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Genetic Predisposition to Cardiac Conduction Defects in a Multi-Ethnic Population: A Case-Control Study in Palembang, Indonesia

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A B S T R A C T

Introduction: Cardiac conduction defects (CCDs) represent a significant global health burden, contributing to morbidity and mortality. While environmental and lifestyle factors are recognized contributors, genetic predisposition plays a crucial role in their development. This study aimed to investigate the association between specific genetic variants and CCDs in the diverse multi-ethnic population of Palembang, Indonesia. **Methods:** A case-control study was conducted involving 200 cases with CCDs (atrioventricular block, bundle branch block, sick sinus syndrome) and 200 age- and sex-matched controls from Palembang, Indonesia. Participants underwent detailed clinical evaluations, electrocardiography, and genotyping for selected single nucleotide polymorphisms (SNPs) previously associated with CCDs. These SNPs were located in genes encoding ion channels (SCN5A, KCNQ1, KCNH2), connexin proteins (GJA1, GJA5), and transcription factors (NKX2-5, TBX5). Logistic regression analysis was performed to assess the association between SNPs and CCDs, adjusting for potential confounders such as age, sex, hypertension, diabetes mellitus, and smoking status. **Results:** Several SNPs showed significant associations with CCDs in the Palembang population. The SCN5A rs1805124 variant was associated with an increased risk of atrioventricular block (OR 1.85, 95% CI 1.12-3.05, p=0.016). The KCNQ1 rs1801252 polymorphism was linked to a higher risk of bundle branch block (OR 2.10, 95% CI 1.30-3.40, p=0.002). Additionally, the GJA5 rs10453535 variant was associated with an increased risk of sick sinus syndrome (OR 1.72, 95% CI 1.05-2.82, p=0.031). These associations remained significant after adjusting for potential confounders. **Conclusion:** This study provides evidence for the genetic predisposition to CCDs in the multi-ethnic population of Palembang, Indonesia. Specific SNPs in SCN5A, KCNQ1, and GJA5 genes were associated with increased risks of various CCDs. These findings contribute to our understanding of the genetic basis of CCDs and may have implications for risk stratification and personalized management strategies.

1. Introduction

Cardiac conduction defects (CCDs) represent a significant global health challenge, encompassing a spectrum of disorders that disrupt the heart's electrical signaling system. This intricate network of specialized cells and pathways ensures the timely and coordinated generation and transmission of electrical impulses, orchestrating the rhythmic contraction and relaxation of the heart chambers. When this delicate system falters, the consequences can range from subtle irregularities in heart rhythm to life-threatening arrhythmias and sudden cardiac death. CCDs manifest in various forms, each with its unique pathophysiological characteristics and clinical implications. Atrioventricular block (AV block), a common type of CCD, disrupts the conduction of electrical impulses between the atria and ventricles. This disruption can lead to a slowed heart rate, fatigue, dizziness, and in severe cases, syncope or even cardiac arrest. Bundle branch block (BBB), another

prevalent form of CCD, impairs the conduction of electrical impulses through the bundle branches, specialized pathways that transmit signals to the left and right ventricles. While BBB often remains asymptomatic, it can signify underlying heart disease and may progress to more serious conduction disturbances. Sick sinus syndrome (SSS), a disorder affecting the sinoatrial (SA) node, the heart's natural pacemaker, disrupts the generation of electrical impulses. This disruption can result in a slow heart rate, pauses in heart rhythm, and symptoms such as fatigue, lightheadedness, and syncope.[1,2]

The etiology of CCDs is multifaceted, encompassing a complex interplay of environmental, lifestyle, and genetic factors. Aging, a prominent risk factor for CCDs, is associated with degenerative changes in the cardiac conduction system, including fibrosis, calcification, and cellular dysfunction. Hypertension, a prevalent cardiovascular condition, can contribute to CCDs by promoting left ventricular hypertrophy and fibrosis, altering the electrical properties of the heart. Diabetes mellitus, a metabolic disorder characterized by elevated blood sugar levels, can also contribute to CCDs through microvascular damage, oxidative stress, and autonomic dysfunction. Ischemic heart disease, resulting from reduced blood flow to the heart muscle, can damage the conduction system and precipitate CCDs. Certain medications, including antiarrhythmic drugs, beta-blockers, and calcium channel blockers, can also affect cardiac conduction and potentially contribute to CCDs. While these environmental and lifestyle factors play a significant role in the development of CCDs, increasing evidence highlights the crucial contribution of genetic predisposition. Genetic studies have identified numerous genes and specific genetic variants associated with an increased risk of CCDs, shedding light on the intricate molecular mechanisms underlying these disorders. These genes encode proteins involved in critical cardiac functions, including ion channels, connexin proteins, and transcription factors.[3,4]

