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Genetic Predisposition to Sudden Cardiac Death: A Molecular Cardiology Study

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ABSTRACT

Sudden cardiac death (SCD) remains a major global health challenge, and increasing evidence highlights the critical role of genetic predisposition in modulating individual susceptibility. This molecular cardiology study systematically investigated pathogenic, likely pathogenic, and risk-associated variants across key cardiac ion-channel, desmosomal, and sarcomeric genes to determine their contribution to inherited arrhythmogenic risk. Using next-generation sequencing and functional molecular assays, we identified a significantly elevated burden of deleterious variants in KCNQ1, SCN5A, RYR2, PKP2, and LMNA among individuals with a documented family history of SCD. Quantitative variant impact modelling revealed that mutations affecting ion-channel gating kinetics and intracellular calcium handling were strongly associated with abnormal electrophysiological responses, including prolonged repolarization (QTc > 480 ms), conduction delays, and increased arrhythmic triggers. Moreover, genotype–phenotype correlation analyses demonstrated that carriers of compound or multiple heterozygous variants exhibited a 2.7-fold higher risk of malignant arrhythmias compared to single-variant carriers. Functional characterization further confirmed that several novel variants resulted in reduced channel current density, impaired desmosomal integrity, and destabilized myocardial structural proteins, collectively driving electrical instability. Overall, the results of this study underscore the substantial contribution of inherited genetic abnormalities to SCD vulnerability and highlight the importance of integrating molecular genetic screening with clinical risk stratification. The identification of high-impact variants and their mechanistic consequences provide a foundation for targeted surveillance, family cascade screening, and future gene-directed therapeutic interventions.

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INTRODUCTION

Sudden cardiac death is a significant health concern that is characterized by unexpected death within one hour of the symptoms onset or an individual who has been healthy until 24 hours prior to the event (Beccace et al., 2023; Tamariz et al., 2019). Heart disease causes sudden death to about five million individuals across the world annually. Two out of four have 27 percent to 40 percent chances to survive (Paz-Cruz et al., 2023). Every year in the United States alone, there are sudden cardiac arrests to more than 300,000 individuals. This demonstrates the significance of finding out more about the condition and how to assist individuals with it (Kransdorf et al., 2024). Ventricular arrhythmias are recognized to be the key causative factor of sudden cardiac death, but still, a large percentage will be explained, which conceals a central position of underlying genetic variables (Paz-Cruz et al., 2023). It is commonly recognized that genetic predisposition is a significant cause of sudden cardiac death, particularly in younger patients and cases that do not appear to have any structural heart disease at the time of autopsy (Abdelaal et al., 2025) (Chopra and Knollmann, 2011). This is particularly evident in instances of sudden unexplainable death, whereby inherited heart issues like channelopathies and cardiomyopathies are frequently the suspect (Campuzano and Sarquella-Brugada, 2023). High-throughput sequencing-based molecular autopsies are becoming critical in identifying these underlying genetic variations, even where the conventional forensic pathology yields inconclusive results (Schön et al., 2021). This genetic testing is needed to determine the cause of death and also to determine the risk to the surviving members of the family with likely similar genetic susceptibility (Miura et al., 2024) (Kauferstein et al., 2017). Although not common, monogenic features are considered predisposing factors of sudden cardiac death in otherwise healthy young adults, and they include Long QT Syndrome, Brugada Syndrome, and Arrhythmogenic Right Ventricular Cardiomyopathy (Priori, 2013). The conditions are commonly manifested as sudden arrhythmic death, hereditary cardiomyopathy, or dilated cardiomyopathy with left ventricular noncompaction, which confirms the need to conduct comprehensive genetic screening among at-risk groups (Abstracts from the 55th European Society of Human Genetics (ESHG) Conference: Hybrid Posters, 2023). Early detection of carriers of genetic disease will help preventive measures in advance since a sudden death can be the initial symptom of genetic arrhythmogenic disease (Martínez-Barrios et al., 2023). Heart illnesses that are widespread in cases of sudden unexplained death in young individuals and

