and genetic positive relatives were included if they met the criteria for variant interpretation and classification (**Supplemental Methods**). This study population consisted of 91 cases, of which 76 had been involved in our prior study, including 40 homozygous cases [7]. This study focused specifically on phenotype and prognosis of DSG2 c.T1592G (p.Phe531Cys) founder variant and potential impact of VUS, and provided an analysis distinct from our prior study. The study adhered to the Helsinki Declaration as revised in 2013, and was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (approval no. 2023-2078). Written informed consent was obtained from all participants.

Data collection

Diagnosis of ACM was established based on revised 2010 Task Force Criteria (TFC) [11]. Clinical data were at the time of diagnosis for patients or initial evaluation for asymptomatic relatives. Blood samples were collected and DNA was extracted as previously described [10]. This study incorporated rare VUS in genes linked to

arrhythmia or cardiomyopathy, which were computationally predicted to be deleterious (**Supplemental Table 1**). Subjects were classified into: (1) single heterozygous; (2) compound heterozygous (single variant plus rare VUS; abbreviated as compound); and (3) homozygous. Details are summarized in **Supplemental Methods**.

Study endpoints

MVA was defined as spontaneous sustained ventricular tachycardia, ventricular flutter or fibrillation, SCD, aborted cardiac arrest or appropriate implantable cardioverter defibrillator (ICD) therapy. End-stage heart failure (ESHF) was defined as heart transplantation or HF-related death. Cardiac death was defined as HF-related death or SCD. Composite events were defined as heart transplantation or cardiac death. Follow-up period was calculated from the date of enrollment for patients, or initial evaluation for asymptomatic relatives, to the date of adverse events, or last contact.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQR), and categorical variables as counts and percentages. Kaplan–Meier survival curves were generated using age as time scale to compare event-free survival for the first onset of adverse events. Multiple testing adjustments were performed using false discovery rate method. Cox proportional hazards models were used to assess risk factors for adverse events. Variables identified as significant in univariable analysis, and

previously reported as clinically relevant, were incorporated into multivariable stepwise regression analysis to determine optimal predictors for poor prognosis. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Firth's penalized Cox regression ("coxphf" R package) was used for ESHF and composite events due to zero events in single heterozygous group. Subgroup analysis was conducted in participants with 1) cardiac magnetic resonance evaluation, 2) serial echocardiographic measurements, and 3) complete exercise information. A linear mixed-effects model was applied to assess longitudinal changes in echocardiographic parameters over time. Slopes of numeric echocardiographic parameters were calculated as change between two serial echocardiograms over months.

All statistical analysis was performed using R software version 4.4.1. A two-sided P value <0.05 was considered statistically significant.

Results

Clinical characteristics

The study included 91 individuals with DSG2 c.T1592G (p.Phe531Cys) variants, of whom 53 (58.2%) were males. Twenty-one (23.1%) had single heterozygous, 21 (23.1%) had compound, and 49 (53.8%) had homozygous variants. Upon enrollment, 17 (18.7%) already experienced MVA, and 15 (23.4%) had advanced HF with New York Heart Association (NYHA) class III-IV (**Table 1**).

Median number of T wave inversion (TWI) in precordial leads V_1 to V_6 was 3 (IQR: 1-5). Epsilon waves were identified in 42.5% of individuals. Non-sustained ventricular tachycardia (NSVT) were present in 51.6 % of individuals. Compared with single heterozygous variant carriers, compound and homozygous variant carriers exhibited higher number of TWI in precordial leads [0 (IQR: 0-2) vs. 3 (IQR: 1-4), and 4 (IQR: 1-5); both $P<0.05$], and higher proportion of epsilon waves in precordial leads V_1 to V_3 (4.8 vs. 53.3, and 56.8%; both $P<0.01$). NSVT increased across three groups (14.3%, 42.9%, and 71.4%; overall $P<0.001$), driven primarily by significant difference between single heterozygous and homozygous variant carriers ($P<0.001$; **Table 1**).

Median TFC score was 5 (IQR:3-6). Nearly half (49.5%) had biventricular involvement. Compared with single heterozygous variant carriers, compound and homozygous variant carriers had higher TFC score [2 (IQR: 2-2) vs. 5 (IQR: 3-7), and 5 (IQR: 5-7); both pairwise $P<0.001$; **Figure 1A**], higher biventricular involvement

(4.8 vs. 52.4, and 67.3%; both pairwise P<0.05; **Figure 1B**). Median LV ejection fraction (LVEF) on echocardiography was 54.0% (IQR: 46.0–63.3). LVEF decreased across three groups [62.4 (IQR: 52.3-67.4), vs. 58.0 (IQR: 46.0-63.1), and 50.0 (IQR: 44.0-60.0); overall P=0.016], driven primarily by significant difference between single heterozygous and homozygous variant carriers (P=0.007). LV dilatation was observed in 31.6% of individuals, and LV dyskinesia was observed in 36.8%. RV dilatation was present in 74.7% of individuals, and RV dyskinesia was present in 67.5%. Compared with single heterozygous variant carriers, compound and homozygous variant carriers had a larger RV end-diastolic diameter [22.2 (IQR: 20.0-24.0), vs. 44.0 (IQR: 38.5-50.5), and 38.5 (IQR: 33.0-42.0); both pairwise P<0.001], a higher proportion of LV dyskinesia (0 vs. 52.9, and 46.3%; both pairwise P<0.01), RV dilatation (33.3 vs. 81.0, and 89.8%; both pairwise P<0.05), and RV dyskinesia (11.1 vs. 86.7, and 83.0%; both pairwise P<0.001).

Nature history and clinical outcomes

Median age at onset was 28 years (IQR: 17–48). Compared with single heterozygous variant carriers, compound and homozygous variant carriers had younger age at onset [24 years (IQR: 14–38), vs. 25 years (IQR: 15–42), and 51 years (IQR: 35–60); both pairwise P<0.01; **Figure 1C**].

During a median follow-up period of 60.5 months (IQR: 27.5–89.0), 29 variant carriers experienced MVA, 14 experienced ESHF, and 17 experienced composite events. Association of initial symptoms and age at onset with prognosis were shown in **Supplemental Results and Supplemental Figure 1-2**.

Median age at first MVA was 33 years (IQR: 25-49). Homozygous variant carriers had a significantly higher MVA incidence (61.2%) compared with compound (23.8%; P=0.008) and single heterozygous variant carriers (19.0%; P=0.002; **Figure 2A**). Survival analysis showed significantly higher cumulative MVA incidence in homozygous variant carriers than in compound (P=0.013) and single heterozygous variant carriers (P<0.001; **Figure 2B**). There was a trend toward earlier onset of MVA for compound versus single heterozygous group (P=0.089). In addition, compound (23.8%; P=0.048) and homozygous variant carriers (24.5%; P=0.013) had significantly higher incidence of heart transplantation or cardiac death, while no such event were observed in single heterozygous variant carriers (0.0%; **Figure 2A**). Survival analysis showed that compound and homozygous variant carriers had significantly higher cumulative incidences of ESHF and composite events than single heterozygous carriers (all P<0.05), with no significant differences between compound and homozygous carriers (all P>0.05; **Figure 2C-D**). No sex-related differences in cumulative MVA, ESHF, and composite of heart transplantation or cardiac death incidence was found (**Supplemental Figure 3A-C**).

Predictors for adverse prognosis

In primary prevention group without previous history of MVA, significant predictors of MVA during follow-up included younger age at onset, homozygous variant carriers (vs. single heterozygous variant carriers), history of syncope, reduced LVEF, larger RV, NSVT, and higher TFC score. A stepwise multivariable model identified LVEF,

right ventricular diameter (RVD), and NSVT as significant independent predictors for MVA (**Table 2**).

For ESHF and composite events, younger age at onset, NYHA class III–IV, reduced LVEF, larger RV, and NSVT were significant risk factors. Compound and homozygous variant carriers held significantly higher risk of ESHF and composite events than single heterozygous variant carriers (HR for ESHF=13.36, HR for composite events=15.78, respectively). A stepwise multivariable model identified reduced LVEF and NSVT as significant independent predictors for ESHF and composite events (**Table 2**).

Subgroup analysis

In 34 patients with cardiac magnetic resonance imaging evaluation, homozygous variant carriers exhibited non-significantly larger RV. In 29 patients with late gadolinium enhancement (LGE), a high LGE prevalence was observed in both RV (93.1%) and LV (82.8%) myocardium, and 75.9% of patients showed biventricular involvement. Fat replacement in RV and LV was observed in 88.9% and 55.6%, respectively (**Supplemental Table 2**). Homozygous variant carriers had significantly higher rate of LV fat replacement (72.2 vs. 22.2%; P=0.014). Regarding LGE distribution, apart from extensive RV involvement, LGE was observed in LV inferior and lateral walls (**Figure 3**) of homozygous and compound variant carriers, which was more prominent in homozygous group.

In 22 subjects who underwent serial echocardiographic assessments, there was a gradual increase in left atrial diameter by 0.05 mm per month (95% CI 0.02–0.09; P=0.006), a decrease in LVEF by 0.04% per month (95% CI –0.10 to 0.02, P=0.224), and an increase in RVD by 0.06 mm per month (95% CI 0.01–0.11; P=0.028; **Supplemental Table 3**). Slope of RVD increase was significantly associated with ESHF (unadjusted HR=1.24, 95% CI 1.04–1.48, P=0.018), and remained significant after adjustment (adjusted HR=1.25, 95% CI 1.03–1.52, P=0.023), while decline in LVEF showed a borderline association (unadjusted HR=1.53, 95% CI 1.02–2.28, P=0.038; adjusted HR=1.64, 95% CI 0.94-2.88, P=0.083; **Supplemental Table 4**).