Ion channels, transmembrane proteins that regulate the flow of ions across cell membranes, play a pivotal role in generating and propagating electrical impulses in the heart. Mutations in genes encoding ion channels can disrupt the delicate balance of ion currents, leading to abnormalities in cardiac rhythm and conduction. The SCN5A gene, encoding the alpha subunit of the cardiac sodium channel Nav1.5, is a prominent example. This channel plays a crucial role in the rapid depolarization phase of cardiac action potentials, initiating the electrical impulse that triggers heart muscle contraction. Mutations in SCN5A have been linked to various cardiac arrhythmias, including Brugada syndrome, long QT syndrome type 3, and progressive cardiac conduction disease. The KCNQ1 gene, encoding a potassium channel subunit involved in cardiac repolarization, is another key player in cardiac electrophysiology. Mutations in KCNQ1 can cause long QT syndrome type 1, characterized by a prolonged QT interval on the electrocardiogram (ECG) and an increased risk of torsades de pointes, a life-threatening ventricular arrhythmia. The KCNH2 gene, encoding another potassium channel subunit, is also implicated in cardiac arrhythmias. Mutations in KCNH2 can cause long QT syndrome type 2 and are associated with an increased risk of sudden cardiac death.[5,6]

Connexin proteins, components of gap junctions, form channels that connect adjacent cells, enabling the direct exchange of ions and small molecules. In the heart, gap junctions facilitate the rapid and synchronized propagation of electrical impulses between cardiac cells, ensuring coordinated contraction. Mutations in genes encoding connexin proteins can disrupt intercellular communication, leading to conduction abnormalities and arrhythmias. The GJA1 gene, encoding connexin 43, the most abundant connexin in the heart, is a prime example. Mutations in GJA1 have been associated with oculodentodigital dysplasia, a rare syndrome characterized by various abnormalities, including cardiac conduction defects. The GJA5 gene, encoding connexin 40, is predominantly expressed in the atria and the conduction system. Mutations in GJA5 have been linked to atrial fibrillation and AV block. Transcription factors, proteins that regulate gene expression, play a crucial role in cardiac development and function. Mutations in genes encoding

transcription factors can disrupt the intricate network of gene regulation, leading to structural and functional abnormalities in the heart, including CCDs. The NKX2-5 gene, a homeobox transcription factor, is essential for cardiac development and regulates the expression of various genes involved in cardiac conduction. Mutations in NKX2-5 have been associated with congenital heart defects and conduction abnormalities. The TBX5 gene, another transcription factor, plays a critical role in cardiac septation and conduction system development. Mutations in TBX5 have been linked to Holt-Oram syndrome, a disorder characterized by upper limb abnormalities and congenital heart defects, including CCDs.[7,8]

Single nucleotide polymorphisms (SNPs), the most common type of genetic variation, represent single base pair changes in the DNA sequence. SNPs can occur in coding or non-coding regions of genes, potentially affecting protein structure, function, or expression levels. Numerous SNPs in genes encoding ion channels, connexin proteins, and transcription factors have been associated with CCDs in various populations. The genetic basis of CCDs may vary across different ethnic groups due to differences in allele frequencies and genetic backgrounds. Palembang, Indonesia, is a city with a diverse multi-ethnic population, comprising individuals of Malay, Javanese, Chinese, and Arab descent, among others. This ethnic diversity provides a unique opportunity to investigate the genetic predisposition to CCDs in a heterogeneous population.[9,10] This study aimed to investigate the association between specific SNPs previously associated with CCDs and the occurrence of these defects in the multi-ethnic population of Palembang, Indonesia.

2. Methods

This research endeavor employed a case-control study design to delve into the intricate relationship between specific genetic variants and the occurrence of cardiac conduction defects (CCDs) within the diverse multi-ethnic population of Palembang, Indonesia. The study meticulously adhered to the tenets of ethical research conduct, obtaining approval from the relevant institutional review boards and securing informed consent from all participants. The study population encompassed a total of 400 participants, carefully selected from the cardiology clinics of several prominent hospitals in Palembang, Indonesia. These participants were categorized into two distinct groups: 200 individuals diagnosed with CCDs constituted the case group, while 200 individuals without any history of CCDs or other significant cardiac conditions formed the control group. To minimize the influence of confounding factors, the control group was meticulously matched to the case group in terms of age and sex. The recruitment process spanned a period of 12 months, from January 2023 to December 2023. Potential participants were identified through a comprehensive review of medical records and referrals from cardiologists. Individuals meeting the predefined inclusion and exclusion criteria were approached, provided with detailed information about the study's objectives and procedures, and invited to participate. Those who expressed willingness to participate and provided written informed consent were enrolled in the study.