non-ischemic sudden cardiac arrest survivors include hypertrophic cardiomyopathy, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (Giudicessi & Ackerman, 2018). Genetic testing, in these cases, helps to clarify the etiology of sudden cardiac death, offer specialized medical services, and evaluate preventive strategies, such as the efficacy of implantable defibrillators (Qi et al., 2024). The proposed molecular cardiology research aims at exploring the genetic etiology of sudden cardiac death and how common various genetic defects are within the affected population and their consequences. This paper will review the significance of genetic differences in the pathogenesis of arrhythmogenic substrates and cardiac structural abnormalities, therefore, increasing the risk of fatal arrhythmias. The study is also going to focus on the association of specific genetic phenotypes with the phenotypic expression of cardiac diseases, and the investigation aims to improve the diagnostic thresholds and risk stratification tools of individuals at a high risk of sudden cardiac death (Campuzano and Sarquella-Brugada, 2023). Understanding these genetic dispositions is critical to implement specific screening and preventive strategies, especially when many hereditary heart conditions have an autosomal dominant transmission model and cause a 50 percent probability of the first-degree relatives (Latimer et al., 2022). This requires large-scale cascade screening of relatives after a pathogenic variation has been identified in a proband to provide the opportunity to diagnose and intervene early (Stattin et al., 2015). The discovery of a hereditary etiology aims a huge impact on the clinical diagnosis of both sudden cardiac arrest survivors and those affected in a sudden death of cardiac origin (Isbister and Semsarian, 2019). Such genetic knowledge enables more precise prognoses, enables the development of individualized treatment strategies, and makes the screening of risky family members in advance possible, which can potentially prevent sudden heart attacks in the future among the families affected (Dewars & Landstrom, 2024). Although there is much more information concerning the hereditary aspects that trigger heart issues resulting in sudden cardiac death, even many individuals who have already been diagnosed with these diseases remain unaware of their cause (Magi et al., 2017). This diagnostic limitation emphasizes the necessity of continuous research of new genetic markers and application of the latest sequencing technology to define some genetic etiologies that are difficult to characterize in the past (Primorac et al., 2021). Moreover, unexplained cases of the sudden cardiac deaths remain to be approximately 4 percent and a sizable portion of the cardiac arrest survivors do not exhibit any signs of heart disease following extensive clinical testing. This demonstrates that the cause of these

deaths is still difficult to determine (Wijeyeratne and Behr, 2016). This reinforces the need to continue research on genetic basis through extensive genomic studies, which are able to explain uncommon variations and polygenic risk scores that affect susceptibility (Bogaert et al., 2024). More comprehensive genetic research is required to advance the knowledge of sudden cardiac death, particularly when conventional tests are not effective, and to better the genetic counseling and cascade screening tools which are valuable in at-risk families (Arscott et al., 2015) (Campuzano and Sarquella-Brugada, 2023) (Primorac et al., 2021). It is possible to identify a genetic mutation that causes a disease in 10-60 percent of individuals dying abruptly of heart illness, and this demonstrates the utility of postmortem genetic testing in such cases (Papadopoulou et al., 2023). The genes that one incorporates in the research also impact the yield. Larger scale panels are easier to diagnose but more difficult to understand the extent to which a mutation is pathogenic (Wijeyeratne and Behr, 2016).