In 46 subjects with exercise data, 11 (23.9%) had perform intense exercise (**Supplemental Table 5-6**). A significantly higher cumulative incidence of MVA was observed in intense exercise group (Log-rank=11.1, P<0.001; **Supplemental Figure 4A**), whereas no significant difference was observed for composite events of heart transplantation or cardiac death (Log-rank=0.5, P=0.463; **Supplemental Figure 4B**). In addition, individuals in intense exercise group exhibited an earlier onset (Log-rank=4.9, P=0.027; **Supplemental Figure 4C**). Intense exercise was associated with a significantly increased risk of MVA (HR=7.08, 95% CI 2.42-20.78, P<0.001), but not with composite events (P=0.819). Association between intense exercise and MVA risk (HR=7.51, 95% CI 2.13-26.51, P=0.002) remained significant after adjustment (**Table 3**). Joint stratification by zygosity and intense exercise revealed a gradual increase in MVA incidence and disease penetrance (both p for trend<0.001). Higher

291 frequency of MVA were found in heterozygous variant carriers with intense exercise

292 than those without intense exercise (**Figure 4**).

Discussion

Different from our prior study [7], this study provided a detailed delineation of the phenotypic spectrum and clinical outcomes exclusively on individuals carrying DSG2 c.T1592G (p.Phe531Cys) founder variant and further elaborated the potential impact of VUS and exercise. We found that this founder variant is associated with a distinct ACM phenotype, characterized by RV involvement and a high prevalence of biventricular involvement. In terms of phenotype, compared with single heterozygous group, compound and homozygous carriers had younger age at onset, more TWI in precordial leads, epsilon waves in precordial leads V_1 to V_3, and LV involvement. In terms of clinical outcomes, single heterozygous variant carriers demonstrated the lowest risk of MVA, and had no event of ESHF and composite of heart transplantation or cardiac death developed during follow-up. In contrast, heterozygous variant carriers with additional rare VUS associated with cardiomyopathy or arrhythmia (compound group), and homozygous variant carriers held higher risk for adverse outcomes. In addition, intense exercise may potentially promote phenotypic penetrance in heterozygous variant carriers. These findings indicate that single heterozygous DSG2 c.T1592G (p.Phe531Cys) variant carriers were associated with a less severe phenotype and a favorable prognosis than homozygous variant carriers, however, an additional VUS and intense exercise may act as modulator that promotes phenotypic penetrance and poor prognosis.

Genotype-phenotype association and second-hit

DSG2 is transmembrane cadherin that contributes to intercellular adhesive junctions between cardiomyocytes, anchoring to cytoskeleton to ensure mechanical integrity and electrical coupling of myocardium [12-15]. A specific DSG2 missense variant, c.T1592G , is highly prevalent in East Asia, particularly in China [16,17]. This mutation disrupts protein folding in cardiomyocytes, and increases transforming growth factor β1 expression [18-20]. Both animal models and patients-based data showed that homozygous variant carriers frequently present with biventricular dilation and arrhythmogenesis, while heterozygous variant carriers showed incomplete penetrance, [9,21,22] suggesting that a single variant alone may be insufficient for full phenotypic penetrance [9,23]. However, in clinical practice, some heterozygous variant carriers still manifest ACM phenotype and adverse outcome.

After considering VUS and intense exercise in subgroup analysis, we found that single heterozygous variant carriers were associated with a less severe phenotype and a relatively favorable prognosis than homozygous variant carriers, however, an additional VUS or intense exercise may act as second hit that promotes phenotypic penetrance and poor prognosis. These findings might partly explain heterogeneity in phenotype and prognosis of heterozygous DSG2 c.T1592G (p.Phe531Cys) variant carriers.

Therefore, heterozygous variant carriers might be risk-stratified into single-variant and compound carriers with rare VUS that predicted to be deleterious in genes related to arrhythmia or cardiomyopathy, and followed-up regularly. We recommend annual evaluation of electrophysiological abnormalities (e.g., 24-hour Holter

monitoring and 12-lead ECG) and cardiac structure and function (e.g., echocardiography or cardiac magnetic resonance imaging) for compound variant carriers. In addition, our study showed a significant association of intense exercise with disease penetrance, and MVA, probably due to failed desmosome-related stress-adaptation mechanisms in response to mechanical stress [24-28], supporting avoidance of intense exercise to reduce adverse outcomes.

Adverse outcome

Our cohort showed higher incidence of ESHF and composite of heart transplantation and cardiac death than overall ARVC cohort [29,30], and genotype-specific cohorts, including plakophilin 2 [8], transmembrane protein 43 [31], and desmoplakin variants [32]. In DSG2 cohort, a recent pooled analysis by Marika Martini et al. reported lower HF and heart transplantation rates, which were lower than our cohort [33]. This difference emphasize the severe phenotype of our distinct study populations (**Supplemental Table 6**). First, age at onset in our cohort was younger (28 vs. 36 years). Second, biventricular involvement (49.5 vs. 31.2%) were higher. Third, electrical abnormalities including TWI in precordial leads V_1 to V_3 (75.4 vs. 52.0%), epsilon waves (42.5 vs. 10.2%), RBBB (26.0 vs. 12.6%), PVC burden >500/24 h (69.6 vs. 59.3%), and NSVT (51.6 vs. 30.8%) were more prevalent. Such aggressive phenotypic presentation necessitates targeted evaluation of this high-risk subpopulation.

Notably, our findings indicated a gradual 0.06 mm/month increase in RV diameter, significantly correlating with ESHF risk (+25% for every 1 mm/month).

These findings highlight a substantial risk of premature mortality among DSG2 c.T1592G (p.Phe531Cys) variants, and underscore the importance of serial echocardiographic monitoring for early ESHF detection, and timely intervention.

Interestingly, heterozygous variant carriers showed no ESHF and composite events during follow-up, while compound carriers of VUS and homozygous variant carriers showed significantly higher risks. This pattern indicated that single DSG2 c.T1592G (p.Phe531Cys) variant carriers were associated with a less severe phenotype and a favorable prognosis, and certain VUS may serve as a second-hit when inherited with this variant. This resembles recessive-like pattern seen in Naxos [34] and Carvajal syndromes [35], where biallelic desmosomal defects significantly amplify phenotypic severity, and adverse outcomes. Therefore, compound carriers of VUS might be treated with similar caution as homozygous carriers and warrant close follow-up.

Limitations: Firstly, this study was observational with a small sample size, which may introduce inherent biases and limit the generalizability of findings. Secondly, subgroup analysis was intended to indicate potential directions and generate hypotheses. Further validation is required due to missing data and small sample sizes. Thirdly, the proportion of homozygous carriers is high, which is likely due to recruitment bias toward symptomatic probands, under-ascertainment of heterozygous family members, and limited number of extensively screened families, rather than true population frequency of this variant in China. Last, this study focused exclusively on

individuals carrying DSG2 c.T1592G (p.Phe531Cys) variants and did not include comparison with other DSG2 mutation.

Conclusion

DSG2 c.T1592G (p.Phe531Cys) founder variant defines a distinct ACM subset with high prevalence of biventricular involvement. Single heterozygous variant carriers held less severe phenotype and relatively favorable prognosis, while compound and homozygous held advanced phenotype and poorer prognosis.

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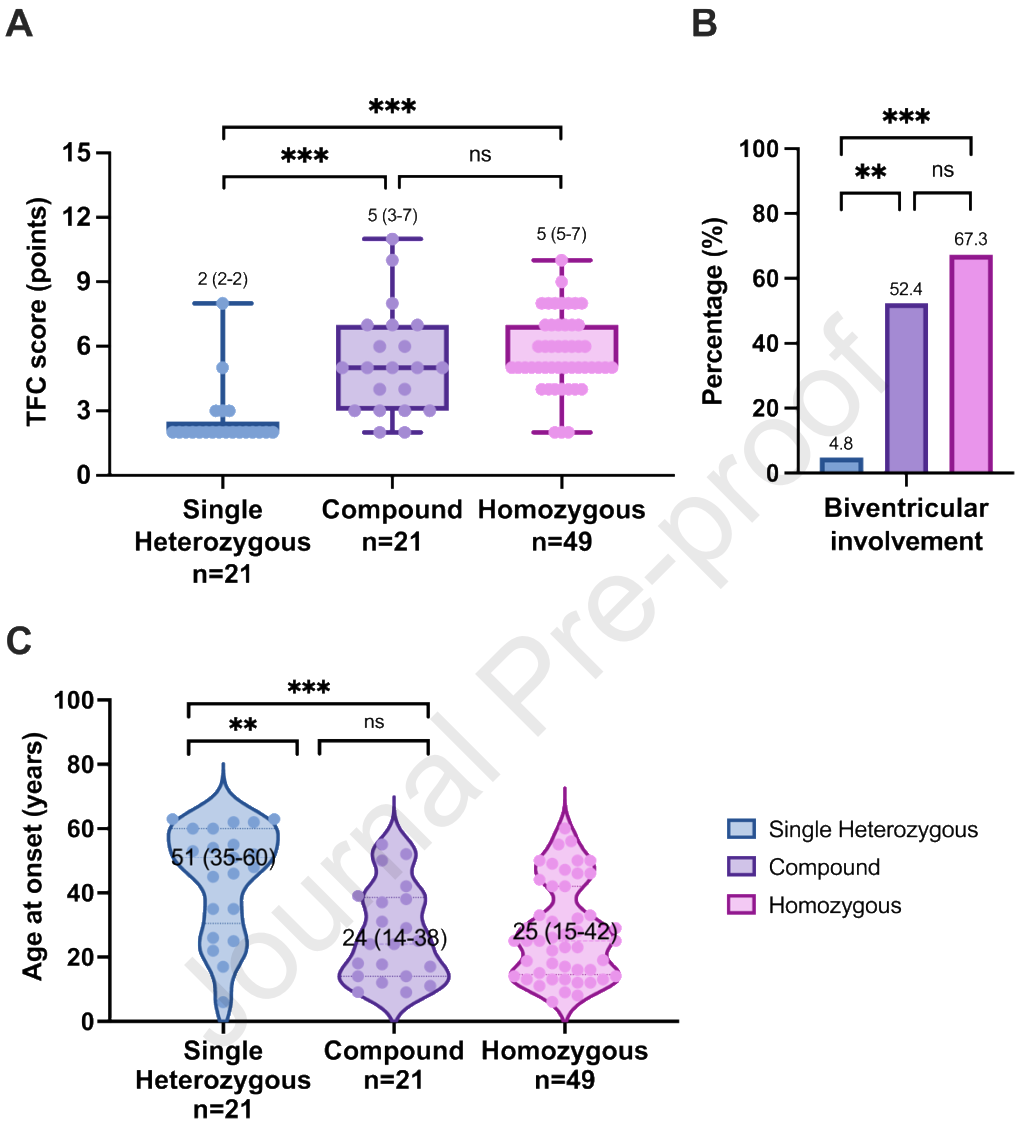
Figure 1.

