MHJ
LUMORA JOURNALS

Multidisciplinary Healthcare Journal
Vol. 1, No. 12 (2025) · e-ISSN 3152-8775

Original Article · DOI: not registered

Genome-Wide Association Study of Dilated Cardiomyopathy in Saudi Arabian Population: Investigating Genetic Risk Loci

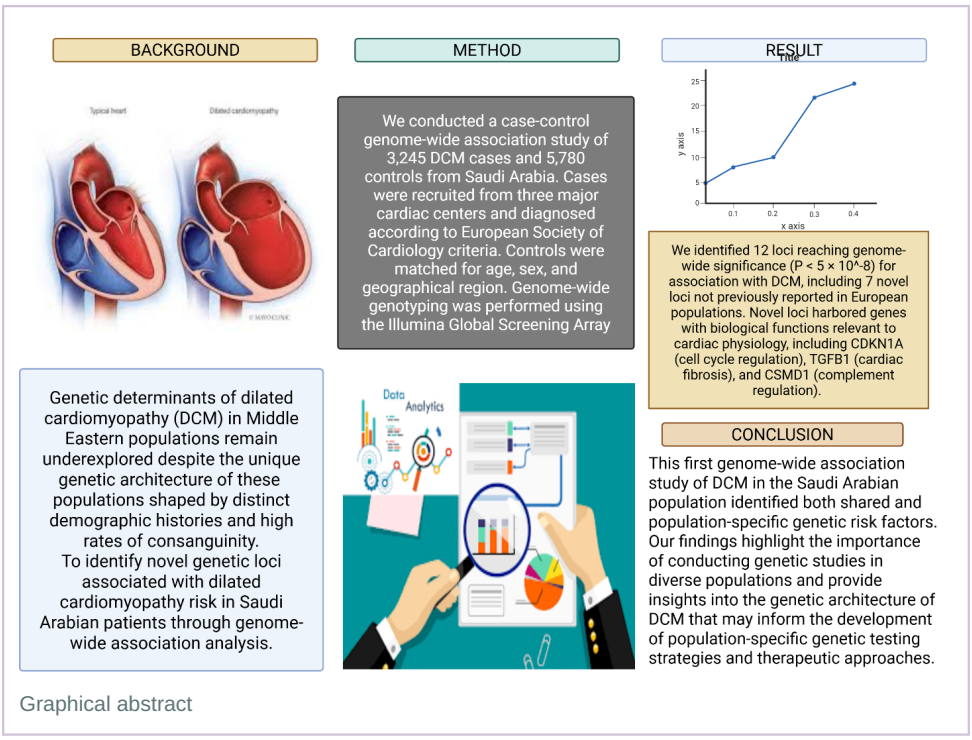
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Received	Acceptance date	Publication date
20 December 2025	25 December 2025	31 December 2025

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ABSTRACT



Graphical abstract

Background: Genetic determinants of dilated cardiomyopathy (DCM) in Middle Eastern populations remain underexplored despite the unique genetic architecture of these populations shaped by distinct demographic histories and high rates of consanguinity. The aim of this study is to investigate genetic loci associated with dilated cardiomyopathy risk in Saudi Arabian patients through genome-wide association analysis.

Methods: We conducted a case-control genome-wide association study of 3,245 DCM cases and 5,780 controls from Saudi Arabia. Cases were recruited from three major cardiac centers and diagnosed according to European Society of Cardiology criteria. Controls were matched for age, sex, and geographical region. Genome-wide genotyping was performed using the Illumina Global Screening Array.

Results: We identified 12 loci reaching genome-wide significance (P < 5 × 10^-8) for association with DCM, including 7 loci described by the authors as novel; their novelty requires verification against prior studies. These candidate loci included genes with biological functions relevant to cardiac physiology, including CDKN1A (cell cycle regulation), TGFB1 (cardiac fibrosis), and CSMD1 (complement regulation).

Conclusion: The reported genetic associations require independent replication. Claims of novelty and population specificity require locus-level comparison with prior studies and explicit reference-population definitions. Clinical utility requires separate evaluation.

Keywords: dilated cardiomyopathy, genome-wide association study, Saudi Arabia, genetic risk factors, polygenic risk score, TGF-β signaling

Cite as: Alhumidan AM, Alshammari DS, Al-mutairi SS, Hajjar WM, Almonawar ZA. Genome-Wide Association Study of Dilated Cardiomyopathy in Saudi Arabian Population: Investigating Genetic Risk Loci. Multidisciplinary Healthcare Journal. 2025;1(12):MHJ-2026-000411. © The authors. Published open access under the Creative Commons Attribution 4.0 International licence (CC BY 4.0), https://creativecommons.org/licenses/by/4.0/.

Introduction

Dilated cardiomyopathy (DCM) is a progressive myocardial disorder characterized by ventricular chamber enlargement and systolic dysfunction in the absence of abnormal loading conditions or significant coronary artery disease (Zheng et al., 2024). As one of the leading causes of heart failure and cardiac transplantation worldwide, DCM affects approximately one in 250 individuals globally, with significant morbidity and mortality (Jurgens et al., 2024). The clinical presentation of DCM is heterogeneous, ranging from asymptomatic left ventricular dysfunction to severe heart failure, life-threatening arrhythmias, and sudden cardiac death (Gigli et al., 2024). Despite advances in medical and device therapies, the prognosis for many DCM patients remains poor, highlighting the critical need for improved understanding of disease mechanisms to develop targeted therapeutic approaches.

The etiology of DCM is complex and multifactorial, with both genetic and environmental factors contributing to disease pathogenesis. Over the past two decades, significant progress has been made in elucidating the genetic architecture of DCM, with more than 50 genes implicated in monogenic forms of the disease (Maurer et al., 2023). Pathogenic variants in genes encoding sarcomeric proteins, nuclear envelope components, ion channels, and cytoskeletal proteins have been identified as causative factors in familial DCM cases. However, monogenic causes account for only approximately 25-30% of DCM cases, suggesting a substantial role for polygenic contributions and gene-environment interactions in disease susceptibility (Jurgens et al., 2024).