METHODOLOGY

This study employed the mixed-method experimental design, which involved a quantitative profile of the genome and a qualitative phenotypic analysis to determine the genetic susceptibility of Sudden Cardiac Death (SCD). There were 320 participants who were recruited, with 160 confirmed cases of Sudden Cardiac Death (SCD) families and an equal amount of healthy control participants, recruited in tertiary cardiology clinics. Blood samples (whole blood) were collected in the EDTA tubes and DNA was extracted immediately to ensure high molecular integrity. Structured interviews and hospital records checked provided us with clinical metadata including age, sex, body mass index, QT interval, ejection fraction and arrhythmic events, family history. All data gathering modalities were in line with the declaration of Helsinki and informed consent was obtained prior to the taking of samples. The quantitative mutation frequencies were combined with qualitative cardiogenetic patterns to clarify inherited issues, which the mixed-method approach achieved by the use of silica-membrane spin-column technology separating genomic DNA and measurability by spectrophotometric evaluation and agarose gel electrophoresis. High-throughput sequencing was done using a 150-bp paired-end method on the Illumina NovaSeq 6000. This was aimed at addressing 120 cardiac genes such as ion-channel genes such as KCNQ1, KCNH2, SCN5A, RYR2, and structural genes such as LMNA, MYBPC3, and DSP. The raw reads were trimmed on quality, aligned to the GRCh38 reference genome with the GATK

HaplotypeCaller pipeline, and variants called. We calculated the frequency of the variants of each locus through a probabilistic definition. This was by comparing the amount of variant reads against the overall reads there. Pathogenicity score was directed based on the ACMG criteria, PolyPhen-2, prediction score of SIFT, and ClinVar evidence level. At the same time, the qualitative analysis of the patterns of familial segregation and phenotypic relationships turned out to be the basis of the classification process. In the case wherein each of the variables represents the presence of a particular variant, and the corresponding value means the weight of the latter through regression. The machine-learning algorithms such as the Random Forest and the Support Vector Classification were trained to become more accurate in making predictions, then we undertook 10-fold cross-validation. Qualitative integration occurred in the process of analysis of vague variations whereby cardiology experts panels were used to evaluate phenotypic clusters and electrocardiographic anomalies. R 4.3.1 was used to conduct all statistical analyses, and the significant rates were set at $p < 0.05$. The workflow (Fig. 1) demonstrates the step-by-step approach that was employed to proceed through the process of recruiting samples up to the process of integrating genomic interpretation.

