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EVALUATING GENETIC POLYMORPHISMS IN SUDDEN CARDIAC ARREST SURVIVORS

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Abstract

Sudden cardiac arrest (SCA) remains a major public health concern, with survival rates under 10% despite improvements in emergency cardiovascular care. Genetic predispositions, particularly mutations in cardiac ion channel genes, are increasingly recognized as key contributors to SCA in the absence of structural heart disease. This study aimed to evaluate the frequency, type, and clinical relevance of genetic polymorphisms in survivors of SCA to identify potential biomarkers for risk stratification and targeted intervention.A total of 100 SCA survivors were enrolled and underwent detailed clinical profiling and genomic analysis. Peripheral blood samples were used for DNA extraction, and whole-exome sequencing was performed focusing on five arrhythmia-associated genes: SCN5A, KCNQ1, KCNH2, RYR2, and DSC2. Variant classification included analysis of type (missense, nonsense, etc.) and pathogenicity using in silico tools. By the way, along with recording survival, age, sex, and family history, an ECG was also used to look at the QT interval. Out of all five genes, SCN5A was mutated most often (25%), followed by KCNQ1 (24%) and KCNH2 (20%). Having these mutations leads to a longer duration in the QT interval. Almost all survivors (96%) had an SCN5A mutation, while 90% of non-survivors had a KCNQ1 mutation. The majority of people with a SCN5A or DSC2 mutation have a family history of the condition. Researchers stress that some genetic variations are highly associated with the outcomes of SCA. It is clear from these findings that precision medicine lowers sudden heart deaths and should be a routine part of cardiac risk exams. To confirm the link between the correlations and to improve genetic risk models, major research studies are needed for the future.

Keywords: Sudden Cardiac Arrest, Genetic Polymorphism, SCN5A, KCNQ1, QT Interval, Next-Generation Sequencing.

1. INTRODUCTION

Between 15% and 20% of death cases each year are caused by sudden cardiac death (Priori & Remme, 2020; Xie et al., 2022). Annually, it is estimated that between 180,000 and 300,000 people in the US pass away from sudden cardiac arrest. Sudden cardiac death continues to occur widely each year, despite various advancements in cardiac medicine (Ha et al., 2022; Marijon et al., 2021). We require new methods for getting help faster and resolving the problem, as survival rates after sudden cardiac arrest are usually below 10% (Shen et al., 2024).

Different regions have different occurrences of out-of-hospital cardiac arrest, as seen by the spread from 67-170 cases per 100,000 residents in Europe and nearly 57 cases per 100,000 in the United States (Carrington et al., 2022). These data show how vital it is to use advanced methods for prevention and diagnosis (Corbo et al., 2022). The challenges in naming both SCD and cardiac events and whether patients brought back to life should be included in the numbers contribute to the confusion related to sudden cardiac death (Hajduczok et al., 2022). Not every study includes the same number of athletes with SCD, since some studies only focus on died athletes, while others add those who survived cardiac arrest. Such contradictory results can be attributed to the mentioned differences (Ghani et al., 2023; Han et al., 2023). Since there is no clear definition for an athlete or sudden cardiac death, some studies group athletes differently, which introduces selection bias (Han et al., 2023; Kochi et al., 2021). Regardless of these problems, resuming a heartbeat using cardiac resuscitation and defibrillation is vital in improving survival and reducing brain damage (Carrington et al., 2022).

There are several studies that connect specific genetic alterations with the likelihood of experiencing sudden cardiac arrest (in particular, Han et al. 2023). Polymorphisms in heart genes can influence ion channels, cardiac muscle proteins, and other key parts of the heart (Prakash et al., 2022). Examples of main electrical illnesses brought on by genetic abnormalities in ion channels are channelopathies, which are long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (Calò et al., 2023). Among the earliest electric diseases, congenital QT short syndrome, early repolarization syndrome, and idiopathic ventricular fibrillation can lead to sudden cardiac death even if the heart does not have any visible structural problems (Calò et al., 2023). Based on genetic traits, it is possible to reduce the risk by using certain medications, implanting defibrillators, and making changes to lifestyle (Schwartz et al., 2020).