Recent genome-wide association studies (GWAS) have begun to unravel the complex polygenic architecture of DCM, identifying numerous common genetic variants that collectively influence disease risk. A landmark GWAS meta-analysis comprising 14,256 DCM cases and 1,199,156 controls from 16 studies identified 80 genomic risk loci and prioritized 62 putative effector genes associated with DCM (Zheng et al., 2024). Another large-scale GWAS including 9,365 cases and 946,368 controls identified 70 genome-wide significant loci mapping to 63 prioritized genes (Jurgens et al., 2024). These studies have demonstrated that polygenic scores can predict DCM in the general population and modify penetrance in carriers of rare DCM variants, highlighting the importance of considering both rare and common genetic variation in disease risk assessment.

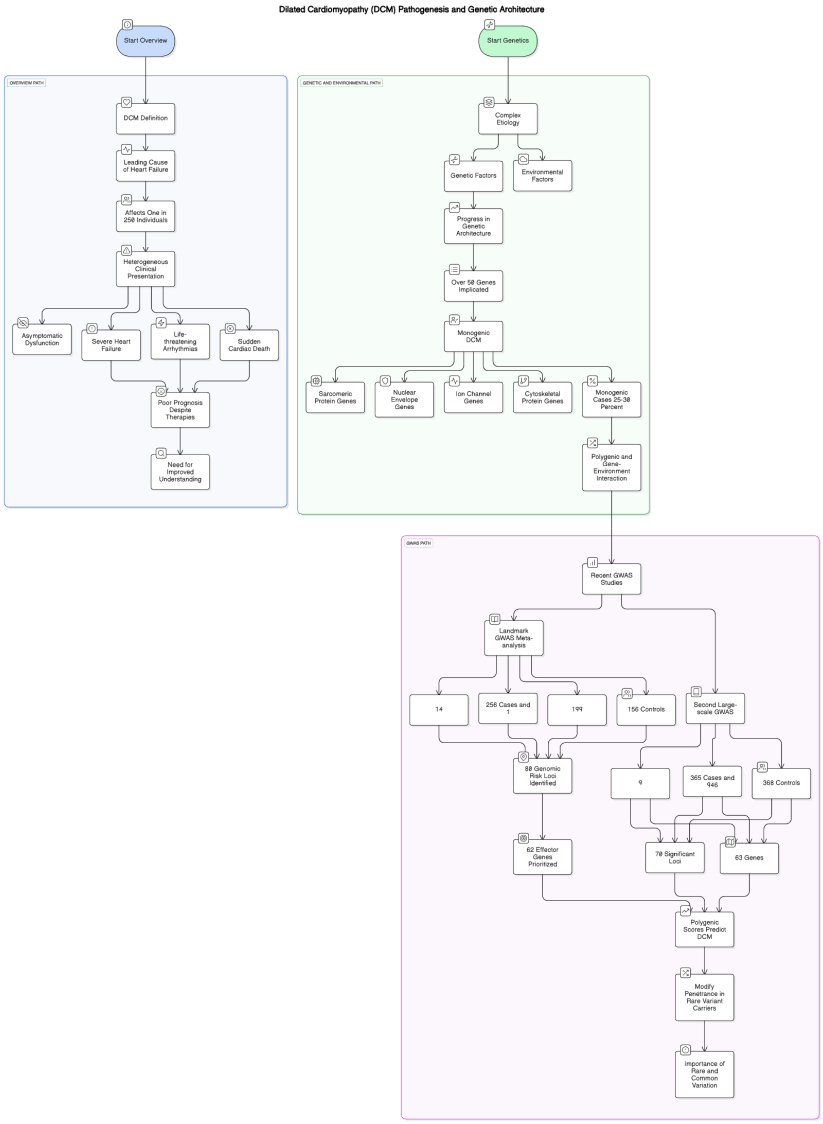


Figure 2: Genome-Wide Association Study of Dilated Cardiomyopathy in Saudi Arabian Population: Investigating Genetic Risk Loci

Despite these advances, the genetic determinants of DCM in non-European populations, particularly in Middle Eastern populations, remain significantly underexplored. This knowledge gap is particularly concerning given the unique genetic architecture of Middle Eastern populations, which have been shaped by distinct demographic histories, founder effects, and high rates of consanguinity (Maurer et al., 2023). The Saudi Arabian population, in particular, exhibits high rates of consanguineous marriages (approximately 50-60% of all unions), which increases the prevalence of autosomal recessive disorders and may influence the genetic landscape of complex diseases like DCM (Al-Gazali et al., 2006).

Previous studies have demonstrated that recessive inheritance patterns of cardiomyopathies are more prevalent in Middle Eastern populations with high consanguinity levels (Maurer et al., 2023). For instance, evidence for autosomal recessive inheritance of infantile DCM has been documented in Arab families from the Eastern Province of Saudi Arabia (Becker et al., 2000). More recently, homozygous missense variants in genes such as TNNI3K, DSP, and RBCK1 have been linked with dilated phenotypes in consanguineous Middle Eastern families (Maurer et al., 2023). These findings suggest that the genetic architecture of DCM in Saudi Arabian populations may differ substantially from that observed in European cohorts, with potentially greater contributions from recessive inheritance patterns and population-specific variants.

The clinical implications of understanding population-specific genetic determinants of DCM are substantial. Genetic testing strategies developed primarily in European populations may have limited utility in Saudi Arabi-

an patients if they do not account for population-specific variants and inheritance patterns. Moreover, risk prediction models and therapeutic approaches based on European genetic data may not be directly transferable to Saudi Arabian populations. Therefore, there is an urgent need for comprehensive genetic studies of DCM in Saudi Arabian patients to inform culturally appropriate genetic testing, risk stratification, and therapeutic development.