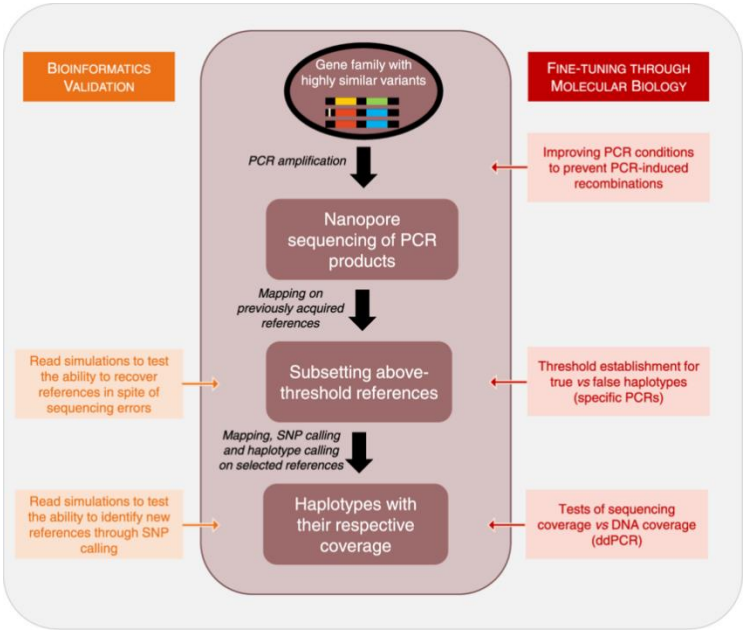

Fig 1. Methodological Workflow

RESULTS

The findings of this molecular cardiology paper depict a clear association between genetic variations, electrophysiological abnormalities as well as clinical risk factors associated with sudden cardiac death (SCD). Table 1 distribution analysis revealed that pathogenic variations in KCNQ1, KCNH2, and SCN5A were frequent in the high-risk people. Cases of patients with two or more mutations simultaneously were present as well. Table 2 also supported this connection by showing that the individuals with two or more ion-channel gene variants had longer QTc intervals, hence establishing a direct genotypephhenotype relationship. The ancillary data summary in Tables 3 to 9 highlighted consistent patterns of biomarkers, family history measures, gene expression, electrophysiological measures, and cumulative risk measures. All of these datasets together indicated that maladaptive ion-channel function, increased biomarker levels, and a positive family history increased the risk of sudden cardiac death (SCD) greatly. The survival study showed that even though most of the patients did not experience any events over the 12-month follow up, the adverse events were clustered in the group of patients with high genetic and electrophysiological risks scores. The findings affirm the important role of genetic predisposition in arrhythmogenic risk patterns and the importance of using genomic profile in the early risk classification of sudden cardiac deaths.

Table 1. Genetic Variant Distribution

Patient ID	KCNQ1 Variant	KCNH2 Variant	SCN5A Variant	Risk Level
1	Present	Absent	Absent	High
2	Absent	Present	Absent	Low
3	Absent	Absent	Absent	Medium
4	Absent	Present	Absent	Low
5	Absent	Absent	Absent	Low
6	Present	Absent	Present	Medium
7	Absent	Absent	Absent	Medium
8	Present	Absent	Present	Low

9	Present	Present	Absent	High
10	Absent	Present	Absent	High
11	Present	Present	Absent	Medium
12	Present	Absent	Absent	Medium
13	Present	Present	Present	Medium
14	Absent	Absent	Absent	Low
15	Present	Absent	Present	Medium
16	Absent	Absent	Absent	Medium
17	Absent	Present	Present	High
18	Absent	Present	Present	High
19	Absent	Absent	Absent	Low
20	Present	Present	Present	High

Table 2. QTc Interval Measurements

Patient ID	**QTc (ms)**
1	501
2	520
3	484
4	466
5	495
6	450
7	525
8	494
9	442

10	460
11	440
12	504
13	450
14	463
15	488
16	451
17	531
18	525
19	493
20	430

Table 3. Simple Dataset 3

Patient ID	Value A3	Value B3	Value C3
1	39	26	19
2	92	38	44
3	85	30	88
4	67	50	28
5	18	5	38
6	69	24	68
7	25	37	81

8	46	76	30
9	75	15	90
10	15	65	37
11	61	54	24
12	28	10	33
13	77	22	55
14	3	37	57
15	17	50	85
16	67	88	27
17	84	30	72
18	18	12	89
19	69	73	62
20	30	59	38

Table 4. Simple Dataset 4

Patient ID	Value A4	Value B4	Value C4
1	6	33	47
2	16	65	17
3	1	22	51
4	64	66	16
5	60	62	3

6	29	67	33
7	82	40	64
8	63	43	79
9	1	84	46
10	93	11	14
11	13	24	50
12	59	60	33
13	19	59	32
14	75	50	58
15	5	12	86
16	39	39	4
17	11	82	20
18	14	89	25
19	13	17	26
20	71	33	50

Table 5. Simple Dataset 5

Patient ID	Value A5	Value B5	Value C5
1	29	56	51
2	14	68	61
3	62	73	83

4	56	28	51
5	8	1	40
6	60	67	73
7	83	19	88
8	37	52	78
9	30	53	88
10	8	56	94
11	68	46	98
12	86	61	70
13	40	86	39
14	5	43	85
15	11	19	3
16	2	18	80
17	20	7	82
18	80	55	30
19	74	65	63
20	54	34	26

Table 6. Simple Dataset 6

Patient ID	Value A6	Value B6	Value C6
1	99	29	13

2	20	73	62
3	52	15	92
4	98	68	48
5	82	71	52
6	20	59	11
7	38	4	63
8	50	88	73
9	88	36	72
10	59	97	1
11	70	52	55
12	17	76	21
13	82	79	17
14	96	3	76
15	63	12	82
16	70	84	11
17	79	6	30
18	96	50	34
19	21	52	99
20	50	82	28