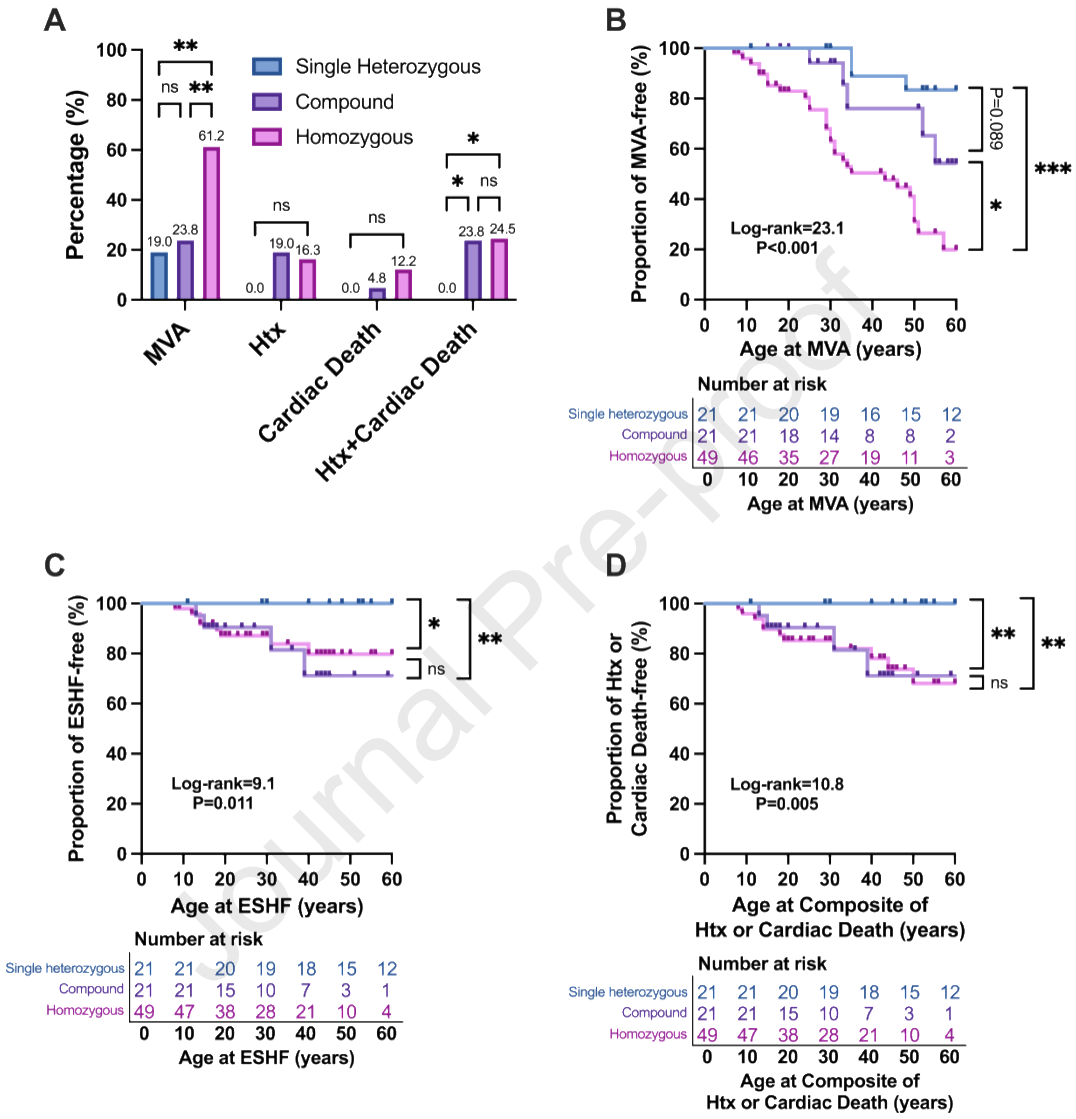
Phenotype of DSG2 c.T1592G (p.Phe531Cys) variant carriers according to zygosity



A, TFC score according to zygosity; B, percentage of biventricular involvement according to zygosity; C, age at onset according to zygosity.

Figure 2.

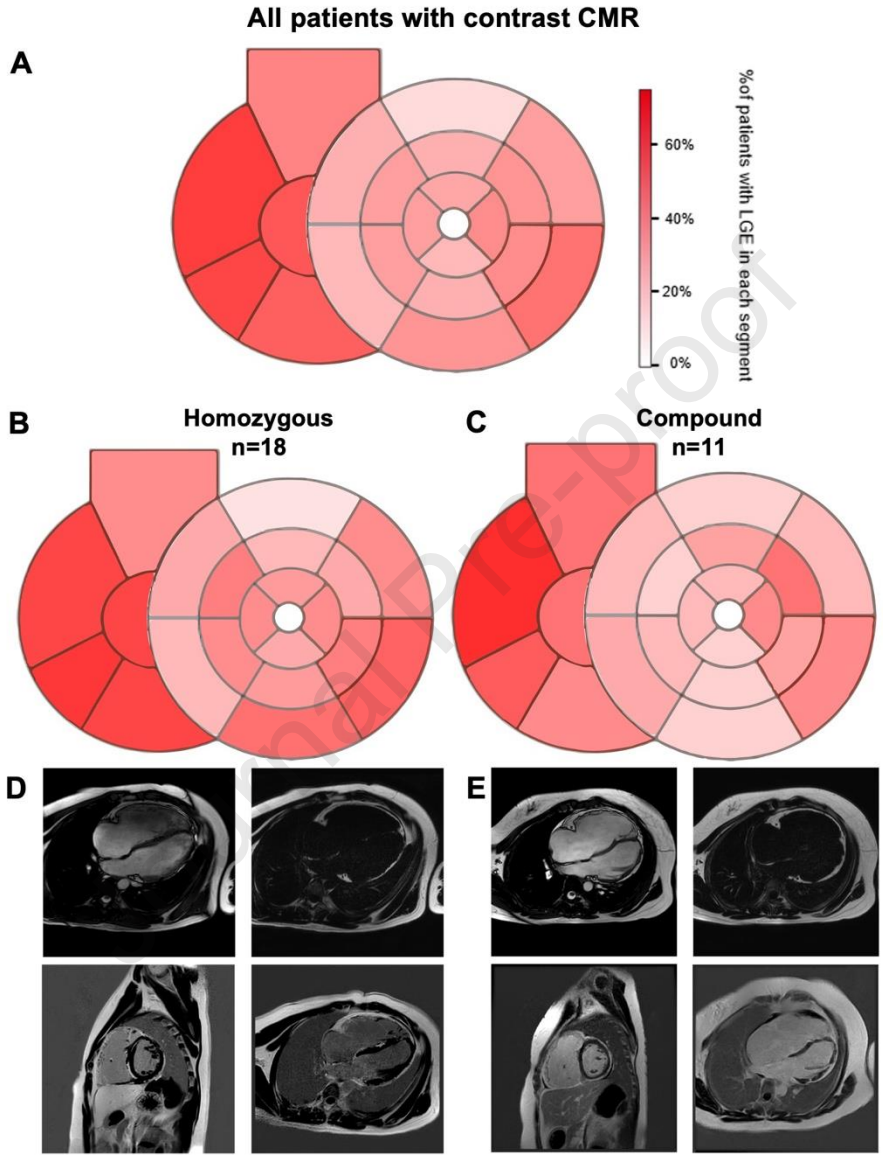
Clinical outcomes of DSG2 c.T1592G (p.Phe531Cys) variant carriers according to zygosity



A, percentage of adverse events according to zygosity; B, survival curve of MVA-free according to zygosity; C, survival curve of ESHF-free according to zygosity; D, survival curve of Htx or cardiac death-free according to zygosity. Abbreviations: Htx, heart transplantation.

Figure 3.

LGE distribution of DSG2 c.T1592G (p.Phe531Cys) variant carriers



A, LGE distribution of DSG2 c.T1592G (p.Phe531Cys) variant carriers (N=29); B, LGE distribution in homozygous variant carriers (N=18); C, LGE distribution in compound variant carriers (N=11); D, Representative cardiac magnetic resonance plot of a homozygous variant carrier, with biventricular fat infiltration and extensive LGE

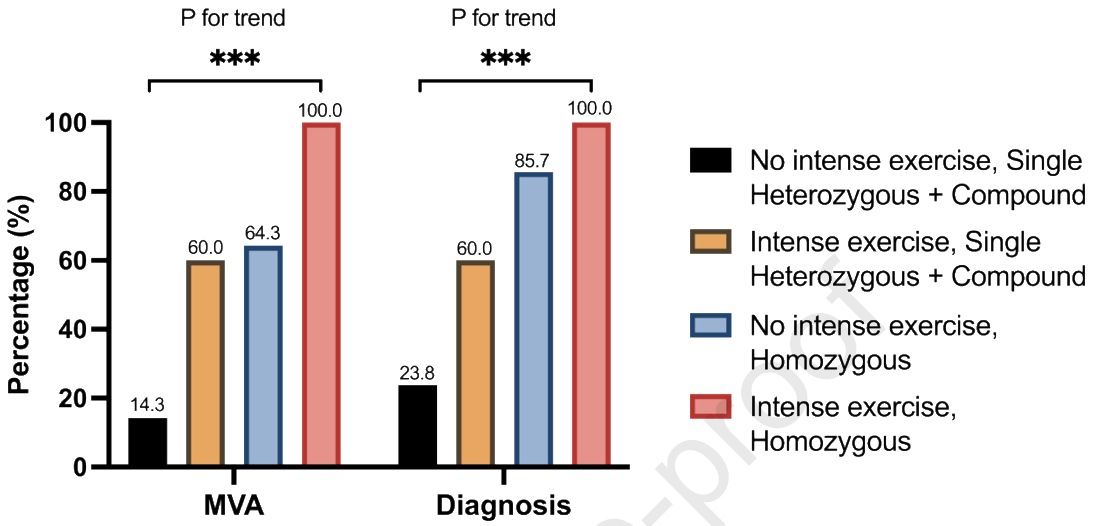
512 in RV and LV; E, Representative cardiac magnetic resonance plot of a compound

513 variant carrier, with extensive LGE in RV and lateral LV involvement.