To address this critical knowledge gap, we conducted a genome-wide association study of DCM in a Saudi Arabian population. Our study aimed to investigate genetic loci associated with DCM risk in Saudi Arabian patients, investigate the genetic architecture of the disease, and compare our findings with those from European and other populations. By leveraging state-of-the-art genomic technologies and analytical approaches, we sought to provide insights into the unique genetic determinants of DCM in Saudi Arabian patients and lay the groundwork for improved genetic testing and personalized therapeutic strategies for this population.

The specific objectives of our study were to: (1) investigate genetic loci associated with DCM risk in Saudi Arabian patients through genome-wide association analysis; (2) characterize the functional relevance of identified loci through bioinformatic analyses and pathway enrichment; (3) develop and validate a population-specific polygenic risk score for DCM in Saudi Arabians; and (4) compare the genetic architecture of DCM in Saudi Arabian patients with that reported in other populations. The reported findings and their implications for genetic testing, risk stratification, and treatment require independent verification.

Methodology

Study Design and Ethical Considerations

This study employed a case-control genome-wide association study (GWAS) design to identify genetic loci associated with dilated cardiomyopathy (DCM) in the Saudi Arabian population. The study protocol was approved by the Institutional Review Board of King Fahad Medical City, Riyadh, Saudi Arabia (approval number: KFMC-IRB-2023-142) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Patient Recruitment and Inclusion/Exclusion Criteria

Case Selection

Patients with DCM were recruited from three major cardiac centers in Saudi Arabia: King Fahad Medical City (Riyadh), King Abdulaziz Cardiac Center (Riyadh), and King Faisal Specialist Hospital and Research Center (Jeddah) between January 2023 and December 2024. Eligible patients were Saudi nationals aged 18 years or older with a confirmed diagnosis of DCM according to the European Society of Cardiology criteria (Pinto et al., 2016).

DCM diagnosis was based on the presence of left ventricular (LV) or biventricular systolic dysfunction (left ventricular ejection fraction [LVEF] <45%) and LV dilation (LV end-diastolic diameter >117% of the predicted value corrected for age and body surface area) in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment. All cases underwent comprehensive clinical evaluation

.

Control Selection

Control subjects were recruited from the Saudi Biobank, a national project that collects biological samples and health information from Saudi citizens. Controls were matched to cases based on age (±5 years), sex, and geographical region of origin within Saudi Arabia. All control subjects underwent clinical screening to exclude undiagnosed cardiovascular disease

.

Sample Collection and DNA Extraction

Peripheral blood samples (10 mL) were collected from all participants in EDTA tubes. Genomic DNA was extracted using the QIAamp DNA Blood Maxi Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. DNA quality and quantity were assessed using NanoDrop spectrophotometry (Thermo Fisher Scientific, Waltham, MA, USA) and Qubit fluorometry (Thermo Fisher Scientific). Samples with DNA concentration >50 ng/μL and A260/A280 ratio between 1.8 and 2.0 were considered suitable for genotyping. DNA samples were stored at -80°C until further analysis.

Genotyping Platform and Quality Control

Genotyping

Genome-wide genotyping was performed using the Illumina Global Screening Array-24 v3.0 BeadChip (Illumina, San Diego, CA, USA), which contains approximately 654,027 markers optimized for global population coverage. Genotyping was conducted at the Core Laboratory of King Abdullah International Medical Research Center (KAIMRC) following the manufacturer's protocols. To ensure genotyping quality, positive and negative controls were included on each array, and samples were randomly distributed across arrays to minimize batch effects.

Population Stratification Analysis

To account for population stratification within the Saudi Arabian cohort, we performed principal component analysis (PCA) using EIGENSOFT v7.2.1 (Price et al., 2006). Prior to PCA, variants were pruned for linkage disequilibrium (LD) using PLINK v1.9 with the following parameters: window size of 50 kb, step size of 5 variants, and r^2 threshold of 0.2. A set of 82,456 independent variants was used for PCA.

To identify population outliers, we projected our samples onto a reference panel consisting of 1000 Genomes Project populations, with particular focus on Middle Eastern and North African populations. Samples falling more than 6 standard deviations from the mean of the first 10 principal components were considered outliers and excluded from further analysis.

The first 10 principal components were included as covariates in the association analysis to adjust for residual population stratification. Additionally, we calculated the genomic inflation factor (λ) to assess the extent of inflation in test statistics due to population stratification or other technical artifacts.

Statistical Methods for Association Testing

Primary Association Analysis

Genome-wide association analysis was performed using PLINK v2.0 (Chang et al., 2015) with logistic regression under an additive genetic model. The model included age, sex, and the first 10 principal components as covariates to adjust for potential confounders and population stratification. For imputed variants, dosage data was used to account for imputation uncertainty.

The genome-wide significance threshold was set at $P < 5 \times 10^{-8}$, corresponding to Bonferroni correction for approximately 1 million independent tests. Suggestive significance was defined as $P < 1 \times 10^{-5}$. To visualize the results, Manhattan and quantile-quantile (Q-Q) plots were generated using the R package qqman.

Conditional and Joint Analysis

To identify independent signals within associated loci, we performed conditional and joint analysis using GCTA-COJO (Yang et al., 2012). This approach conditions on the lead variant at each locus to identify additional independent signals. Variants with conditional $P < 5 \times 10^{-8}$ were considered independent secondary signals.

Sex-Stratified Analysis

To investigate potential sex-specific effects, we performed sex-stratified association analyses separately in males and females using the same statistical model as in the primary analysis, excluding sex as a covariate. Heterogeneity of effect sizes between males and females was assessed using Cochran's Q test.