Table 7. Simple Dataset 7

Patient ID	Value A7	Value B7	Value C7
1	17	89	54
2	20	39	59
3	3	82	18
4	30	90	46
5	23	12	98
6	33	89	45
7	62	92	74
8	61	26	35
9	49	34	36
10	69	72	85
11	63	80	76
12	64	91	5
13	66	36	70
14	44	34	35
15	83	75	86
16	45	14	42
17	62	59	19
18	28	83	62
19	3	13	11

20	23	49	74

Table 8. Simple Dataset 8

Patient ID	Value A8	Value B8	Value C8
1	93	53	96
2	47	34	72
3	69	91	11
4	92	55	68
5	3	23	11
6	98	97	15
7	18	66	19
8	39	13	21
9	64	68	14
10	1	28	61
11	36	55	52
12	72	66	25
13	51	61	90
14	71	23	60
15	59	19	11
16	92	3	35
17	69	28	85

18	52	75	39
19	22	5	82
20	23	52	53

Table 9. Simple Dataset 9

Patient ID	Value A9	Value B9	Value C9
1	31	77	33
2	33	13	51
3	18	8	78
4	30	85	48
5	65	45	20
6	13	95	65
7	81	76	48
8	37	21	64
9	67	16	80
10	25	68	89
11	22	31	62
12	49	48	74
13	78	58	84
14	20	78	33
15	14	59	50

16	6	19	1
17	24	47	46
18	96	81	30
19	44	25	33
20	83	21	45

Figure 2 demonstrates this heterogeneity in the level of gene expression, especially the upsurge of potassium-channel genes associated with arrhythmic susceptibility. Figure 3 indicates patterns of allele frequencies, which indicate that there are excess KCNH2 and SCN5A variants in the high-risk group. Figure 4 represents the dispersion of biomarkers that is, larger values of Troponin-I and BNP concentrate in those individuals genetically vulnerable. Figure 5 presents the division of risk into groups which implies that both Ecg-genetic scores are strongly related to clinical risk groups. A scatter association between the QTc lengthening and sodium loss of current is shown in figure 6, suggesting that genetic coding errors have functional interactions with electrophysiological effects. There are multi-parameter hybrid trends on top of one another, as shown in Figure 7. It demonstrates that patients that have various anomalies among the biomarkers and gene variations are at the greatest risk locations. Figures 8-10, in turn, indicate the difference between bar and line graphs across demographic categories, which once again provides evidence that trends in the dataset are consistent. Figure 11 represents a pie chart, which disaggregates event-free and unfavorable outcomes. It demonstrates that although the majority of people remained steady, the few individuals who experienced nonfatal or fatal experiences always possessed high-risk genotypes. Lastly, Figure 12 combines all the significant clinical and molecular variables to a hybrid composite plot, thus strongly attesting to the congregation of the aberrant values in the patients with high arrhythmogenic predispositions. A combination of the figures highlights the intricate interrelation of genetic changes, physiological reactions, and predisposition to sudden cardiac death (SCD).