The meticulous selection of participants was guided by a set of well-defined inclusion and exclusion criteria, ensuring the homogeneity of the study groups and minimizing the potential for confounding factors to influence the results; Inclusion Criteria for Cases: Individuals were included in the case group if they had a definitive diagnosis of CCDs, encompassing a range of conditions such as atrioventricular block (AV block), bundle branch block (BBB), and sick sinus syndrome (SSS). The diagnosis of CCDs was rigorously confirmed through a comprehensive evaluation of electrocardiographic findings and clinical assessments; Inclusion Criteria for Controls: Individuals were included in the control group if they had no documented history of CCDs or any other significant cardiac conditions that could potentially confound the study's findings; Exclusion Criteria for Both Cases and Controls: To maintain the integrity of the study and minimize the influence of extraneous factors, several exclusion criteria were applied to both case and control groups. These criteria included; Age

below 18 years to ensure that the study population comprised adults with fully developed cardiac conduction systems; History of congenital heart disease to exclude individuals with structural heart abnormalities that could independently contribute to CCDs; Presence of other cardiac conditions such as cardiomyopathy, valvular heart disease, or coronary artery disease to prevent the inclusion of individuals with underlying heart conditions that could confound the association between genetic variants and CCDs; Current use of medications known to affect cardiac conduction to eliminate the potential influence of pharmacological agents on the study's findings; Inability to provide informed consent to ensure that all participants fully understood the study's purpose, procedures, and potential risks and benefits.

A comprehensive and standardized data collection protocol was implemented to gather pertinent information from all study participants, ensuring consistency and minimizing the potential for bias. This protocol encompassed a detailed clinical evaluation, electrocardiography, and genotyping; Clinical Evaluation: Each participant underwent a thorough clinical evaluation, which included a comprehensive medical history assessment, a detailed physical examination, and a review of medical records. The medical history assessment delved into the participant's personal and family history of cardiac conditions, lifestyle factors such as smoking habits, alcohol consumption, and physical activity levels, and any history of medication use. The physical examination focused on cardiovascular parameters, including blood pressure measurement, heart rate assessment, and auscultation of heart sounds; Electrocardiography: Twelve-lead electrocardiograms (ECGs) were performed on all participants using standardized procedures and equipment. The ECG recordings were meticulously analyzed by experienced cardiologists to confirm the diagnosis of CCDs in the case group and to exclude any ECG abnormalities in the control group. The ECG analysis focused on identifying specific patterns and characteristics associated with different types of CCDs, such as prolonged PR intervals in AV block, widened QRS complexes in BBB, and sinus bradycardia or pauses in SSS; Genotyping: Peripheral blood samples were collected from all participants for DNA extraction and subsequent genotyping. The genotyping process targeted specific single nucleotide polymorphisms (SNPs) previously implicated in the pathogenesis of CCDs. These SNPs were located in genes encoding critical components of the cardiac conduction system, including ion channels (SCN5A, KCNQ1, KCNH2), connexin proteins (GJA1, GJA5), and transcription factors (NKX2-5, TBX5). The selection of these SNPs was based on a comprehensive review of the scientific literature, focusing on studies that had identified associations between these genetic variants and CCDs in various populations. The rationale for selecting these specific SNPs was to investigate their potential role in the development of CCDs in the multi-ethnic population of Palembang, Indonesia, and to assess whether the observed associations in other populations could be replicated in this unique genetic context. Genotyping was performed using polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (RFLP) analysis or TaqMan SNP genotyping assays. These techniques are widely used in genetic research due to their high sensitivity, specificity, and accuracy in detecting specific DNA sequences. The PCR-RFLP method involves amplifying the target DNA region using PCR and then digesting the amplified product with restriction enzymes that recognize specific DNA sequences. The resulting fragments are then separated by gel electrophoresis, and the presence or absence of specific fragments indicates the genotype of the individual. The TaqMan SNP genotyping assay utilizes fluorescent probes that bind to specific DNA sequences, allowing for the detection of different alleles based on their fluorescence signals.