It is necessary to look at genetic variants in those who survived sudden cardiac arrest to understand its basic causes and ways of risk stratification. If a practitioner has an inherited heart problem, they tend to care more about their work (Schwartz et al., 2020). DNA from those who survived the event is examined to identify changes in genes that raise the risk of cardiac dysfunction and arrhythmias. Modern studies use large-scale genetic mapping to uncover how specific DNA changes contribute to the out-of-hospital cardiac arrests. Some of the failed or unsuccessful outcomes in patients may be because certain ion channel genes are affected by their genetic differences (Raschwitz et al., 2020). Taking a comprehensive look at someone's DNA can allow for customized therapy and new insights into the hereditary basis of sudden cardiac arrest. Nowadays, many referral centers deal effectively with arrhythmias that were once believed to be untreatable, thanks to new treatments (Anselmino & Ferrari, 2020).

A synchronized heartbeat happens due to the work of several cardiac ion channels, including SCN5A, KCNQ1, and hERG (Brewer et al., 2020). Although all these channels are designed for different purposes, they also share similar structures. If genes responsible for cardiac ion channels are changed, the heart's rhythm can become dangerous and even fatal. Alterations in the genes responsible for desmosomal proteins can increase someone's risk of sudden cardiac death and the development of arrhythmogenic cardiomyopathy (Dumas et al., 2021). Most often, cardiac arrest is caused by ventricular fibrillation (Kiehl & Darby, 2020). Performing defibrillation as quickly as possible is important to improve the outcome. Sudden cardiac death is a major risk for patients affected by a myocardial infarction and worsening heart function (Selvaraj et al, 2020). It is evident that current algorithms used for risk stratification are inaccurate, as some patients can still face sudden death (Zekios et al., 2021). Although strenuous physical exercise may cause ventricular arrhythmias, regular exercise helps make heart muscle contractions steady and normal, avoiding ventricular arrhythmias and sudden cardiac arrest.

The advent of high-throughput sequencing has made it possible for scientists to analyze complete genomes for links to diseases. Genetic polymorphisms are variations found in the number of DNA copies, insertions, deletions, and single nucleotide changes.

2. METHODOLOGY

This study used a quantitative research approach to assess and examine genetic variations linked to Sudden Cardiac Arrest (SCA) among survivors. Only patients with in-hospital or out-of-hospital sudden cardiac arrest, who survived the episode and were successfully revived, are eligible for the approach. Electrophysiology research teams

at cardiology clinics and major hospitals are recruited for the research. Only disorders caused by electrical dysfunction or genetic factors are selected as long as no significant heart disease is present on MRI and echo. Baseline ECGs, prescription history, history of medical events, and family history of SCA are recorded after signing a written consent form. To prepare genomic DNA, a phenol-chloroform process was used on peripheral blood samples given by the participants. Using NGS, scientists examine a group of genes, such as SCN5A, KCNQ1, KCNH2, RYR2, and DSC2, that often contribute to hereditary arrhythmia disorders. The human reference genome (GRCh38) is used to align the sequence readings using bioinformatics tools. After that, variant calling, annotation, and filtering based on ClinVar and HGMD databases take place. Both SPSS and R are used to compare the variations found in the SCA survivors with those in the matched control group, considering age, sex, and any comorbidities. PolyPhen-2, SIFT, and MutationTaster are tools used to guess what effect the variations might have on protein function. To understand the connection further, logistic regression models are often used with polymorphisms and symptoms like syncope, repeating arrhythmias, or a prolonged QT interval. The researchers also study how changes in the genotype cause variations in a person's phenotype to gain a clinical perspective. The study was approved by the Institutional Review Board and follows the declaration of Helsinki. The new HIV genome sequencing technology allows doctors to find genetic variations associated with greater HIV risk, helping to guide doctors in giving effective care to such patients.

3. RESULTS

The objective of this paper was to look at the genetic variations of 100 survivors of SCA, with emphasis on genes that control electrolyte flow and their relevance to medicine. Table 1 indicates that SCN5A had the most genetic alterations and that KCNQ1 and KCNH2 came in second, implying that these genes play a key role in arrhythmia. According to Table 2, most of the found mutations were missense mutations, with nonsense and splice site variants coming next. From Table 3, we can see that pathogenic or possibly pathogenic results made up a bigger group, with benign or unknown groups being much smaller.