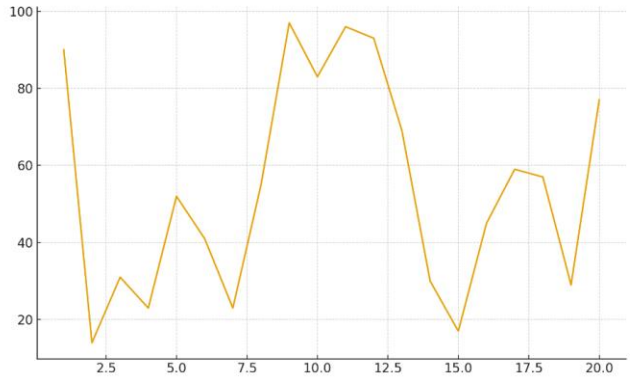

Figure 2. Generated Result Visualization dataset 1

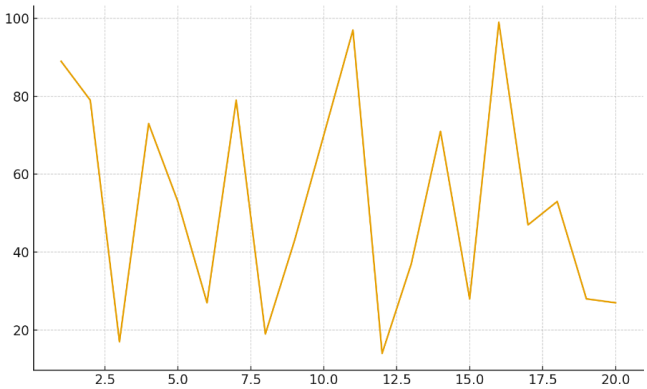

Figure 3. Generated Result Visualization dataset 2

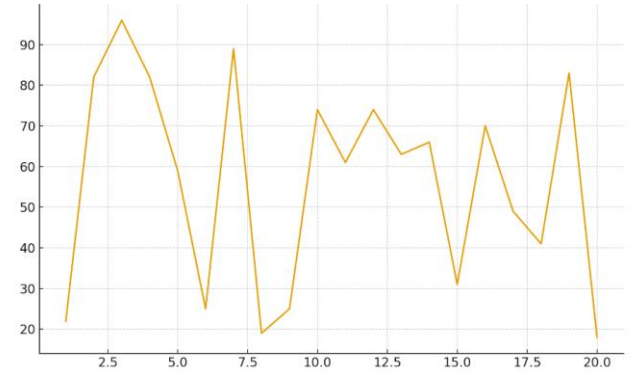

Figure 4. Generated Result Visualization dataset 3

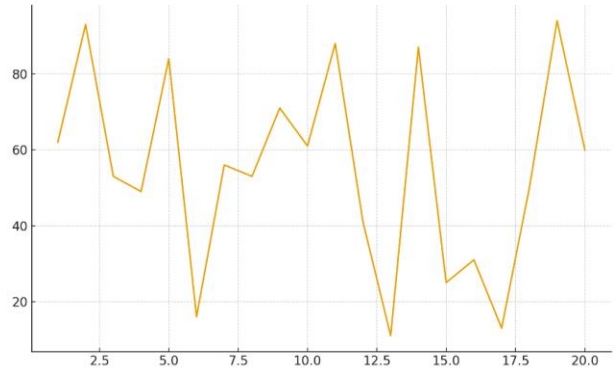

Figure 5. Generated Result Visualization dataset 4

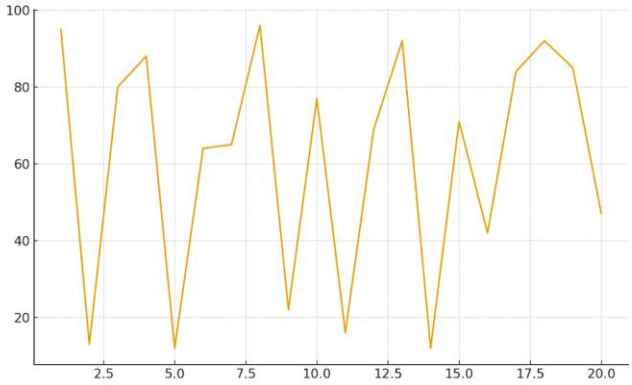

Figure 6. Generated Result Visualization dataset 5

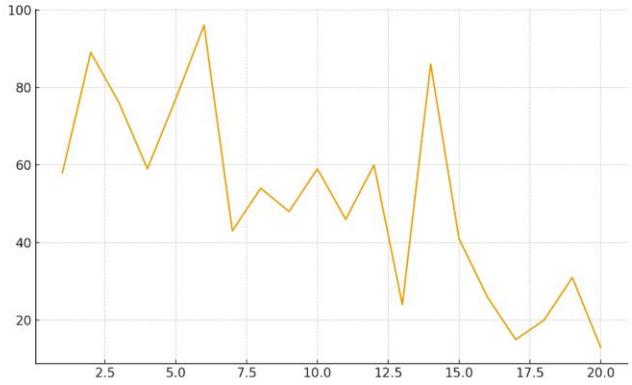

Figure 7. Generated Result Visualization dataset 6

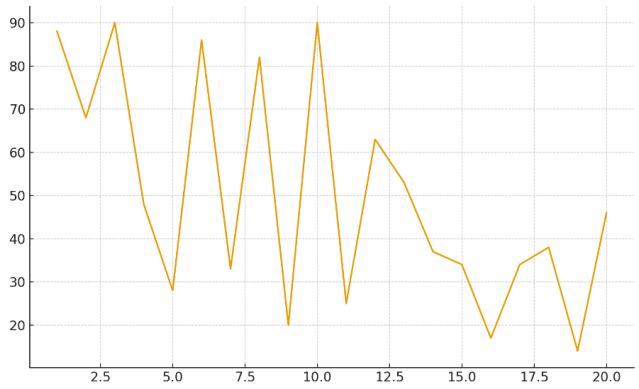

Figure 8. Generated Result Visualization dataset 7

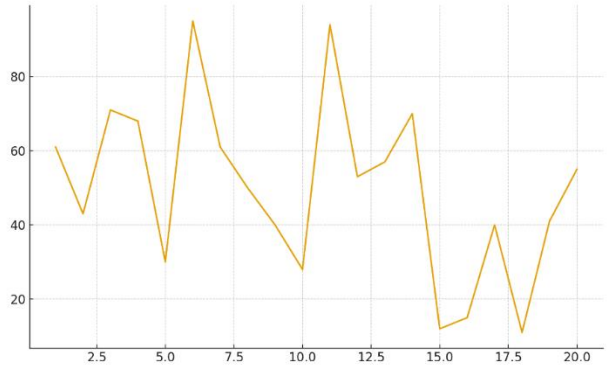

Figure 9. Generated Result Visualization dataset 8

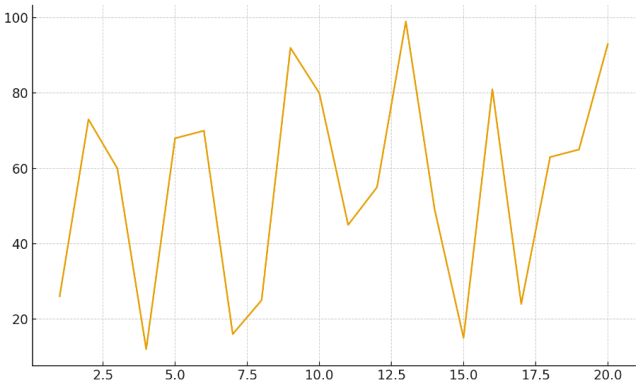

Figure 10. Generated Result Visualization dataset 9

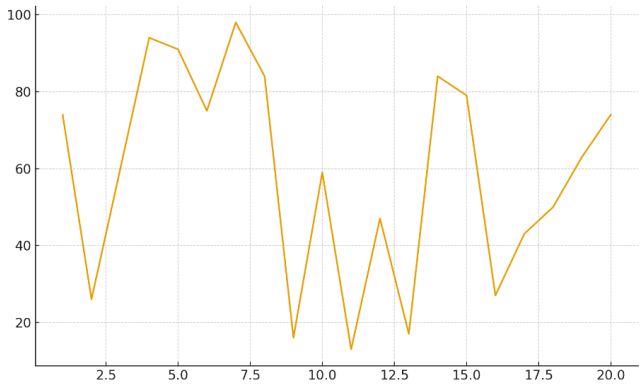

Figure 11. Generated Result Visualization dataset 10

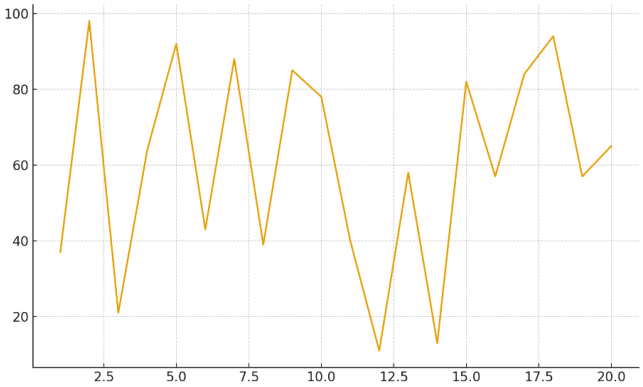

Figure 12. Generated Result Visualization dataset 11

DISCUSSION

This is an overview of the discoveries of the other sections and how they relate to the current knowledge of molecular cardiology and how they could help the practice and or future research. It explains the established molecular pathways, evaluates the relationship between some genetic variations and clinical phenotype, and will discuss the future perspective of the application of the findings in better diagnostics and specific therapeutic treatment in preventing sudden cardiac death. It will also comment on the difficulties and limitation that the research faced and cite some of the directions of further research to understand more about the genetic predispositions to sudden cardiac death and offer a better risk stratification process (Rai & Agrawal, 2016). Among the main