514 **Figure 4.**

515 MVA and disease penetrance of DSG2 c.T1592G (p.Phe531Cys) variant carriers

516 according to intense exercise and zygosity



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519 **Table 1.**

520 Baseline characteristics of DSG2 c.T1592G (p.Phe531Cys) variant carriers according to zygosity

521

Characteristics	Overall (N=91)	Single Heterozygous (N=21)	Compound (N=21)	Homozygous (N=49)	P value	P for Single Heterozygous vs Compound	P for Single Heterozygous vs Homozygous	P for Compound vs Homozygous
Proband, n (%)	59 (64.8%)	3 (14.3%)	19 (90.5%)	37 (75.5%)	< 0.001	< 0.001	< 0.001	0.423
Male gender, n (%)	53 (58.2%)	11 (52.4%)	9 (42.9%)	33 (67.3%)	0.135			
Body mass index, kg/m2	23.6 (20.7-26.6)	25.5 (24.2-27.2)	24.1 (19.7-26.9)	22.0 (19.2-23.5)	0.012	0.512	0.002	0.394
Age at onset, y	28 (17-48)	51 (35-60)	24 (14-38)	25 (15-42)	< 0.001	0.002	0.001	0.783
Age at onset ≤16, n (%)	20 (22.0%)	1 (4.8%)	6 (28.6%)	13 (26.5%)	0.093			

Age at confirmatory diagnosis, y	35 (18-50)	51 (35-60)	25 (15-39)	29 (15-48)	0.004	0.005	0.008	0.640
First presenting symptom, n (%)					0.008	0.015	0.266	0.308
Asymptomatic	24 (26.4%)	10 (47.6%)	3 (14.3%)	11 (22.4%)				
Arrhythmia	45 (49.5%)	10 (47.6%)	9 (42.9%)	26 (53.1%)				
Resuscitated sudden cardiac arrest	8 (8.8%)	1 (4.8%)	1 (4.8%)	6 (12.2%)				
Heart failure	14 (15.4%)	0 (0.0%)	8 (38.1%)	6 (12.2%)				
Previous MVA events, n (%)	17 (18.7%)	2 (9.5%)	3 (14.3%)	12 (24.5%)	0.284			
NYHA class III-IV, n (%)	15 (23.4%)	1 (5.6%)	5 (41.7%)	9 (26.5%)	0.061			

Electrocardiogram, n (%)								
TWI in precordial leads V_1 to V_3	7 (33.3%)	14 (93.3%)	31 (93.9%)	52 (75.4%)	< 0.001	0.003	< 0.001	1.000
Number of TWI in precordial leads, n	3 (1-5)	0 (0-2)	3 (1-4)	4 (1-5)	< 0.001	0.013	< 0.001	0.125
Right bundle branch block	19 (26.0%)	2 (9.5%)	4 (26.7%)	13 (35.1%)	0.102			
Left bundle branch block	2 (4.8%)	0 (0.0%)	1 (10.0%)	1 (4.2%)	0.599			
Epsilon wave in precordial V1 to V3	34 (42.5%)	1 (4.8%)	8 (53.3%)	25 (56.8%)	< 0.001	0.009	< 0.001	1.000

QRS duration, ms	111 (98-127)	109 (94-113)	100 (92-121)	115 (100-139)	0.088			
Premature ventricular contraction >500/24 h	39 (69.6%)	1 (25.0%)	11 (73.3%)	27 (73.0%)	0.131			
NSVT	47 (51.6%)	3 (14.3%)	9 (42.9%)	35 (71.4%)	< 0.001	0.251	< 0.001	0.123
Medicines, n (%)								
Beta blocker	24 (66.7%)	3 (100.0%)	7 (70.0%)	14 (60.9%)	0.387			
Antiarrhythmic medicine	24 (66.7%)	3 (100.0%)	4 (40.0%)	17 (73.9%)	0.073			
Amiodarone	14 (46.7%)	2 (100.0%)	1 (11.1%)	11 (57.9%)	0.020	0.055	0.505	0.038
Sotalol	10 (33.3%)	1 (50.0%)	2 (22.2%)	7 (36.8%)	0.652			
Echocardiography								

Left atrium diameter, mm	31.0 (27.0-35.0)	35.0 (32.3-37.0)	29.5 (27.8-33.0)	29.0 (24.0-32.0)	0.059			
LVEF, %	54.0 (46.0-63.3)	62.4 (52.3-67.4)	58.0 (46.0-63.1)	50.0 (44.0-60.0)	0.016	0.087	0.007	0.265
LV end-diastolic diameter, mm	48.0 (43.0-52.0)	48.3 (45.0-51.3)	50.0 (45.0-58.0)	45.5 (42.0-51.5)	0.495			
RVD, mm	36.0 (24.0-42.0)	22.2 (20.0-24.0)	44.0 (38.5-50.5)	38.5 (33.0-42.0)	< 0.001	< 0.001	< 0.001	0.092
LV dilatation, n (%)	24 (31.6%)	5 (27.8%)	5 (29.4%)	14 (34.1%)	0.868			
LV dyskinesia, n (%)	28 (36.8%)	0 (0.0%)	9 (52.9%)	19 (46.3%)	< 0.001	0.002	0.002	0.954
RV dilatation, n (%)	68 (74.7%)	7 (33.3%)	17 (81.0%)	44 (89.8%)	< 0.001	0.021	< 0.001	0.776
RV dyskinesia, n (%)	54 (67.5%)	2 (11.1%)	13 (86.7%)	39 (83.0%)	< 0.001	< 0.001	< 0.001	1.000

Radiofrequency catheter ablation, n (%)	11 (12.1%)	2 (9.5%)	4 (19.0%)	5 (10.2%)	0.535
Atrial flutter	2 (18.2%)	0 (0.0%)	0 (0.0%)	2 (40.0%)	
Atrioventricular nodal reentry tachycardia	1 (9.1%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	
Premature ventricular contraction	1 (9.1%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	
Ventricular tachycardia	7 (63.6%)	2 (100.0%)	2 (50.0%)	3 (60.0%)	
ICD implantation, n (%)	16 (18.2%)	2 (9.5%)	4 (20.0%)	10 (21.3%)	0.495
Primary prevention	6 (37.5%)	0 (0.0%)	1 (25.0%)	5 (50.0%)	
Secondary prevention	10 (62.5%)	2 (100.0%)	3 (75.0%)	5 (50.0%)	

522

Table 2.

Prognostic factors for clinical outcomes in DSG2 c.T1592G (p.Phe531Cys) variant carriers

Characteristics	Univariable Cox Regression			Stepwise Multivariable Cox Regression		
	Unadjusted HR	95% CI	P value	Adjusted HR	95% CI	P value
MVA in primary prevention subgroup						
Age of onset, y	0.97	0.94-0.99	0.014			
Male (vs. Female)	1.90	0.72-5.02	0.194			
Zygosity (Compound vs. Single Heterozygous) *	2.24	0.31-16.19	0.423			
Zygosity (Homozygous vs. Single Heterozygous) *	11.53	2.55-52.16	0.002			
Syncope (yes vs. no)	2.54	1.03-6.30	0.044			
NYHA class III-IV (vs. class I-II	1.6	0.35-7.45	0.547			
LVEF, %	0.94	0.91-0.98	0.005	0.95	0.91-0.99	0.013
RVD, mm	1.07	1.02-1.13	0.008	5.07	1.11-23.21	0.037
RV dilation (yes vs. no)	9.69	2.21-42.51	0.003			
Number of TWI in precordial leads, n	1.18	0.96-1.46	0.116			

Premature ventricular contraction counts>500	2.63	0.57-12.10	0.215			
NSVT (yes vs. no)	4.61	1.80-11.78	0.001	3.31	1.23-8.90	0.018
TFC score, points	1.21	1.02-1.42	0.025			
ESHF in total population						
Age of onset, y	0.95	0.9-0.99	0.018			
Male (vs. Female)	1.19	0.38-3.75	0.768			
Zygosity (Homozygous + Compound vs. Single Heterozygous) †	13.36	1.74-1716.53	0.007	4.95	0.47-673.39	0.212
Syncope (yes vs. no)	1.99	0.64-6.18	0.233			
NYHA class III-IV (vs. class I-II	11.3	2.98-42.85	<0.001			
LVEF, %	0.92	0.88-0.97	0.001	0.92	0.88-0.97	0.001
RVD, mm	1.13	1.05-1.23	0.002			
RV dilation (yes vs. no)	2.91	0.63-13.38	0.169			
Number of TWI in precordial leads, n	1.24	0.93-1.63	0.139			
Premature ventricular contraction counts>500	0.81	0.19-3.43	0.779			
NSVT (yes vs. no)	5.36	1.17-24.56	0.031	3.25	0.89-16.58	0.075
Composite events in total population						

Age of onset, y	0.96	0.93-1.00	0.030			
Male (vs. Female)	0.95	0.35-2.64	0.929			
Zygosity (Homozygous + Compound vs. Single Heterozygous) †	15.78	2.11-2018.88	0.002	5.34	0.54-720.65	0.178
Syncope (yes vs. no)	1.34	0.48-3.75	0.583			
NYHA class III-IV (vs. class I-II	6.66	2.17-20.46	0.001			
LVEF, %	0.93	0.9-0.97	<0.001	0.93	0.90-0.97	0.001
RVD, mm	1.13	1.05-1.21	0.001			
RV dilation (yes vs. no)	3.68	0.83-16.39	0.087			
Number of TWI in precordial leads, n	1.13	0.89-1.43	0.317			
Premature ventricular contraction counts>500	1.17	0.3-4.53	0.825			
NSVT (yes vs. no)	6.84	1.54-30.42	0.012	3.49	1.03-16.89	0.043

* For MVA, compound and homozygous variant carriers were compared separately with heterozygous variant carriers.