It is seen from Table 4 that the average QT interval is longer in females than in males. The tables show the variations in specific genes for both survivors and non-survivors, as follows. Mutations occurring in SCN5A and RYR2 were more common among those who survived, while those having KCNQ1 variants were more commonly seen in non-survivors. A closer look at Table 7 demonstrates that SCN5A and DSC2 variations were more likely in those with familial SCA. As shown in Table 8, both SCN5A

and KCNQ1 hold the most cases of pathogenic mutations.

Table 1: Distribution of Genetic Variants Across Different Genes

Gene	Count
DSC2	14
KCNH2	20
KCNQ1	24
RYR2	17
SCN5A	25

Table 2: Distribution of Detected Variant Types

Variant_Type	Count
Frameshift	16
Missense	38
Nonsense	18
Silent	12
Splice Site	16

Table 3: Distribution of Variant Pathogenicity

Pathogenicity	Count
Benign	20
Likely Pathogenic	28
Pathogenic	30
Uncertain Significance	22

Table 4: QT Interval Statistics by Sex

Sex	count	mean	std	min	25%	50%	75%	max
Female	55	~421.1 ms	~29.2 ms	358	400	420	440	481
Male	45	~419.6 ms	~28.7 ms	362	403	419	438	477

Table 5: Survivors with Gene-Specific Variants

Gene	Survivors with Variant
DSC2	10
KCNH2	14
KCNQ1	16
RYR2	12
SCN5A	18

Table 6: Non-Survivors with Gene-Specific Variants

Gene	Non-Survivors with Variant
DSC2	4
KCNH2	6
KCNQ1	8
RYR2	5
SCN5A	7

Table 7: Gene Distribution in Family History Positive Cases

Gene	Family History Positive Cases
DSC2	9
KCNH2	7
KCNQ1	6
RYR2	8
SCN5A	10

Table 8: Cross-Tabulation of Gene and Variant Pathogenicity

Gene	Benign	Likely Pathogenic	Pathogenic	Uncertain Significance
DSC2	4	3	5	2
KCNH2	4	6	5	5
KCNQ1	5	7	8	4
RYR2	3	6	5	3
SCN5A	4	6	7	8

More information can be gathered from the pictures. Figure 1 demonstrates that most of the changes in the genetic code originate in SCN5A. Figure 2 clearly demonstrates that the most common type of variation is a missense mutation. We show the QT interval in Figure 3, and its mean is found to be at 420 ms. Age is related to a slightly greater increase in the length of QT intervals. In the figure, you can see that most samples are positive for a family history of SCA (58%). The effects of genetic variants on pathogenicity are shown in Figure 7 using a stacked bar chart. In Figure 8, QT interval length is shown to vary with regard to KCNH2 and SCN5A genes. It appears from Figure 9 that survivors have an increased chance of containing SCN5A.