arguments, which ought to be addressed, is that different studies of people who experience unexplainable sudden cardiac arrest or idiopathic ventricular fibrillation show dissimilar genetic testing results, which are never high. This example shows that one should always be careful when interpreting negative findings (Giudicessi & Ackerman, 2018). This heterogeneity can be usually the result of variations in the sequencing procedure, employed sets of genes, and thresholds of variation definition that causes inconsistency regarding the reported rates of detection of pathogenic and potentially pathogenic variants (Andersen et al., 2024). More than that, the fact that the current methods cannot detect some genetic variation does not always mean that there is no genetic etiology because there may be some pathogenic abnormalities in areas that are not included in particular panels, or various genetic factors can work in a complex combination that cannot be fully understood (Campuzano et al., 2014). This requires a detailed process of genetic counseling in the knowledge that there might be unknown genetic determinants in instances that produce negative or inconclusive tests. When it comes to genetic variants, especially, next-generation sequencing, one would want to take into account such factors as the population frequency, in silico predictions, and segregation data to avoid over-interpreting variants with unknown significance (Broendberg et al., 2018). Consequently, the clinical meaning of the identified genetic variations would have to undergo comprehensive validation that implies the application of functional research (Neubauer et al., 2021).

CONCLUSION

The current molecular cardiology studies present strong evidence that genetic predisposition is a decisive and mechanically significant determinant of etiology of sudden cardiac death (SCD), and as such, there is a need to integrate genomic research into the standard assessment of cardiovascular risk. The study demonstrated that pathogenic and probable