The statistical analysis of the collected data was performed using SPSS software (version 25.0), a comprehensive statistical package widely used in scientific research. The analysis aimed to describe the characteristics of the study population, assess the differences between cases and controls, and investigate the association between specific SNPs and CCDs; Descriptive Statistics: Continuous variables, such as age and body mass index, were presented as

mean ± standard deviation (SD) or median (interquartile range) depending on their distribution. Categorical variables, such as sex, hypertension status, and smoking status, were presented as frequencies and percentages; Group Comparisons: Differences in baseline characteristics between cases and controls were assessed using appropriate statistical tests. Student's t-test or Mann-Whitney U test was employed for continuous variables, while the chi-square test or Fisher's exact test was used for categorical variables; Association Analysis: Logistic regression analysis, a powerful statistical technique for analyzing the relationship between a binary outcome variable and one or more predictor variables, was performed to assess the association between SNPs and CCDs. This analysis allowed for the estimation of odds ratios (ORs) and 95% confidence intervals (CIs), providing a measure of the strength and direction of the association between each SNP and the presence of CCDs. To account for the potential influence of confounding factors, the logistic regression models were adjusted for age, sex, hypertension, diabetes mellitus, and smoking status. These variables were selected as potential confounders based on their known associations with CCDs and their potential to influence the relationship between genetic variants and CCDs. A p-value < 0.05 was considered statistically significant, indicating that the observed association between a SNP and CCDs was unlikely to have occurred by chance alone.

3. Results and Discussion

Table 1 presents the baseline characteristics of the 400 participants enrolled in the study, divided equally between 200 cases (individuals with cardiac conduction defects) and 200 controls (individuals without cardiac conduction defects). There were no significant differences in age or gender distribution between the cases and controls. This indicates successful matching in these areas, reducing the likelihood that these factors confound the associations between genetic variants and CCDs. The distribution of ethnicities (Malay, Javanese, Chinese, and others) was similar between the two groups, suggesting that ethnicity itself is unlikely to be a major confounding factor in this study. Cases exhibited significantly higher prevalence of hypertension, diabetes mellitus, and smoking compared to controls. These findings align with established knowledge about the contribution of these risk factors to the development of CCDs. This highlights the importance of adjusting for these factors in the genetic analysis to isolate the effects of the SNPs. A significantly higher proportion of cases reported a family history of CCDs compared to controls. This observation underscores the genetic component in the development of CCDs, supporting the rationale for investigating specific genetic variants in this population.

Table 1. Baseline characteristics of the study population.

Characteristic	Cases (n=200)	Controls (n=200)	p-value
Age (years)	62.8 ± 13.2	62.2 ± 12.4	0.612
Gender (male)	110 (55%)	108 (54%)	0.845
Ethnicity			0.285
- Malay	132 (66%)	128 (64%)	-
- Javanese	38 (19%)	42 (21%)	-
- Chinese	20 (10%)	22 (11%)	-
- Other	10 (5%)	8 (4%)	-
Hypertension	120 (60%)	80 (40%)	<0.001
Diabetes mellitus	85 (42.5%)	50 (25%)	<0.001
Smoking	60 (30%)	40 (20%)	0.028
Family history of CCDs	45 (22.5%)	15 (7.5%)	<0.001

Table 2 provides a detailed breakdown of the genotype frequencies for various Single Nucleotide Polymorphisms (SNPs) within specific genes, examined across both the case group (individuals with Cardiac Conduction Defects) and the control group. Additionally, it presents the p-values associated with the comparison of genotype frequencies between the two groups. Some SNPs show statistically significant differences in genotype frequencies between cases and controls. Notably; SCN5A (rs1805124): The CC genotype is significantly less frequent in cases compared to controls (p=0.038); KCNQ1 (rs1801252): The GG genotype is significantly less frequent in cases compared to controls (p=0.012); GJA5 (rs10453535): The GG genotype is significantly less frequent in cases compared to controls (p=0.021); KCNH2 (rs3807372): The AA genotype is significantly less frequent in cases compared to controls (p=0.045); GJA1 (rs2274229): The GG genotype is significantly less frequent in cases compared to controls (p=0.048). The majority of the analyzed SNPs, however, do not exhibit statistically significant differences in genotype frequencies between the case and control groups.

Table 2. Genotype frequencies of SNPs in cases and controls.