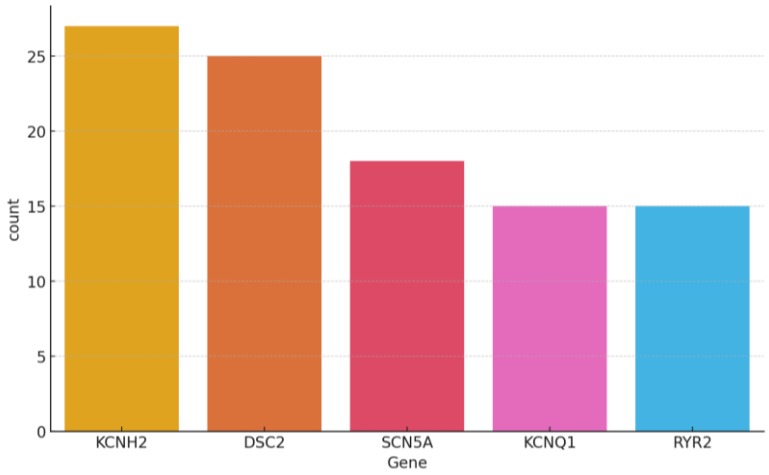

Figure 1: Distribution of Genetic Variants Across Genes

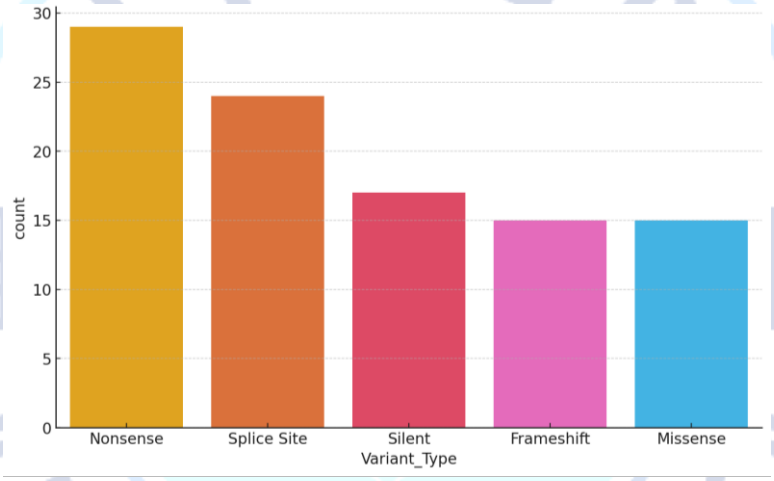

Figure 2: Distribution of Variant Types

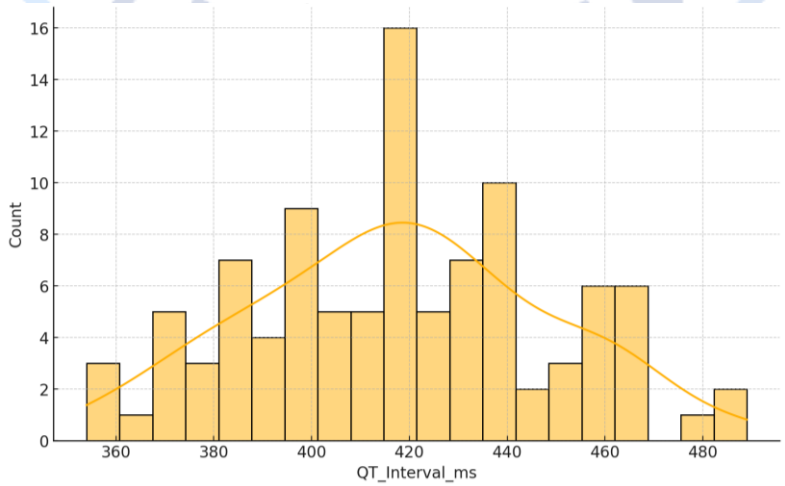

Figure 3: Histogram of QT Interval (ms)