† For ESHF and composite of heart transplantation or cardiac death, compound and homozygous variant carriers were combined and compared with heterozygous variant carriers, because no ESHF or composite events occurred in heterozygous variant

carriers and survival analysis demonstrated no significant differences between compound and homozygous variant carriers.

Abbreviations: Htx, heart transplantation.

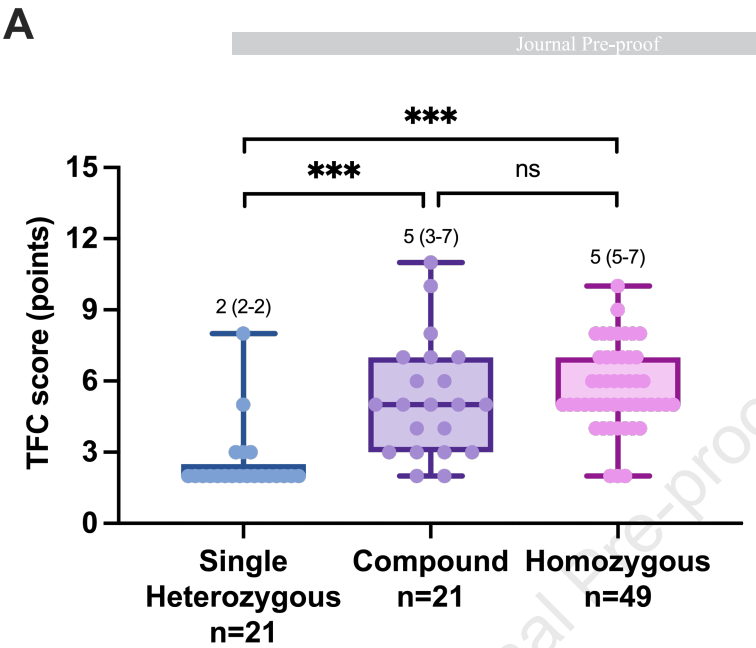
Table 3.

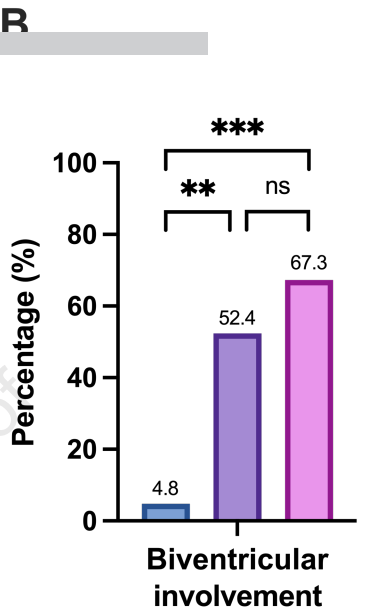
Prognostic value of intense exercise for clinical outcomes in DSG2 c.T1592G (p.Phe531Cys) variant carriers

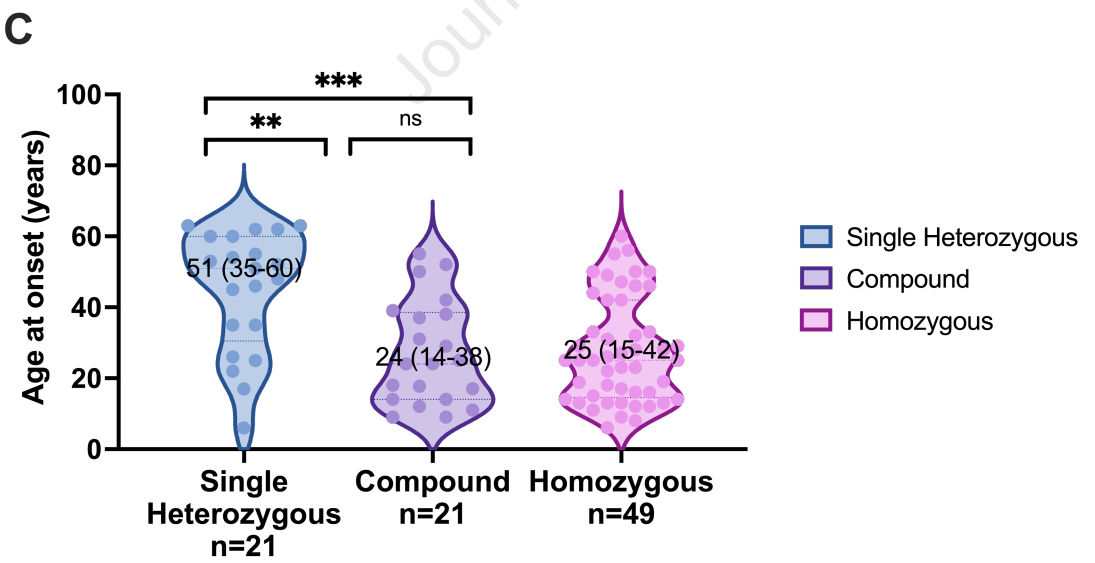
	Univariable Cox Regression			Multivariable Cox Regression*		
Characteristics	**Unadjusted HR**	**95% CI**	**P value**	**Adjusted HR**	**95% CI**	**P value**
MVA	7.08	2.42-20.78	<0.001	7.51	2.13-26.51	0.002
Htx+Cardiac Death	0.83	0.17-4.01	0.819	0.71	0.14-3.64	0.686

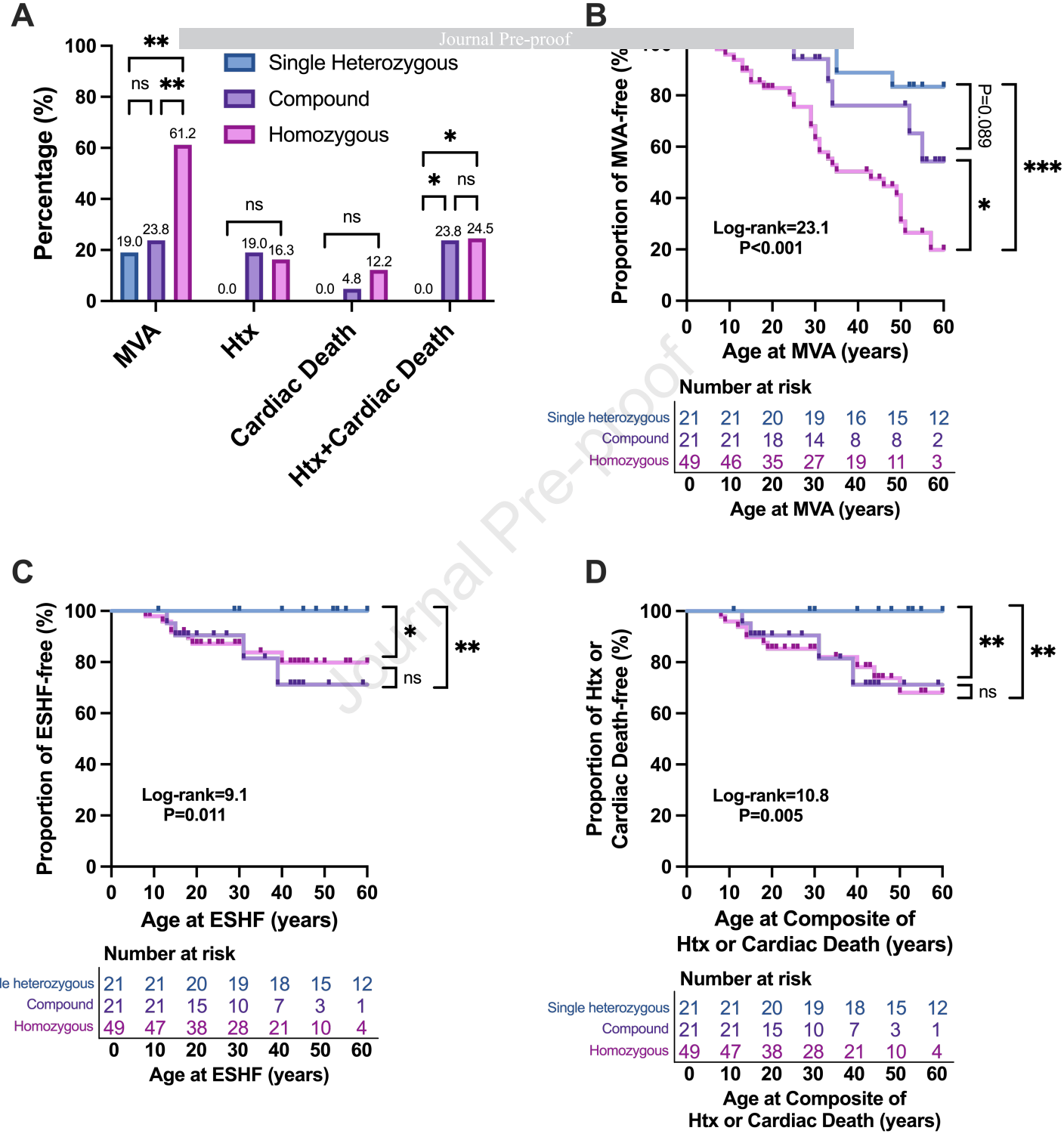
* Adjusted for age at onset and sex.