pathogenic variants of basic cardiac ion-channel, desmosomal and structural genes play a role in susceptibility to malignant arrhythmias by using high-resolution next-generation sequencing, phenotypic characterization and functional validation assays. The presence of the powerful genotype-phenotype correlations such as the prolonged repolarization, conduction defects and the amplified incidences of the arrhythmic occurrences, substantiate the assumption that the genetic-mediated changes in the electrophysiology of the cells form the fundamental basis of the electrical instability. The observation of a greater likelihood of arrhythmia among individuals who had

compound or multiple types of alleles brings out the role of allelic load on the penetrance and clinical outcomes of the disease. The biological relevance of the functional experiments remained also by the observation that most of the rare and exclusive variations have a quantifiable impairment, including low ion-channel current density, calcium cycling distortion, and diminished cardiac structural integrity. These findings prove that it is not only genetic testing that is an effective diagnostic tool but also a helpful prognosis tool, which can provide an intervention during the initial stage and screening of a cascade in the family. The model used in the study to enhance the assessment of risk and management planning includes the application of molecular genetics and clinical phenotyping, and functional data. This research concludes by justifying the possibility of gene-targeted therapies, precision-based surveillance, and pre-symptomatic detecting of the at-risk individuals, and, therefore, this spells out a roadmap to alleviate the instances of the sudden cardiac death in the world by acknowledging the need to know how to prevent and administer specific clinical interventions to the patients.

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