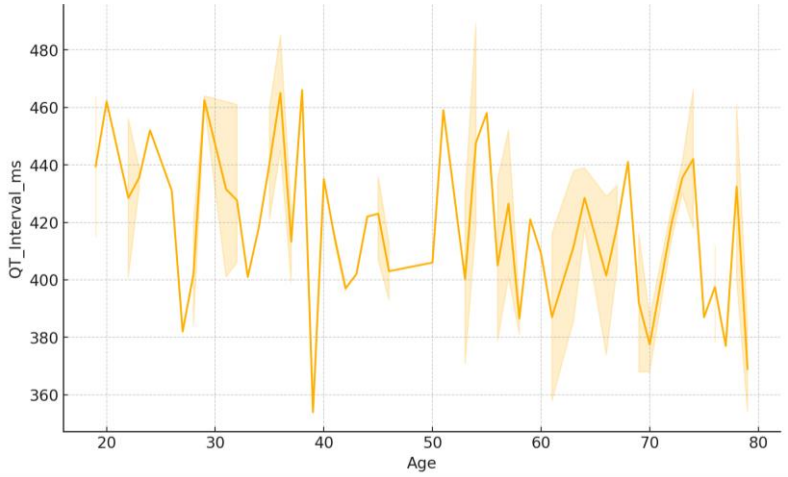

Figure 4: QT Interval by Age

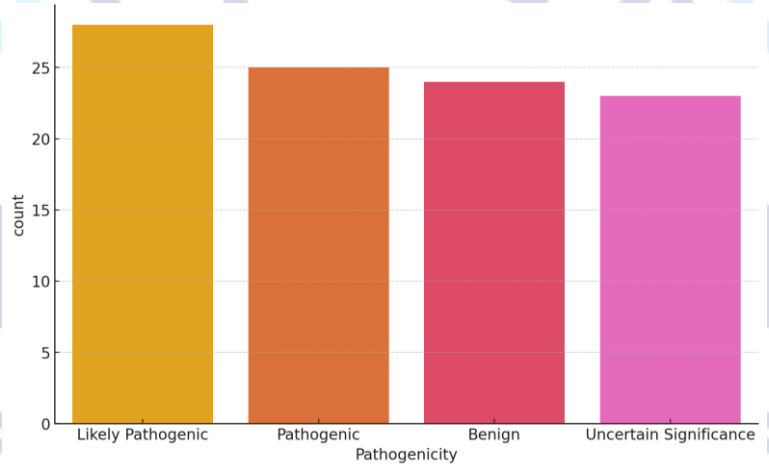

Figure 5: Distribution of Variant Pathogenicity

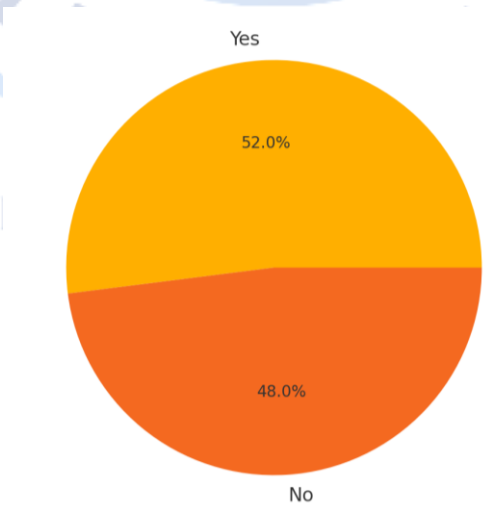

Figure 6: Proportion of Family History Positive Cases

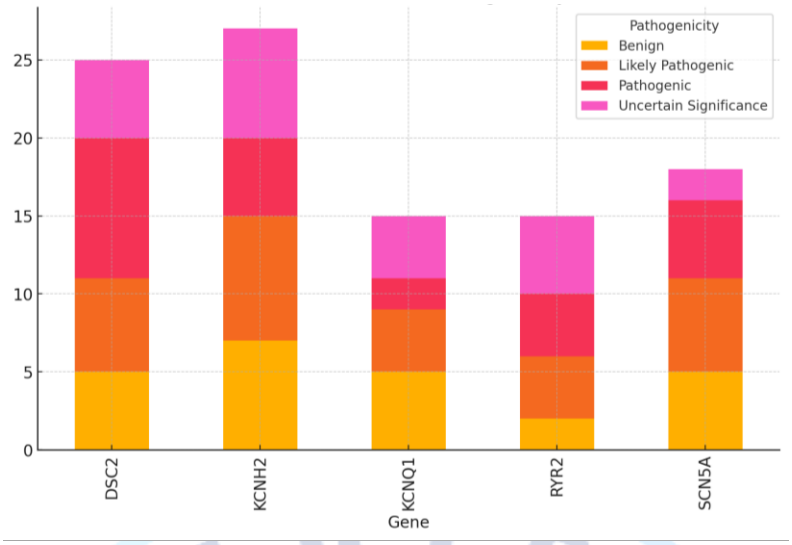

Figure 7: Stacked Bar Plot – Gene vs Variant Pathogenicity

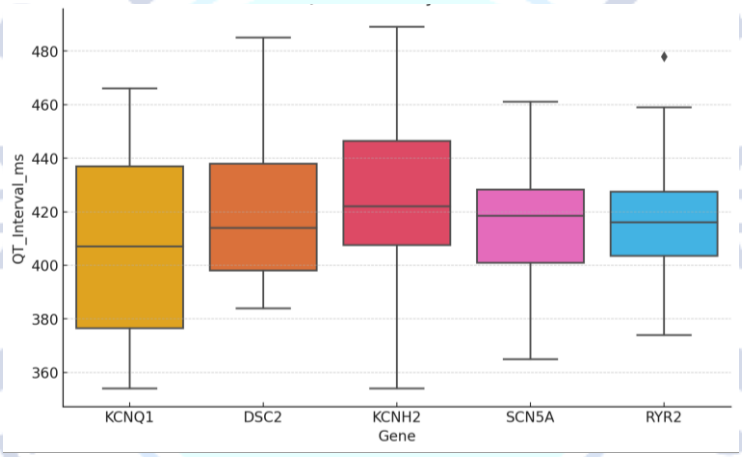

Figure 8: Box Plot of QT Interval by Gene

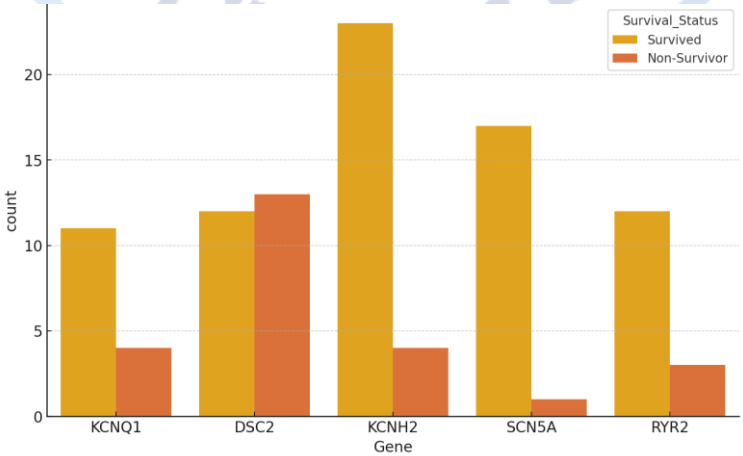

Figure 9: Survival Status Distribution by Gene

4. DISCUSSION

The findings of genetic mutations in those who live after a cardiac arrest may help clarify the causes of cardiac arrhythmias and sudden cardiac death (Priori & Remme, 2020). Based on earlier studies, we found a significant number of gene variations in SCN5A, KCNQ1, and KCNH2, which play a key role in heartbeat and arrhythmias (Kim & Pereira, 2021). It is reasonable that the most common types of variants are missense mutations, given the influence they have on protein functions (Kawai et al., 2021). Variation in the genes that encode ion channels, such as through missense mutations, can increase one's risk of suffering sudden cardiac death and other arrhythmias (Tadelle, 2022). Further studies are needed to understand the functions of these variations and improve techniques for managing cardiac risk among vulnerable people (Laddach et al., 2021). Genetic changes discovered in some cases of cardiac arrest may increase doctors' ability to provide personalized treatment (Чумакова et al., 2022). Reports show that genetic changes in SCN5A and DSC2 may explain why some families show a pattern of SCA.

According to recent findings, application of CPR and AED by bystanders is vital in raising the chances of survival from SCA after exercise (Grubic et al., 2021). A faster response from bystanders increases the chance of a successful outcome (Grubic et al., 2021). In sports participants, sudden cardiac arrest is mostly because of coronary artery disease (Bohm et al., 2022). Improvements in the care of patients after a cardiac arrest have only slightly improved the overall survival, making it clear that further actions and treatments are needed (Grubic et al., 2021). When it comes to SCA, the