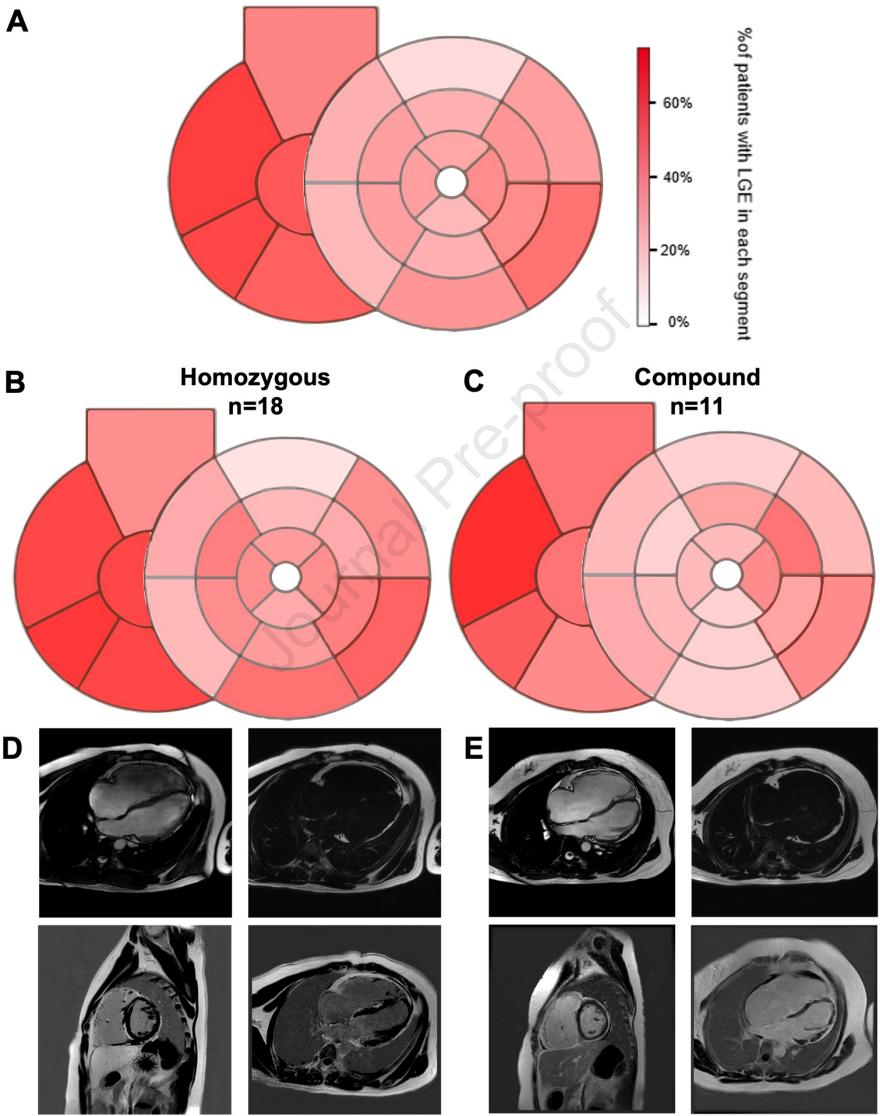
Abbreviations: Htx, heart transplantation.

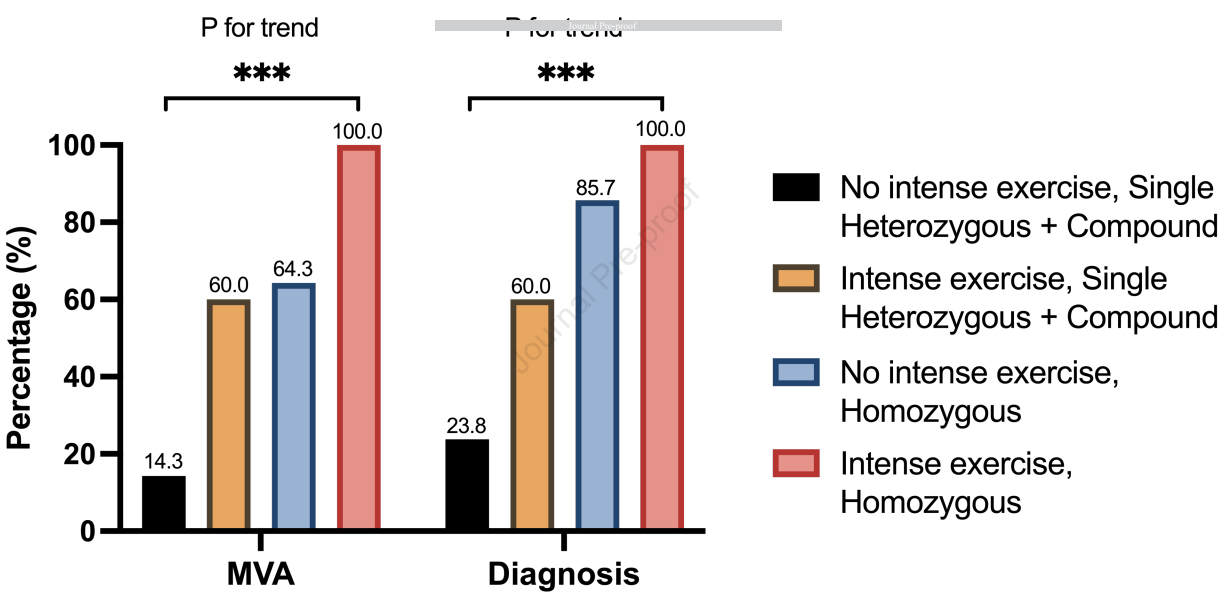











P for trend
***
100.0
60.0
64.3
14.3
MVA
P for trend
***
100.0
85.7
60.0
23.8
Diagnosis
Percentage (%)
100
80
60
40
20
0
No intense exercise, Single Heterozygous + Compound
Intense exercise, Single Heterozygous + Compound
No intense exercise, Homozygous
Intense exercise, Homozygous

Clinical Features and Outcome of Arrhythmogenic Cardiomyopathy due to a Desmoglein-2 Founder Variant: A Multicenter Study

Supplemental Materials

Content

Supplemental Methods

Clinical data collection

Collected clinical data included demographic information, regular exercise habit 3 years before enrollment, presenting symptoms, New York Heart Association (NYHA) functional class, medication, and surgical history. In addition, electrocardiographic features were recorded using 12-lead ECG, and 24-hour ambulatory ECG monitoring. Echocardiographic features were recorded using transthoracic echocardiography, and cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement (LGE).

Age at onset refers to the age of: 1) a symptomatic patient first presented to clinic with symptoms such as palpitations, syncope, dyspnea, edema, or chest distress; or 2) an asymptomatic individual was first found to have abnormal ECG findings or abnormal cardiac imaging findings, or identification of DSG2 c.T1592G (p.Phe531Cys) variant. Non-sustained ventricular tachycardia (NSVT) was defined as ≥3 consecutive ventricular beats at a rate >100 beats per minute, lasting <30 seconds. Sustained ventricular tachycardia (VT) was defined as VT lasting ≥30 seconds or requiring intravenous medication or cardioversion for termination. For adults, left ventricular (LV) dilatation was defined according to international ethnic-specific reference values [1,2]. RV dilatation was defined as a parasternal long-axis RV outflow tract (RVOT) diameter ≥29 mm or a parasternal short-axis RVOT diameter ≥32 mm according to revised 2010 Task Force Criteria (TFC) [3]. For children, LV and RV

dilatation were defined according to echocardiographic nomograms by body surface area, with values exceeding >2 Z-scores considered dilatation [4]. TFC score were calculated based on each diagnostic criterion, with major criteria assigned 2 points each and minor criteria 1 point each.

As for exercise assessment, all individuals were interviewed in clinic or via telephone by trained physicians regarding their regular exercise habits during three years before enrollment. The type of exercise during leisure, work, and transportation, as well as the frequency (days/week) and duration (minutes/day), were recorded [5,6]. The intensity of exercise was evaluated based on the Multi-Ethnic Study of Atherosclerosis Typical Week Physical Activity Survey [7], and classified as light, moderate, or vigorous. Vigorous-intensity activity was defined as intense exercise.

Among the total cohort of 91 subjects, 46 participants were included in exercise analysis. The reasons of missing exercise data were: 1) refusal to provide, 2) lack of knowledge regarding their own exercise habits, and 3) recall difficulties. Only complete and reliable exercise data were included in exercise analysis. We compared baseline characteristics between subjects included in exercise analysis and overall cohort and found no significant differences in baseline characteristics between two groups (**Supplemental Table 4**)

Genetic analysis

Whole-exome sequencing was performed on the Illumina NovaSeq 6000 platform with 100× coverage. Variant pathogenicity was assessed according to the American