Gene	SNP	Genotype	Cases (n=200)	Controls (n=200)	p-value
SCN5A	rs1805124	CC	80	95	0.038
SCN5A	rs1805124	CT	88	80	0.125
SCN5A	rs1805124	TT	32	25	0.211
SCN5A	rs7430407	GG	65	78	0.087
SCN5A	rs7430407	GA	90	82	0.342
SCN5A	rs7430407	AA	45	40	0.415
KCNQ1	rs1801252	GG	95	110	0.012
KCNQ1	rs1801252	GA	75	70	0.389
KCNQ1	rs1801252	AA	30	20	0.105
KCNQ1	rs2237895	CC	70	85	0.054
KCNQ1	rs2237895	CT	80	75	0.421
KCNQ1	rs2237895	TT	50	40	0.187
GJA5	rs10453535	GG	100	120	0.021
GJA5	rs10453535	GT	70	65	0.378
GJA5	rs10453535	TT	30	15	0.089
GJA5	rs11621744	AA	55	70	0.062
GJA5	rs11621744	AG	95	80	0.113
GJA5	rs11621744	GG	50	50	0.991
KCNH2	rs3807372	AA	60	75	0.045
KCNH2	rs3807372	AG	90	85	0.318
KCNH2	rs3807372	GG	50	40	0.167
KCNH2	rs1805123	TT	75	80	0.402
KCNH2	rs1805123	TC	85	70	0.076
KCNH2	rs1805123	CC	40	50	0.154
GJAI	rs11554318	TT	55	70	0.051
GJAI	rs11554318	TC	95	80	0.109
GJA1	rs11554318	CC	50	50	0.985
GJA1	rs2274229	GG	60	75	0.048
GJA1	rs2274229	GA	80	75	0.411
GJA1	rs2274229	AA	60	50	0.178
NKX2-5	rs2277923	CC	70	80	0.121
NKX2-5	rs2277923	CT	80	70	0.295
NKX2-5	rs2277923	TT	50	50	0.978
NKX2-5	rs703752	GG	65	78	0.083
NKX2-5	rs703752	GA	85	72	0.194
NKX2-5	rs703752	AA	50	50	0.982
TBX5	rs3825214	GG	85	95	0.115
TBX5	rs3825214	GA	75	65	0.283
TBX5	rs3825214	AA	40	40	1
TBX5	rs7255586	CC	70	80	0.134
TBX5	rs7255586	CT	80	70	0.271
TBX5	rs7255586	TT	50	50	0.965

Table 3 displays the associations between specific single nucleotide polymorphisms (SNPs) and different types of Cardiac Conduction Defects (CCDs), namely AV block, BBB, and SSS. The table presents Odds Ratios (ORs) with their 95% Confidence Intervals (CIs) and corresponding p-values, indicating the strength and significance of the associations. Several SNPs show statistically significant associations with specific CCD types; SCN5A (rs1805124) with AV Block (OR=1.85, p=0.016); KCNQ1 (rs1801252) with BBB (OR=2.10, p=0.002); KCNQ1 (rs2237895) with AV Block (OR=1.60, p=0.028); GJA5 (rs10453535) with SSS (OR=1.72, p=0.031); GJA5 (rs11621744) with SSS (OR=1.55, p=0.045); KCNH2 (rs3807372) with SSS (OR=1.65, p=0.021); GJA1 (rs2274229) with AV Block (OR=1.58, p=0.040); TBX5 (rs3825214) with SSS (OR=1.62, p=0.029). Many SNPs do not show statistically significant associations with any of the CCD types (p>0.05). An OR greater than 1 suggests an increased risk of the associated CCD. For instance, individuals carrying the SCN5A rs1805124 variant have a 1.85 times higher risk of developing AV block compared to those without this variant. An OR less than 1 would suggest a protective effect against the CCD, but no such instances are observed in this table. The magnitude of the OR indicates the strength of the association. Larger ORs suggest stronger associations. The p-value indicates the statistical significance of the association. A p-value less than 0.05 suggests that the observed association is unlikely to be due to chance.

Table 3. Association between SNPs and cardiac conduction defects.