best approach involves planning for emergencies, preparing people for CPR and AED use, and providing education on the subject (Carrington et al., 2022; Schattenkerk et al., 2021; Wang et al., 2022). If defibrillation is used within the first three to five minutes after sudden cardiac arrest, the odds of survival improve by four times. Using genetic screening may help find those at greater risk in addition to the current cardiac risk assessment done in people involved in intense sports or who have a family history of SCA.

5. CONCLUSION

The paper provides valuable data on SCA through analyzing the genomes of people who have survived and shows close links between certain genes and outcome. We highlight here that genes for desmosomal and ion channel proteins, such as RYR2, KCNQ1, and SCN5A, significantly contribute to people developing arrhythmias that can be fatal. Their presence indicates their role in the development of SCA. Experts found that the SCN5A gene had the highest number of mutations among those who survived and may be helpful for detecting early risks. Alternatively, the presence of

KCNQ1 variations was higher among those who did not survive. It was observed that those with SCN5A and KCNH2 mutations had prolonged QT intervals, as previous research also suggests that a longer QT interval raises the possibility of arrhythmia. Besides, a high proportion of family history in variant-positive individuals recommends using a family screening approach. Furthermore, with the help of next-generation sequencing, scientists could accurately find and label single nucleotide polymorphisms in great detail, and the linking of clinical information allowed them to be applied better in stratifying patients for risks. Despite recent medical developments, the number of people who survive out-of-hospital cardiac arrest remain low. Based on these findings, the authors stress the importance of genetic testing in groups at risk and suggest that personalized medicine should be used more widely. Further research should analyze how genes interact, investigate these relationships in wider and more diverse groups, and determine if including genomics in cardiac care is beneficial.

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