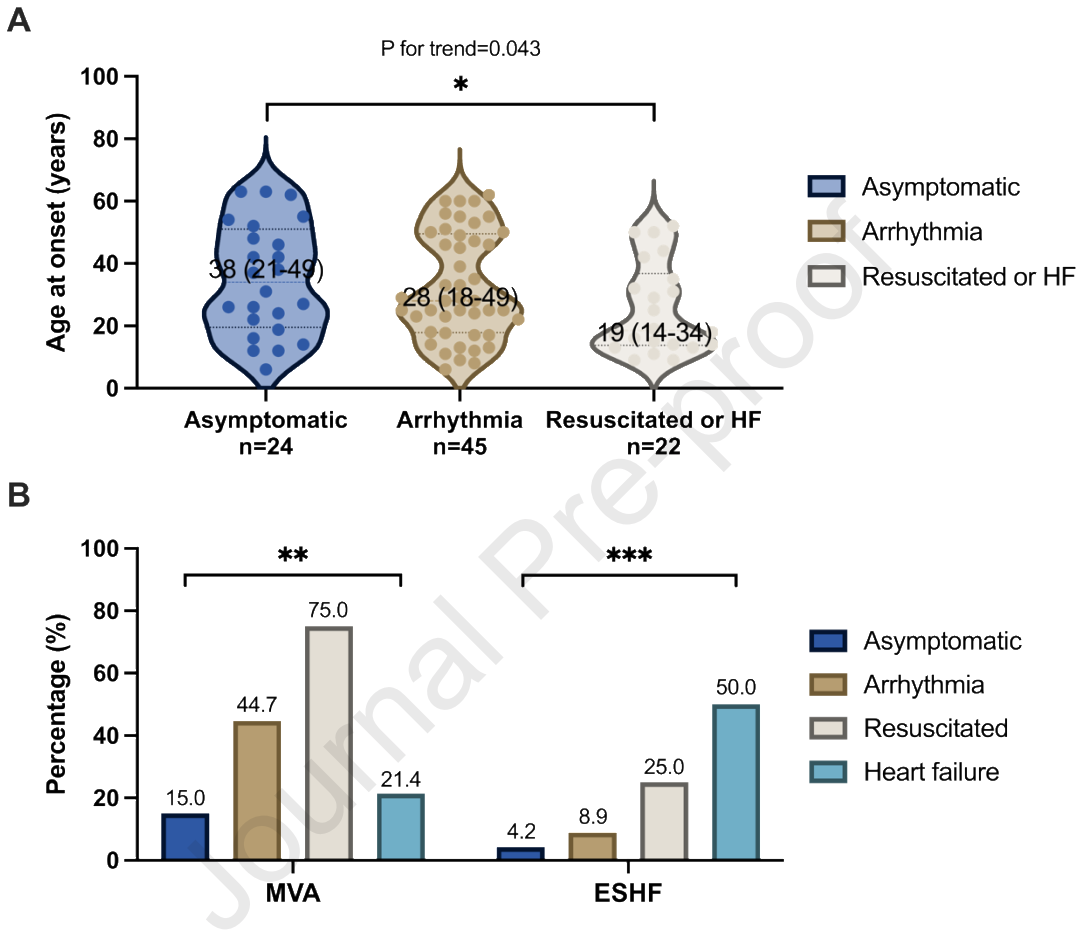
College of Medical Genetics and Genomics (ACMG) guidelines. For familial cascade screening, Sanger sequencing was employed to verify identified variants in relatives. To ensure specificity of genotype-phenotype correlations, we excluded patients who carried: (1) concurrent pathogenic or likely pathogenic variants in other cardiomyopathy-associated genes, or (2) additional pathogenic or likely pathogenic DSG2 mutations known to be associated with cardiomyopathy according to ACMG guideline. Furthermore, rare variants of uncertain significance (VUS) in genes associated with arrhythmia or cardiomyopathy were evaluated. Primary filtering criterion was based on overall allele frequency in gnomADV4.0, which was used as threshold (<0.1‰) for inclusion of VUS. Those predicted to be deleterious by in silico prediction tools were included in subsequent analysis (**Supplemental Table 1**). Subjects with DSG2 c.T1592G (p.Phe531Cys) variants were classified into following groups: (1) single heterozygous; (2) compound heterozygous (single variant plus rare VUS; abbreviated as compound); and (3) homozygous.

Supplemental Results

Initial symptoms and age at onset are associated with disease prognosis. Among individuals with resuscitation or heart failure as the first presenting symptom, median age at onset was 19 years (IQR: 14–34), which was significantly younger compare to those with arrhythmia [28 years (IQR: 18–49)] or asymptomatic [38 years (IQR: 21–49); P for trend=0.043; **Supplemental Figure 1A**]. Individuals with resuscitation (75.0%) or arrhythmia (44.7%) as the first presenting symptom were more likely to experience MVA, compared to those with heart failure (21.4%) or asymptomatic (15.0%; P=0.009). Individuals with heart failure (50.0%) or resuscitation (25.0%) as the first presenting symptom were more likely to experience ESHF, compared to those with arrhythmia (8.9%) or asymptomatic (4.2%; P<0.001; **Supplemental Figure 1B**). Individuals with earlier onset age (<16 years old) had higher risk of heart transplantation (30.0 vs. 8.5%; P=0.012), cardiac death (25.0 vs. 2.8%; P=0.001), and composite of heart transplantation or cardiac death (45.0 vs. 11.3%; P<0.001). There was no significant difference in the incidence of first MVA (35.0 vs. 45.1%; P=0.421; **Supplemental Figure 2**).

Supplemental Figures

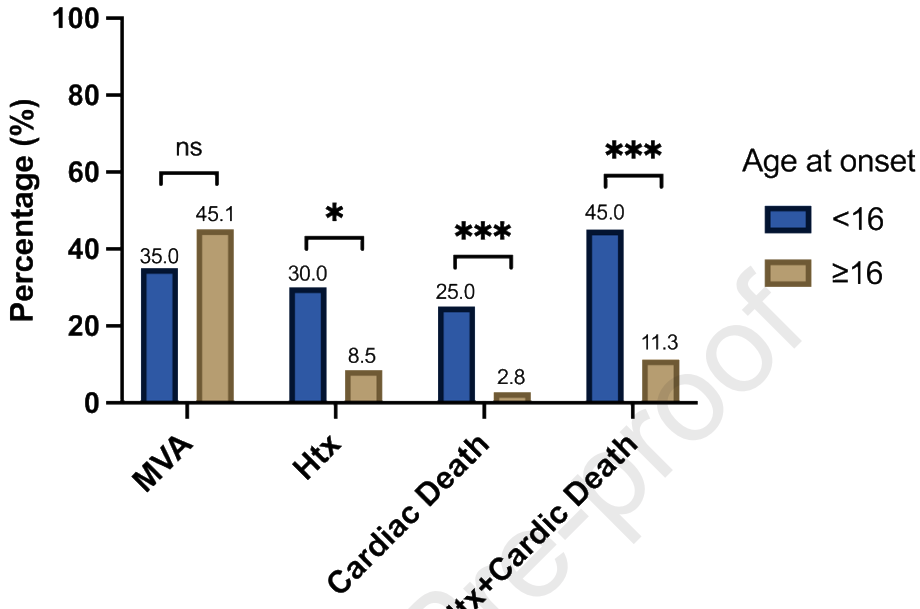
Supplemental Figure 1. Age of onset and clinical outcomes of DSG2 c.T1592G (p.Phe531Cys) variant carriers according to first presenting symptom



A, age of onset according to first presenting symptom; B, clinical outcomes according to first presenting symptom.

118 Supplemental Figure 2. Clinical outcomes of DSG2 c.T1592G (p.Phe531Cys) variant

119 carriers according to age at onset.



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121 Abbreviations: Htx, heart transplantation.

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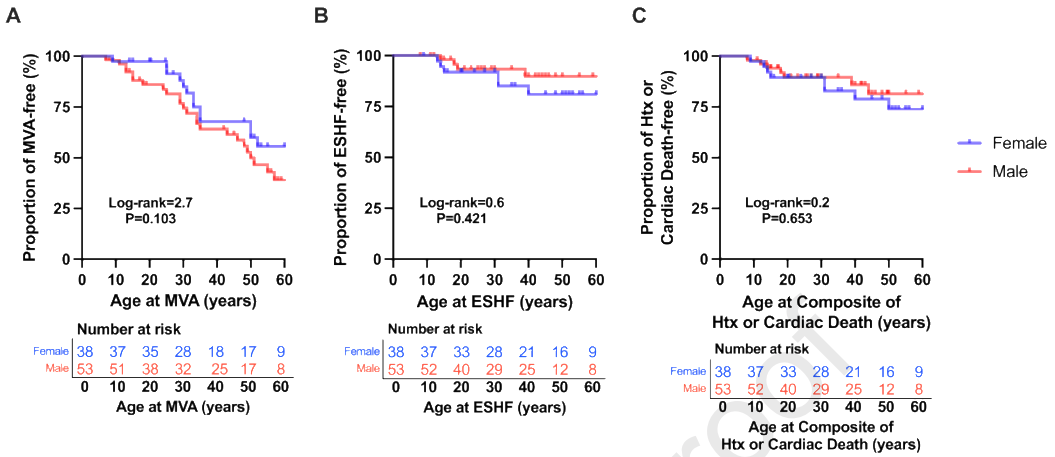
123 Supplemental Figure 3. Clinical outcomes of DSG2 c.T1592G (p.Phe531Cys) variant

124 carriers according to sex.



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126 A, survival curve of MVA-free according to sex; B, survival curve of ESHF-free

127 according to sex; C, survival curve of Htx or cardiac death-free according to sex.

128 Abbreviations: Htx, heart transplantation.

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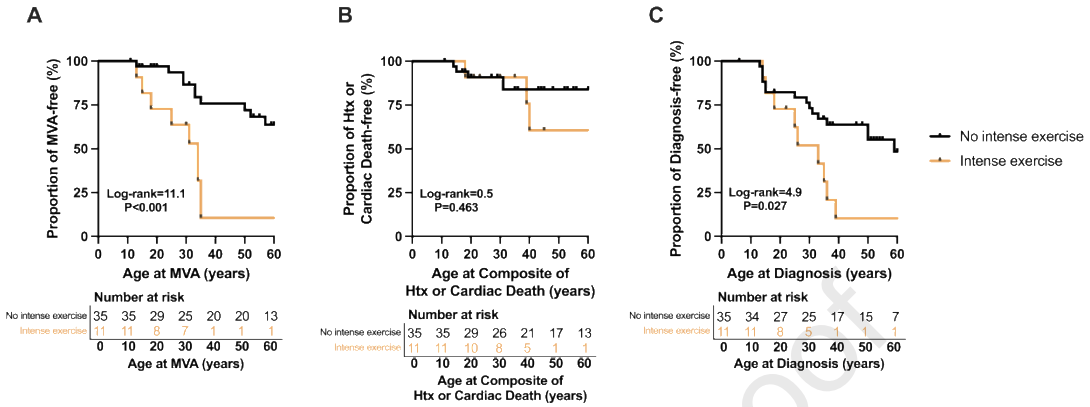
Supplemental Figure 4. Survival curve of adverse outcomes-free and disease penetrance in DSG2 c.T1592G (p.Phe531Cys) variant carriers according to intense exercise.