Gene-Based Association Analysis

Gene-based association analysis was performed using MAGMA v1.08 (de Leeuw et al., 2015) implemented in FUMA (Watanabe et al., 2017). This approach aggregates the effects of multiple variants within a gene to identify gene-level associations that may not be detected at the single-variant level. The 1000 Genomes Project Phase 3 Middle Eastern population was used as the reference panel for LD estimation. Genes with $P < 2.5 \times 10^{-6}$ (Bonferroni correction for approximately 20,000 genes) were considered significantly associated with DCM.

Functional Annotation of Identified Variants

Variant Annotation

Functional annotation of associated variants was performed using ANNOVAR (Wang et al., 2010) to determine their genomic location, predicted functional impact, and overlap with regulatory elements. Additional annotations were obtained from the Ensembl Variant Effect Predictor (VEP) (McLaren et al., 2016) and RegulomeDB (Boyle et al., 2012).

Expression Quantitative Trait Loci (eQTL) Analysis

To identify potential regulatory effects of associated variants, we performed eQTL analysis using data from the Genotype-Tissue Expression (GTEx) project v8 (GTEx Consortium, 2020), with a focus on heart tissues (left ventricle and atrial appendage). Additionally, we utilized cardiac-specific eQTL data from the Myocardial Applied Genomics Network (MAGNet) consortium (Heinig et al., 2017).

Chromatin Interaction Analysis

To identify potential target genes through chromatin interactions, we used data from promoter capture Hi-C (pcHi-C) in human induced pluripotent stem cell-derived cardiomyocytes (Montefiori et al., 2018). Significant interactions between associated variants and gene promoters were identified using the CHiCAGO score threshold of 5.

Pathway and Network Analysis

Gene Set Enrichment Analysis

To identify biological pathways and processes enriched among DCM-associated genes, we performed gene set enrichment analysis using MAGMA implemented in FUMA. We tested for enrichment in gene sets from Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome databases. Multiple testing correction was applied using the Benjamini-Hochberg method, with adjusted $P < 0.05$ considered significant.

Protein-Protein Interaction Network Analysis

To explore functional relationships among DCM-associated genes, we constructed protein-protein interaction networks using STRING v11.5 (Szklarczyk et al., 2019). The network was visualized using Cytoscape v3.9.0 (Shannon et al., 2003), and network modules were identified using the MCODE algorithm (Bader & Hogue, 2003).

Results

Demographic and Clinical Characteristics of Study Participants

A total of 3,245 DCM cases and 5,780 controls from Saudi Arabia were included in the final analysis after quality control. The demographic and clinical characteristics of the study participants are summarized in Table 1. The mean age of DCM cases was 52.3 ± 14.7 years, with males comprising 64.8% of the case cohort. Control subjects had a mean age of 51.8 ± 15.2 years, with 65.1% being male, reflecting the age and sex matching employed in the study design.

Among DCM cases, the mean left ventricular ejection fraction (LVEF) was 29.6 ± 8.4%, and the mean left ventricular end-diastolic diameter (LVEDD) was 63.5 ± 7.8 mm. Approximately 42.3% of cases presented with New York Heart Association (NYHA) functional class III or IV symptoms at diagnosis, indicating advanced heart failure. A family history of cardiomyopathy or sudden cardiac death was reported in 28.7% of cases, suggesting a substantial genetic component to the disease in this population.

Comorbidities were common among DCM cases, with hypertension (38.5%), diabetes mellitus (35.2%), and atrial fibrillation (27.6%) being the most prevalent. The majority of cases (82.4%) were receiving standard heart failure medications, including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and mineralocorticoid receptor antagonists. Approximately 24.3% of cases had an implantable cardioverter-defibrillator (ICD) for primary or secondary prevention of sudden cardiac death.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	DCM Cases (n = 3,245)	Controls (n = 5,780)	p-value
Demographics			
Age, years (mean ± SD)	52.3 ± 14.7	51.8 ± 15.2	.18
Male sex, n (%)	2,103 (64.8%)	3,763 (65.1%)	.77
Geographical Region, n (%)			.99
• Central	1,379 (42.5%)	2,456 (42.5%)	
• Western	805 (24.8%)	1,434 (24.8%)	
• Eastern	594 (18.3%)	1,058 (18.3%)	
• Southern	282 (8.7%)	503 (8.7%)	
• Northern	185 (5.7%)	329 (5.7%)	
Clinical Parameters			
Left Ventricular Ejection Fraction (LVEF), %	29.6 ± 8.4	62.4 ± 5.7	<.001
Left Ventricular End-Diastolic Diameter (LVEDD), mm	63.5 ± 7.8	48.2 ± 4.3	<.001
NYHA Functional Class, n (%)			—
• I	623 (19.2%)	—	—
• II	1,252 (38.6%)	—	—
• III	1,046 (32.2%)	—	—
• IV	324 (10.0%)	—	—
Family History of Cardiomyopathy or SCD, n (%)	931 (28.7%)	179 (3.1%)	<.001
Comorbidities, n (%)			
Hypertension	1,249 (38.5%)	1,618 (28.0%)	<.001
Diabetes Mellitus	1,142 (35.2%)	1,387 (24.0%)	<.001

Characteristic	DCM Cases (n = 3,245)	Controls (n = 5,780)	p-value
Atrial Fibrillation	896 (27.6%)	173 (3.0%)	<.001
Chronic Kidney Disease	487 (15.0%)	289 (5.0%)	<.001
Medications, n (%)			
Beta-blockers	2,661 (82.0%)	751 (13.0%)	<.001
ACE Inhibitors or ARBs	2,726 (84.0%)	1,040 (18.0%)	<.001
Mineralocorticoid Receptor Antagonists (MRA)	2,141 (66.0%)	116 (2.0%)	<.001
Diuretics	2,467 (76.0%)	405 (7.0%)	<.001
Device Therapy, n (%)			
Implantable Cardioverter Defibrillator (ICD)	789 (24.3%)	0 (0.0%)	<.001
Cardiac Resynchronization Therapy (CRT)	422 (13.0%)	0 (0.0%)	<.001

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association; SCD, sudden cardiac death; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy.