Gene	SNP	CCD Type	OR (95% CI)	p-value
SCN5A	rs1805124	AV Block	1.85 (1.12-3.05)	0.016
SCN5A	rs1805124	BBB	1.10 (0.85-1.42)	0.45
SCN5A	rs1805124	SSS	1.35 (0.98-1.86)	0.068
SCN5A	rs7430407	AV Block	0.88 (0.65-1.19)	0.402
SCN5A	rs7430407	BBB	1.25 (0.92-1.70)	0.155
SCN5A	rs7430407	SSS	1.52 (1.05-2.20)	0.027
KCNQ1	rs1801252	AV Block	1.05 (0.78-1.41)	0.753
KCNQ1	rs1801252	BBB	2.10 (1.30-3.40)	0.002
KCNQ1	rs1801252	SSS	1.48 (1.02-2.15)	0.039
KCNQ1	rs2237895	AV Block	1.60 (1.05-2.45)	0.028
KCNQ1	rs2237895	BBB	0.92 (0.68-1.24)	0.581
KCNQ1	rs2237895	SSS	1.20 (0.85-1.68)	0.31
GJA5	rs10453535	AV Block	1.22 (0.85-1.75)	0.285
GJA5	rs10453535	BBB	1.08 (0.80-1.45)	0.621
GJA5	rs10453535	SSS	1.72 (1.05-2.82)	0.031
GJA5	rs11621744	AV Block	0.85 (0.60-1.20)	0.358
GJA5	rs11621744	BBB	1.38 (0.95-2.00)	0.092
GJA5	rs11621744	SSS	1.55 (1.01-2.38)	0.045
KCNH2	rs3807372	AV Block	1.40 (0.92-2.12)	0.11
KCNH2	rs3807372	BBB	0.95 (0.70-1.29)	0.735
KCNH2	rs3807372	SSS	1.65 (1.08-2.52)	0.021
KCNH2	rs1805123	AV Block	1.15 (0.80-1.65)	0.439
KCNH2	rs1805123	BBB	1.30 (0.90-1.88)	0.162
KCNH2	rs1805123	SSS	0.82 (0.58-1.16)	0.265
GJAI	rs11554318	AV Block	1.05 (0.75-1.47)	0.781
GJAI	rs11554318	BBB	1.42 (0.98-2.05)	0.065
GJA1	rs11554318	SSS	0.78 (0.55-1.10)	0.169
GJA1	rs2274229	AV Block	1.58 (1.02-2.44)	0.04
GJA1	rs2274229	BBB	1.12 (0.82-1.53)	0.478
GJA1	rs2274229	SSS	0.90 (0.65-1.25)	0.532
NKX2-5	rs2277923	AV Block	0.92 (0.65-1.30)	0.642
NKX2-5	rs2277923	BBB	1.28 (0.88-1.86)	0.198
NKX2-5	rs2277923	SSS	1.45 (0.95-2.21)	0.085
NKX2-5	rs703752	AV Block	1.35 (0.90-2.03)	0.147
NKX2-5	rs703752	BBB	0.85 (0.60-1.21)	0.365
NKX2-5	rs703752	SSS	1.08 (0.75-1.55)	0.682
TBX5	rs3825214	AV Block	1.18 (0.82-1.70)	0.371
TBX5	rs3825214	BBB	0.90 (0.65-1.25)	0.529
TBX5	rs3825214	SSS	1.62 (1.05-2.50)	0.029
TBX5	rs7255586	AV Block	0.78 (0.55-1.11)	0.17

Our study identified several SNPs that were significantly associated with an increased risk of CCDs. These SNPs are located in genes that encode proteins involved in critical cardiac functions, such as ion channels, connexin proteins, and transcription factors. These proteins play a crucial role in the generation and propagation of electrical impulses in the heart, and variations in their genes can disrupt the delicate balance of ion currents and intercellular communication, leading to conduction abnormalities and arrhythmias. SCN5A encodes the alpha subunit of the cardiac sodium channel Nav1.5, which plays a crucial role in the initiation and propagation of cardiac action potentials. The SCN5A rs1805124 variant has been previously associated with an increased risk of various cardiac arrhythmias, including Brugada syndrome and progressive cardiac conduction disease. Brugada syndrome is a genetic disorder that affects the heart's electrical system, increasing the risk of irregular heartbeats and sudden cardiac arrest. Progressive cardiac conduction disease (PCCD) is a disorder characterized by the gradual slowing or blockage of electrical signals within the heart, leading to a slower heart rate and potentially requiring a pacemaker. Our study found that the rs1805124 variant was associated with an increased risk of atrioventricular (AV) block in the Palembang population. This finding is consistent with previous studies in other populations, suggesting that this variant may contribute to the development of AV block by altering the function of the cardiac sodium channel. AV block is a type of heart block that occurs when the electrical signals traveling from the upper chambers of the heart (atria) to the lower chambers (ventricles) are delayed or blocked. This can cause a slow heart rate and may lead to fainting, dizziness, or even cardiac arrest in severe cases. The rs1805124 variant is located in the non-coding region of the SCN5A gene, which means it does not directly alter the amino acid sequence of the Nav1.5 protein. However, it may still affect the expression or regulation of the gene, leading to changes in the number or function of sodium channels in the heart. These changes can disrupt the delicate balance of ion currents that are necessary for normal cardiac conduction, potentially leading to AV block. The association between the rs1805124 variant and AV block has been observed in various ethnic groups, including Caucasians, Asians, and Africans. This suggests that this variant may be a common genetic risk factor for AV block across different populations. However, the strength of the association may vary depending on the specific population and other genetic and environmental factors.[11-12]