A, survival curve of MVA-free according to intense exercise; B, survival curve of Htx or cardiac death-free according to intense exercise; C, survival curve of diagnosis-free according to intense exercise. Abbreviations: Htx, heart transplantation.

Supplemental Tables

Supplemental Table 1. List of variants of uncertain significance in the compound group

Gene	Transcript	Coding DNA change	Protein change
DSG2	NM_001943.5	c.1739G>C	p.C580S
DSP	NM_004415.4	c.38C>T	p.T13I
CTNNA3	NM_013266.4	c.2377G>A	p.G793R
TMEM43	NM_024334.3	c.265G>C	p.V89L
DSG2	NM_001943.5	c.2445T>G	p.S815R
DSG2	NM_001943.5	c.1141A>T	p.N381Y
SCN5A	NM_000335.5	c.5131G>A	p.G1711S
DSG2	NM_001943.5	c.1879+3A>C	p.?
DSG2	NM_001943.5	c.391G>A	p.A131T
TTN	NM_001267550.2	c.1800+1G>A	p.?
KCNE5	NM_012282.4	c.276C>A	p.D92E
KCNE5	NM_012282.4	c.277G>T	p.E93*
DSG2	NM_001943.5	c.995G>A	p.G332E
DSG2	NM_001943.5	c.1480G>A	p.D494N
SLC25A3	NM_005888.4	c.158-5_158-2del	p.?
DSG2	NM_001943.5	c.337G>T	p.V113F

144 Supplemental Table 2. Cardiac magnetic resonance imaging characteristics of DSG2

145 c.T1592G (p.Phe531Cys) variant carriers according to zygosity

Characteristics	Number assessed	Overall (N=34)	Single Heterozygous + Compound (N=13)	Homozygous (N=21)	P value
RV end-diastolic diameter, mm	34	51.0 (44.0-57.3)	50.0 (44.0-55.0)	52.0 (48.0-59.0)	0.269
RV ejection fraction %	34	16.0 (12.0-25.7)	18.8 (15.0-27.3)	12.7 (11.2-20.6)	0.281
RV end-diastolic volume index, mL/m²	34	170.7 (144.8-209.1)	161.2 (126.6-178.8)	179.8 (148.3-211.3)	0.130
RV end-systolic volume index, mL/m²	34	145.7 (105.9-185.4)	138.4 (95.6-151.0)	156.5 (117.9-196.5)	0.144
LV end-diastolic diameter, mm	34	46.0 (44.0-54.5)	51.5 (46.3-57.8)	44.0 (42.0-50.0)	0.312
LVEF, %	34	44.3 (33.8-53.0)	43.3 (28.2-50.0)	44.5 (35.8-53.5)	0.423

LV end-diastolic volume index, mL/m²	34	79.6 (57.9-98.2)	87.9 (75.8-94.7)	76.3 (56.8-99.7)	0.536
LV end-systolic volume index, mL/m²	34	47.6 (28.0-65.9)	49.7 (38.2-70.8)	42.1 (26.3-63.2)	0.460
LGE in RV, n (%)	29	27 (93.1%)	10 (90.9%)	17 (94.4%)	0.715
LGE in LV, n (%)	29	24 (82.8%)	9 (81.8%)	15 (83.3%)	0.917
LGE in both RV and LV, n (%)	29	22 (75.9%)	8 (72.7%)	14 (77.8%)	0.758
Fat in RV, n (%)	29	24 (88.9%)	9 (100.0%)	15 (83.3%)	0.194
Fat in LV, n (%)	29	15 (55.6%)	2 (22.2%)	13 (72.2%)	**0.014**

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149 Supplemental Table 3. Estimated echocardiographic changes per month in DSG2

150 c.T1592G (p.Phe531Cys) variant carriers

Characteristics	Number assessed	Estimate per month	95% CI	P value
Left atrium diameter, mm	22	0.05	0.02-0.09	0.006
LVEF, %	22	-0.04	-0.10-0.02	0.224
RVD, mm	22	0.06	0.01-0.11	0.028

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Supplemental Table 4. Prognostic value of echocardiographic changes for ESHF in DSG2 c.T1592G (p.Phe531Cys) variant carriers

Characteristics	Univariable Cox Regression			Multivariable Cox Regression*		
	Unadjusted HR	95% CI	P value	Adjusted HR	95% CI	P value
RVD slope	1.24	1.04-1.48	0.018	1.25	1.03-1.52	0.023
LVEF slope	1.53	1.02-2.28	0.038	1.64	0.94-2.88	0.083

* Adjusted for age at onset and sex.

156 Supplemental Table 5. Baseline characteristics of DSG2 c.T1592G (p.Phe531Cys)

157 variant carriers according to intense exercise

Characteristics	No intense exercise (N=35)	Intense exercise (N=11)	p value
Proband, n (%)	19 (54.3%)	9 (81.8%)	0.103
Zygosity, n (%)			0.544
Single Heterozygous	13 (37.1%)	4 (36.4%)	
Compound	8 (22.9%)	1 (9.1%)	
Homozygous	14 (40.0%)	6 (54.5%)	
Male gender, n (%)	14 (40.0%)	9 (81.8%)	0.016
Body mass index, kg/m2	24.2 (20.7-26.7)	23.7 (21.4-24.9)	0.545
Age at onset, y	33 (17-53)	26 (20-34)	0.246
Age at confirmatory diagnosis, y	38.0 (27.0-54.5)	26.0 (20.0-35.5)	0.096
First presenting symptom, n (%)			0.267
Asymptomatic	12 (34.3%)	2 (18.2%)	
Arrhythmia	13 (37.1%)	3 (27.3%)	
Resuscitated	4 (11.4%)	4 (36.4%)	
Heart failure	6 (17.1%)	2 (18.2%)	
NYHA class III-IV, n (%)	10 (32.3%)	3 (30.0%)	0.894
Electrocardiogram, n (%)			

Number of TWI in precordial leads, n	3 (0-5)	4 (4-6)	0.062
Epsilon wave in precordial V1 to V3	11 (35.5%)	2 (20.0%)	0.360
Premature ventricular contraction >500/24 h	10 (66.7%)	5 (83.3%)	0.445
NSVT	15 (42.9%)	8 (72.7%)	0.084
Medicines, n (%)			
Beta blocker	11 (64.7%)	6 (66.7%)	0.920
Antiarrhythmic medicine	11 (64.7%)	7 (77.8%)	0.492
Amiodarone	8 (47.1%)	5 (55.6%)	0.680
Sotalol	6 (35.3%)	4 (44.4%)	0.648
TFC score, points	4 (2-7)	6 (5-7)	0.280

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160 Supplemental Table 6. Baseline characteristics of DSG2 c.T1592G (p.Phe531Cys)

161 variants according to presence of exercise data

Characteristics	Without exercise data (N=45)	With exercise data (N=46)	p value
Proband, n (%)	31 (68.9%)	28 (60.9%)	0.423
Zygosity, n (%)			0.006
Single Heterozygous	4 (8.9%)	17 (37.0%)	
Compound	12 (26.7%)	9 (19.6%)	
Homozygous	29 (64.4%)	20 (43.5%)	
Male gender, n (%)	30 (66.7%)	23 (50.0%)	0.107
Body mass index, kg/m2	23.2 (19.3-26.2)	23.8 (21.0-26.6)	0.519
Age at onset, y	25 (16-46)	32 (17-52)	0.197
Age at confirmatory diagnosis, y	28 (16-46)	36 (23-53)	0.112
First presenting symptom, n (%)			0.005
Asymptomatic	10 (22.2%)	14 (30.4%)	
Arrhythmia	29 (64.4%)	16 (34.8%)	
Resuscitated	0 (0.0%)	8 (17.4%)	
Heart failure	6 (13.3%)	8 (17.4%)	
Previous MVA events, n (%)	6 (15.0%)	11 (23.9%)	0.301

NYHA class III-IV, n (%)	2 (8.7%)	13 (31.7%)	0.037
Electrocardiogram, n (%)			
Number of TWI in precordial leads, n	3 (1-5)	4 (0-5)	0.501
Epsilon wave in precordial V1 to V3	21 (53.8%)	13 (31.7%)	0.045
Premature ventricular contraction >500/24 h	24 (68.6%)	15 (71.4%)	0.822
NSVT	24 (53.3%)	23 (50.0%)	0.750
Medicines, n (%)			
Beta blocker	7 (70.0%)	17 (65.4%)	0.792
Antiarrhythmic medicine	6 (60.0%)	18 (69.2%)	0.599
Amiodarone	1 (25.0%)	13 (50.0%)	0.351
Sotalol	0 (0.0%)	10 (38.5%)	0.129
TFC score, points	5 (4-6)	5 (2-7)	0.742

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163 Supplemental Table 7. Comparison of phenotypes and outcomes between the DSG2

164 cohort from Marika Martini et al and this study

Characteristics	Martini et al.[8]	This study
DSG2 cohort source	Padua cohort (N=80) + previously published cases (N=122)	Chinese cohort (N=91)
Ethnicity	Predominantly Caucasian (82.2%)	All Chinese
Genotype	DGS2	NM_001943.5 (DSG2): c.1592T>G (p.Phe531Cys)
Phenotype		
Proband, n (%)	60.9%	64.8%
Male gender, n (%)	64.8%	58.2%
Age at onset, y	36 years	28 years
RV dilatation, n (%)	67.7%	74.7%
Biventricular involvement, n (%)	31.2%	49.5%
TWI in V1-V3, n (%)	52.0%	75.4%
Epsilon wave, n (%)	10.2%	42.5%
PVC >500/24 h, n (%)	59.3%	69.6%
NSVT, n (%)	30.8%	51.6%
RBBB, n (%)	12.6%	26.0%
RV dyskinesia, n (%)	66.7%	67.5%
LVEF, %	55.5%	54.0%
Outcomes		
MVA, n (%)	35.3%	36.2%
HF, n (%)	10.9%	15.4%
Heart transplantation, n (%)	5.9%	13.2%
Independent predictors of outcomes	NSVT	LVEF; NSVT

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