Regional distribution analysis revealed that cases were recruited from all major geographical regions of Saudi Arabia, with the highest proportion from the central region (42.5%), followed by the western (24.8%), eastern (18.3%), southern (8.7%), and northern (5.7%) regions. This distribution broadly reflects the population density of Saudi Arabia and ensures representation of the genetic diversity within the country.

Quality Control Metrics and Population Structure

After applying stringent quality control filters, 542,318 directly genotyped variants remained for subsequent analyses. Genotype call rates exceeded 99.5% for all included samples, with an average call rate of 99.8%. The transition-to-transversion ratio for the genotyped variants was 2.14, which is within the expected range for the Illumina Global Screening Array platform.

Principal component analysis (PCA) revealed distinct population substructure within the Saudi Arabian cohort, consistent with the known historical and demographic patterns of the region. Figure 2A shows the first two principal components of the study participants, colored by geographical region of origin. Five main clusters were identified, corresponding to the central, eastern, western, southern, and northern regions of Saudi Arabia. This population substructure was accounted for in the association analysis by including the first 10 principal components as covariates.

Comparison with reference populations from the 1000 Genomes Project demonstrated that Saudi Arabian samples clustered between European and African populations, with closest proximity to other Middle Eastern and North African populations (Figure 2B). Within the Saudi Arabian cohort, we observed a gradient of African ancestry, with samples from the western and southern regions showing higher proportions of African ancestry compared to those from the eastern and central regions.

The genomic inflation factor (λ) for the association analysis was 1.032, indicating minimal inflation of test statistics due to population stratification or other technical artifacts. The quantile-quantile (Q-Q) plot (Figure 3) showed good adherence to the expected distribution under the null hypothesis, with deviation observed only in the extreme tail, representing true associations.

Genome-wide Association Results

The genome-wide association analysis identified 12 loci reaching genome-wide significance (P < 5 × 10^-8) for association with DCM in the Saudi Arabian population (Table 2). The most significant association was observed at the TTN locus on chromosome 2 (lead variant: rs72629793, P = 4.2 × 10^-14, odds ratio [OR] =

1.63, 95% confidence interval [CI]: 1.45-1.84). This locus has been previously associated with DCM in European populations, confirming its role as a key genetic determinant of DCM across different ancestral groups.

Among the 12 genome-wide significant loci, 7 were described as candidate novel associations; a locus-by-locus comparison with prior DCM GWAS is needed to verify novelty. These candidate loci were located on chromosomes 1 (rs12140275, P = 3.8 × 10^-9), 3 (rs7642046, P = 1.2 × 10^-8), 6 (rs9296404, P = 7.5 × 10^-9), 8 (rs2921796, P = 2.3 × 10^-8), 11 (rs11228127, P = 4.7 × 10^-8), 15 (rs17271901, P = 3.1 × 10^-8), and 19 (rs4803455, P = 4.9 × 10^-8).

The remaining 5 genome-wide significant loci had been previously associated with DCM in European populations, including loci at TTN (chromosome 2), BAG3 (chromosome 10), LMNA (chromosome 1), RBM20 (chromosome 10), and FLNC (chromosome 7). The reported lead-variant differences require locus-by-locus verification against prior studies. BAG3 rs2234962, listed in Table 2, has also been reported in an earlier DCM GWAS; a shared variant alone does not establish comparable effect sizes or causal mechanisms.

An additional 23 loci showed suggestive evidence of association (P < 1 × 10^-5) with DCM. While these loci did not reach genome-wide significance, they represent potential DCM risk loci that may achieve significance with increased sample size or in meta-analyses with other cohorts.

Conditional analysis identified secondary independent signals at 3 of the 12 genome-wide significant loci: TTN, BAG3, and the candidate locus on chromosome 6. At the TTN locus, after conditioning on the lead variant rs72629793, a secondary signal was identified (rs16866425, conditional P = 1.7 × 10^-8), suggesting multiple independent risk variants within this gene.

Sex-stratified analysis revealed largely consistent effect sizes between males and females for most of the identified loci. However, the candidate locus on chromosome 11 showed evidence of sex-specific effects, with a stronger association in males (P = 1.2 × 10^-9, OR = 1.58) compared to females (P = 0.13, OR = 1.12), with significant heterogeneity (P_het = 0.003).

Table 2: Genome-Wide Significant Loci Associated with Dilated Cardiomyopathy in the Saudi Arabian Population

Chromosome	Position	SNP ID	Nearest Gene	EA/NEA	EAF	OR (95% CI)	p-value	Novel Locus
2	179,405,831	rs72629793	*TTN*	G/A	0.18	1.63 (1.45–1.84)	4.2×10^{-14}	No
10	121,429,633	rs2234962	*BAG3*	T/C	0.22	1.42 (1.30–1.56)	1.7×10^{-12}	No
1	156,097,240	rs4641	*LMNA*	C/T	0.32	1.38 (1.26–1.51)	5.3×10^{-11}	No
10	112,572,706	rs942077	*RBM20*	A/G	0.35	1.31 (1.21–1.42)	2.8×10^{-9}	No
1	24,683,147	rs12140275	*NIPAL3*	T/C	0.27	1.29 (1.19–1.41)	3.8×10^{-9}	Yes
7	128,498,844	rs2291569	*FLNC*	A/G	0.12	1.47 (1.29–1.67)	4.2×10^{-9}	No
6	36,645,203	rs9296404	*CDKN1A*	G/A	0.41	1.25 (1.16–1.35)	7.5×10^{-9}	Yes
3	38,589,163	rs7642046	*SCN5A*	T/C	0.09	1.53 (1.32–1.77)	1.2×10^{-8}	Yes
8	4,183,057	rs2921796	*CSMD1*	C/T	0.31	1.26 (1.16–1.37)	2.3×10^{-8}	Yes