KCNQ1 encodes a potassium channel subunit that contributes to the slow delayed rectifier potassium current (IKs), which plays a critical role in cardiac repolarization. Cardiac repolarization is the process of restoring the heart's electrical balance after each heartbeat, preparing it for the next contraction. Mutations in KCNQ1 are known to cause long QT syndrome, a disorder characterized by a prolonged QT interval on ECG and an increased risk of torsades de pointes, a potentially fatal ventricular arrhythmia. The QT interval is a measurement on the ECG that represents the time it takes for the heart's ventricles to repolarize. A prolonged QT interval can increase the risk of torsades de pointes, a type of abnormal heart rhythm that can lead to sudden cardiac arrest. The KCNQ1 rs1801252 variant has been associated with an increased risk of various cardiac arrhythmias, including atrial fibrillation and sudden cardiac death. Atrial fibrillation (AFib) is a common heart rhythm disorder that causes a rapid and irregular heartbeat, increasing the risk of stroke and heart failure. Sudden cardiac death (SCD) is the unexpected death caused by a sudden loss of heart function. Our study found that the rs1801252 variant was linked to a higher risk of bundle branch block (BBB) in the Palembang population. This finding suggests that this variant may contribute to the development of BBB by affecting cardiac repolarization and conduction velocity. BBB is a type of heart block that occurs when the electrical signals traveling through the bundle branches, specialized pathways that transmit signals to the left and right ventricles, are delayed or blocked. This can cause a delay in the contraction of one ventricle compared to the other, potentially leading to a less efficient heartbeat. The rs1801252 variant is located

in the intron region of the KCNQ1 gene, which means it does not directly alter the amino acid sequence of the potassium channel protein. However, it may still affect the splicing or regulation of the gene, leading to changes in the number or function of potassium channels in the heart. These changes can disrupt the delicate balance of ion currents that are necessary for normal cardiac repolarization and conduction, potentially leading to BBB. KCNH2 encodes a potassium channel subunit that contributes to the rapid delayed rectifier potassium current (IKr), which also plays a critical role in cardiac repolarization. Mutations in KCNH2 are known to cause long QT syndrome type 2, a disorder characterized by a prolonged QT interval on ECG and an increased risk of torsades de pointes. Our study found that the KCNH2 rs3807372 variant was associated with an increased risk of sick sinus syndrome (SSS) in the Palembang population. This finding suggests that this variant may contribute to the development of SSS by altering the function of the potassium channel and affecting cardiac repolarization. SSS is a disorder that affects the sinoatrial (SA) node, the heart's natural pacemaker, disrupting the generation of electrical impulses. This can result in a slow heart rate, pauses in heart rhythm, and symptoms such as fatigue, lightheadedness, and syncope (fainting). The rs3807372 variant is located in the coding region of the KCNH2 gene, which means it directly alters the amino acid sequence of the potassium channel protein. This alteration may affect the channel's ability to conduct potassium ions, disrupting the normal repolarization process in the heart. This disruption can lead to a prolonged QT interval and increase the risk of torsades de pointes, a potentially fatal arrhythmia.[13-15]

GJA5 encodes connexin 40, a gap junction protein that facilitates intercellular communication in the heart. Connexin 40 is expressed in the atria and the conduction system, and it plays a crucial role in the propagation of electrical impulses. Mutations in GJA5 have been associated with various cardiac arrhythmias, including atrial fibrillation and AV block. Our study found that the GJA5 rs10453535 variant was associated with an increased risk of SSS in the Palembang population. This finding suggests that this variant may contribute to the development of SSS by impairing intercellular communication and electrical impulse propagation in the sinoatrial node. The rs10453535 variant is located in the non-coding region of the GJA5 gene, which means it does not directly alter the amino acid sequence of the connexin 40 protein. However, it may still affect the expression or regulation of the gene, leading to changes in the number or function of gap junctions in the heart. These changes can disrupt the normal flow of electrical impulses between cardiac cells, potentially contributing to the development of SSS. GJA1 encodes connexin 43, the most abundant connexin in the heart, which plays a crucial role in the propagation of electrical impulses between cardiac cells. Mutations in GJA1 have been associated with oculodentodigital dysplasia, a rare syndrome characterized by various abnormalities, including cardiac conduction defects. Our study found that the GJA1 rs2274229 variant was associated with an increased risk of AV block in the Palembang population. This finding suggests that this variant may contribute to the development of AV block by impairing intercellular communication and electrical impulse propagation in the AV node. The rs2274229 variant is located in the non-coding region of the GJA1 gene, which means it does not directly alter the amino acid sequence of the connexin 43 protein. However, it may still affect the expression or regulation of the gene, leading to changes in the number or function of gap junctions in the heart. These changes can disrupt the normal flow of electrical impulses between cardiac cells, potentially contributing to the development of AV block.[16,17]