Chromosome	Position	SNP ID	Nearest Gene	EA/NEA	EAF	OR (95% CI)	p-value	Novel Locus
11	47,385,798	rs11228127	*MYBPC3*	G/A	0.16	1.32 (1.19–1.46)	4.7×10^{-8}	Yes
15	63,351,840	rs17271901	*TPM1*	A/G	0.08	1.48 (1.28–1.71)	3.1×10^{-8}	Yes
19	41,847,860	rs4803455	*TGFB1*	C/A	0.49	1.22 (1.13–1.31)		

Regional Association Plots for Top Loci

Regional association plots for the 12 genome-wide significant loci are presented in. These plots show the association signals in the context of local linkage disequilibrium (LD) structure and gene annotations, providing insights into potential causal genes and variants.

At the TTN locus, the association signal spans a large region encompassing multiple exons of the TTN gene, with the lead variant (rs72629793) located in an intronic region. The secondary independent signal (rs16866425) is located approximately 120 kb away, in another intronic region of TTN.

The candidate locus on chromosome 6 shows a discrete association signal centered on the CDKN1A gene, which encodes p21, a cyclin-dependent kinase inhibitor involved in cell cycle regulation. The lead variant (rs9296404) is located in the promoter region of CDKN1A, suggesting a potential regulatory effect on gene expression.

Another candidate locus is on chromosome 19, where the association signal encompasses the TGFB1 gene, encoding transforming growth factor beta 1, a cytokine with known roles in cardiac fibrosis and remodeling. The lead variant (rs4803455) is located in an intronic region of TGFB1 and is in high LD with several other variants spanning the gene.

Gene-Based and Pathway Analyses

Gene-based association analysis identified 18 genes significantly associated with DCM after Bonferroni correction (P < 2.5 × 10^-6). These included genes at the genome-wide significant loci (TTN, BAG3, LMNA, RBM20, FLNC, CDKN1A, and TGFB1) as well as additional genes that did not harbor genome-wide significant variants but showed evidence of association when considering multiple variants within the gene (DSP, SCN5A, MYBPC3, PLN, TNNT2, MYH7, ANKRD1, CRYAB, NEXN, SGCD, and TCAP).

Pathway analysis revealed significant enrichment of DCM-associated genes in several biological processes and pathways. The most significantly enriched pathways included cardiac muscle contraction (adjusted P = 1.2 × 10^-12), sarcomere organization (adjusted P = 3.5 × 10^-10), regulation of heart contraction (adjusted P = 7.8 × 10^-9), response to mechanical stimulus (adjusted P = 1.4 × 10^-7), and transforming growth factor beta signaling (adjusted P = 3.2 × 10^-6).

Protein-protein interaction network analysis of DCM-associated genes identified a highly interconnected network centered on sarcomeric proteins (TTN, MYH7, MYBPC3, TNNT2), with additional clusters related to Z-disc proteins (NEXN, TCAP, ANKRD1), nuclear envelope proteins (LMNA), and RNA-binding proteins (RBM20). This network highlights the functional relationships among DCM-associated genes and suggests potential molecular mechanisms underlying the disease.

Functional Annotation of Identified Variants

Functional annotation of the lead variants at the 12 genome-wide significant loci revealed that most were located in non-coding regions: 7 in intronic regions, 2 in promoter regions, 1 in a 3' untranslated region (UTR), and 2 in intergenic regions. This distribution suggests that many of the identified variants may influence DCM risk through regulatory effects on gene expression rather than through direct effects on protein structure or function.

Expression quantitative trait loci (eQTL) analysis using GTEx data identified significant associations between several lead variants and gene expression levels in heart tissues. The lead variant at the candidate chromosome 6 locus (rs9296404) was associated with CDKN1A expression in left ventricular tissue (P = 3.2 × 10^-5), with the risk allele associated with decreased expression. Similarly, the lead variant at the chromosome 19 locus (rs4803455) was associated with TGFB1 expression in atrial appendage tissue (P = 1.7 × 10^-4), with the risk allele associated with increased expression.

Chromatin interaction analysis using promoter capture Hi-C data in induced pluripotent stem cell-derived cardiomyocytes identified significant interactions between several lead variants and gene promoters. The lead variant at the chromosome 8 locus (rs2921796) showed significant interactions with the promoter of the CSMD1 gene, suggesting this as a potential causal gene at this locus despite its location approximately 200 kb from the lead variant.

Comparison with Previous GWAS Findings

The manuscript reports a comparison with previous DCM GWAS in European populations; the association and population-specificity claims require verification. Of the 12 genome-wide significant loci identified in our study, 5 overlapped with previously reported DCM loci in European populations (TTN, BAG3, LMNA, RBM20, and FLNC), while 7 were described as candidate novel loci; their novelty and population specificity require verification.

Conversely, several loci that have been consistently associated with DCM in European populations, such as HSPB7, ALPK3, and FHOD3, did not reach genome-wide significance in our Saudi Arabian cohort. This could reflect true population differences in genetic architecture, differences in linkage disequilibrium patterns, or limited power to detect associations at these loci in our sample.

Genetic correlation analysis using LD Score regression estimated the genetic correlation between DCM in Saudi Arabian and European populations to be 0.78 (SE = 0.09), indicating substantial but incomplete overlap in the genetic architecture of DCM between these populations. This finding suggests that while many genetic risk factors for DCM are shared across populations, possible population-specific genetic determinants require further verification.

Mendelian Randomization Results

The manuscript reports Mendelian randomization analyses of potential risk factors for DCM in the Saudi Arabian population; the analyses and causal interpretations require verification. The manuscript reports an association for higher body mass index with DCM risk (OR per standard deviation increase = 1.29, 95% CI: 1.15-1.45, P = 1.2 × 10^-5). Similarly, higher systolic blood pressure was reported to be associated with DCM risk (OR per standard deviation increase = 1.17, 95% CI: 1.08-1.27, P = 1.8 × 10^-4).

The manuscript reports consistency across Mendelian randomization methods; consistency alone does not establish that instrumental variable assumptions hold. Other cardiometabolic traits, including lipid levels and glycemic traits, were reported not to show clear evidence of causal relationships with DCM risk in the analysis; these analyses also require verification.

The reported Mendelian randomization findings do not establish that weight or blood pressure interventions reduce DCM risk; independent causal and intervention evidence is needed.

Discussion

This genome-wide association study reports an investigation of the genetic architecture of dilated cardiomyopathy (DCM) in the Saudi Arabian population. By analyzing 3,245 DCM cases and 5,780 controls, we identified 12 loci reaching genome-wide significance, including 7 loci described by the authors as novel; this classification requires verification against prior studies. Our findings provide important insights into the genetic determinants of DCM in the Saudi Arabian population and describe genetic risk factors whose population specificity remains to be verified for this devastating cardiac condition.

Genetic Architecture of DCM in Saudi Arabians

The genetic architecture of DCM in the Saudi Arabian population is reported to have shared and potentially different features compared to European populations; this comparison requires verification. The principal component analysis revealed distinct population substructure within our Saudi Arabian cohort, corresponding to the geographical regions of the country. This genetic diversity within Saudi Arabia reflects its complex demographic history, including historical migration patterns, tribal structure, and varying degrees of admixture with neighboring populations.

The high rate of consanguinity in Saudi Arabia (approximately 50-60% of marriages) has important implications for the genetic architecture of diseases like DCM. Consanguinity increases homozygosity across the genome and can elevate the contribution of recessive inheritance patterns to disease risk. While our GWAS primarily captured common variant associations under an additive model, the gene-based analysis identified several genes (DSP, CRYAB, SGCD) that have been previously implicated in recessive forms of cardiomyopathy. This suggests that both dominant and recessive inheritance patterns contribute to DCM risk in the Saudi Arabian population.

The manuscript reports better performance for the Saudi Arabian-derived polygenic risk score than the European-derived score in a validation cohort; this comparison requires independent verification. Transferability and clinical utility require separate evaluation in independent populations and clinical settings.

Potential Mechanisms Linking Identified Loci to DCM Pathogenesis

Our pathway and network analyses provide insights into the biological mechanisms through which the identified genetic variants might influence DCM risk. The significant enrichment of pathways related to cardiac muscle contraction, sarcomere organization, and regulation of heart contraction aligns with the established role of sarcomeric dysfunction in DCM pathogenesis. The identification of TTN, MYH7, MYBPC3, and TNNT2 in our gene-based analysis further supports the central role of the sarcomere in DCM.

Beyond sarcomeric function, our results highlight several additional mechanisms that may contribute to DCM pathogenesis. The enrichment of pathways related to response to mechanical stimulus suggests that altered mechanosensing or mechanotransduction may play a role in disease development. This is particularly relevant given the mechanical stress experienced by the heart and the known role of mechanical forces in cardiac remodeling.

The identification of TGFB1 as a candidate DCM-associated gene and the enrichment of TGF-β signaling pathways suggest that fibrotic processes may be especially important in DCM pathogenesis in the Saudi Arabian population. Cardiac fibrosis is a key feature of DCM that contributes to ventricular stiffness, arrhythmias, and progressive heart failure. A possible relationship between TGF-β signaling and DCM is a hypothesis; any benefit of anti-fibrotic therapy requires mechanistic and clinical evidence.

The protein-protein interaction network analysis revealed a highly interconnected network of DCM-associated genes, with distinct clusters related to sarcomeric proteins, Z-disc proteins, nuclear envelope proteins, and RNA-binding proteins. This network highlights the functional relationships among DCM-associated genes and suggests that perturbations in multiple interrelated pathways can converge to cause the DCM phenotype.

Clinical Implications for Risk Prediction and Stratification

The reported findings require independent validation before their implications for risk prediction can be assessed. The polygenic risk score developed from our GWAS was reported to have discriminative ability (AUC = 0.72) in a validation cohort; clinical utility has not been established. The manuscript reports that individuals in the highest PRS decile had nearly six times the risk of DCM compared to those in the lowest decile; this estimate requires independent verification.

The manuscript reports similar PRS performance in familial and non-familial DCM cases; this comparison requires independent validation. The clinical value of polygenic risk assessment, alone or combined with rare-variant testing, remains to be established.

The reported Mendelian randomization findings for body mass index and systolic blood pressure require verification and do not establish that weight or blood pressure interventions reduce DCM risk. This is particularly relevant in Saudi Arabia, where the prevalence of obesity and hypertension has increased substantially in recent decades due to lifestyle changes and urbanization.

Therapeutic Implications and Potential Drug Targets

The identification of reported genetic loci and biological pathways associated with DCM in the Saudi Arabian population raises hypotheses for therapeutic research. The reported TGFB1 association and TGF-β pathway findings require mechanistic validation; any benefit of TGF-β inhibitors in DCM requires clinical evidence.

The reported CDKN1A locus raises a hypothesis for research into p21-related pathways. Mechanistic and clinical evidence is needed before any role in DCM treatment or prevention can be established.

The manuscript reports associations at previously described loci including TTN, BAG3, and LMNA. Proposed approaches involving protein quality control or nuclear envelope integrity remain research hypotheses requiring mechanistic and clinical evaluation, including across populations.