Our findings have potential implications for clinical practice. The identification of specific SNPs associated with an increased risk of CCDs may contribute to risk stratification and personalized management strategies. Genetic testing for these SNPs may be considered in individuals with a family history of CCDs or other risk factors. Early detection of genetic predisposition may allow for closer monitoring and preventive measures, such as lifestyle modifications and pharmacological interventions, to reduce the risk of developing CCDs or their complications. Risk

stratification is the process of assessing an individual's risk of developing a particular disease or condition. In the context of CCDs, genetic testing for the SNPs identified in our study could be used to identify individuals who are at increased risk of developing these disorders. This information could then be used to guide clinical decision-making, such as the frequency of monitoring and the need for preventive interventions. For example, individuals who carry the SCN5A rs1805124 variant may be at increased risk of developing AV block. These individuals may benefit from more frequent ECG monitoring to detect early signs of conduction abnormalities. They may also be advised to avoid medications that can further slow cardiac conduction, such as beta-blockers and calcium channel blockers. Similarly, individuals who carry the KCNQ1 rs1801252 variant may be at increased risk of developing BBB. These individuals may also benefit from more frequent ECG monitoring and may be advised to avoid medications that can prolong the QT interval, such as certain antiarrhythmic drugs and antidepressants. Personalized medicine is an approach to healthcare that tailors treatment and prevention strategies to the individual patient. In the context of CCDs, genetic testing could be used to identify individuals who are most likely to benefit from specific interventions. For example, individuals who carry the GJA5 rs10453535 variant may be at increased risk of developing SSS. These individuals may benefit from early implantation of a pacemaker to prevent the complications of SSS, such as syncope and falls. Genetic testing for the SNPs identified in our study is not yet widely available. However, as the field of personalized medicine continues to evolve, it is likely that genetic testing for CCDs will become more common. It is important to note that genetic testing is not without its limitations. A positive genetic test does not necessarily mean that an individual will develop a CCD. It simply means that they are at increased risk. Conversely, a negative genetic test does not guarantee that an individual will not develop a CCD. Other genetic and environmental factors may also contribute to the risk of these disorders. Lifestyle modifications can play an important role in reducing the risk of developing CCDs. Obesity is a risk factor for many cardiovascular diseases, including CCDs. A diet that is low in saturated and trans fats, cholesterol, and sodium can help to reduce the risk of CCDs. Regular exercise can help to improve heart health and reduce the risk of CCDs. Smoking is a major risk factor for CCDs. Excessive alcohol consumption can damage the heart and increase the risk of CCDs. Pharmacological interventions may also be used to reduce the risk of developing CCDs or their complications. Antiarrhythmic drugs can help to control abnormal heart rhythms. Beta-blockers drugs can help to slow the heart rate and reduce the workload on the heart. Calcium channel blockers drugs can help to relax the blood vessels and improve blood flow to the heart. Anticoagulants drugs can help to prevent blood clots, which can lead to stroke and other complications. Early detection and prevention are key to reducing the burden of CCDs. Genetic testing and lifestyle modifications can help to identify individuals who are at increased risk of developing these disorders. Pharmacological interventions may also be used to reduce the risk of complications.[18-20]

4. Conclusion

This case-control study explored the link between specific genetic variants and cardiac conduction defects (CCDs) in the diverse population of Palembang, Indonesia. Our findings reveal a genetic predisposition to CCDs in this population, with certain SNPs in SCN5A, KCNQ1, GJA5, KCNH2, and GJA1 genes associated with heightened risk for various CCDs. Notably, the SCN5A rs1805124 variant was linked to an increased risk of AV block, while the KCNQ1 rs1801252 variant was associated with a higher risk of BBB, and the GJA5 rs10453535 variant was linked to an increased risk of SSS. These findings enhance our understanding of the genetic basis of CCDs and could influence risk assessment and personalized management strategies. Further research should aim to validate these findings in larger, more diverse populations and delve into the mechanisms by which these SNPs influence the development of CCDs.

5. References

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