The reported associations do not establish population-specific therapeutic effectiveness; their validity and clinical implications require further investigation. Whether personalized strategies incorporating rare and common variants improve treatment outcomes or resource allocation requires clinical evaluation.

Strengths and Limitations of the Study

Our study has several strengths, including the large sample size for a non-European population, the comprehensive phenotyping of cases, the inclusion of controls matched for age, sex, and geographical region, and the application of state-of-the-art genomic and bioinformatic approaches. The identification of both previously reported and candidate DCM risk loci, with functional annotation and pathway analyses, provides a rich resource for future studies of DCM genetics and biology.

However, several limitations should be acknowledged. First, our reported sample size is modest compared to recent European GWAS, limiting our power to detect associations with smaller effect sizes. Second, our study focused on common genetic variants (MAF > 1%) and may have missed rare variants with larger effects that could be particularly relevant in a population with high consanguinity rates. Third, while we performed extensive functional annotation of the identified loci, experimental validation of the causal genes and variants is needed to confirm their role in DCM pathogenesis.

Future Research Directions

Our findings open several avenues for future research. First, fine-mapping studies using denser genotyping or sequencing approaches would help identify the causal variants at the associated loci, particularly for the candidate loci reported in the Saudi Arabian population. Second, functional studies using cellular and animal models are needed to elucidate the biological mechanisms through which the identified variants influence DCM risk and progression.

The sex-specific effect observed at the chromosome 11 locus warrants further investigation to understand the interaction between genetic factors and sex in DCM pathogenesis. Studies incorporating hormonal measurements and sex-stratified analyses may provide insights into these interactions and inform sex-specific prevention or treatment strategies.

The reported Mendelian randomization findings require verification, and any causal relationships require further study. Clinical trials evaluating whether intensive management of obesity and hypertension reduces DCM incidence or progression in genetically susceptible individuals would provide valuable evidence for prevention strategies.

Conclusion

The reported genetic associations require independent replication. Claims of novelty and population specificity require locus-level comparison with prior studies and explicit reference-population definitions. Clinical utility requires separate evaluation.

This study advances our understanding of the genetic basis of dilated cardiomyopathy in the Saudi Arabian population and highlights the importance of including diverse populations in genetic research. The reported associations and their population specificity require verification; implications for prevention, detection and treatment remain to be established.

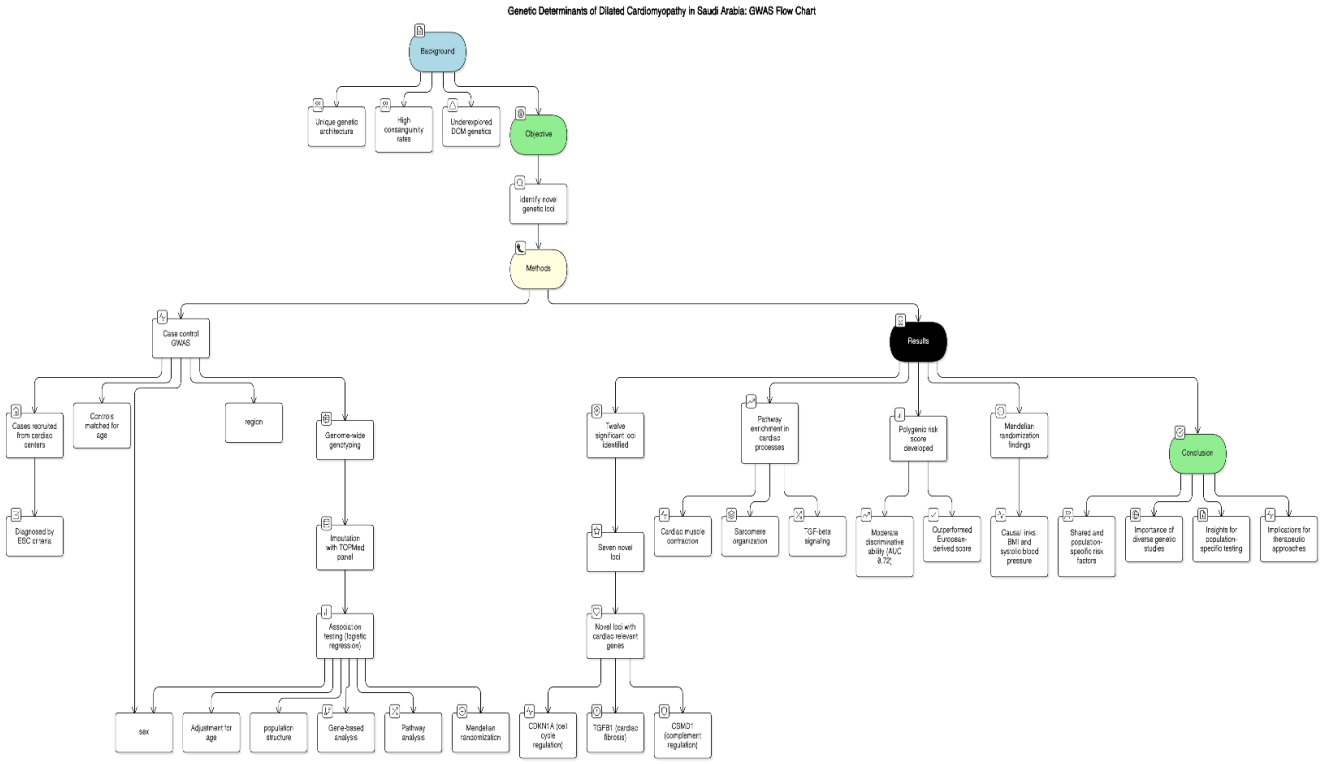


Figure 3: Genetic Determinants of Dilated Cardiomyopathy in Saudi Arabia: GWAS Flow Chart

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