

Research Article

AXIN1 Gene Polymorphism in Fatal Cardiomyopathy Cases: A Cross-Sectional Autopsy Study in Myanmar

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Abstract

Background: Cardiomyopathies are important causes of sudden cardiac death, and genetic variation contributes to their pathogenesis. AXIN1 encodes a scaffold protein that negatively regulates the Wnt/ β -catenin pathway, which has essential roles in cardiac development and remodelling. The AXIN1 single-nucleotide polymorphism rs1805105 has been associated with susceptibility to dilated cardiomyopathy in a Chinese Han population, but evidence from medicolegal autopsy populations in Myanmar is lacking. **Objective:** To determine the distribution of AXIN1 rs1805105 genotypes and examine their association with types of fatal cardiomyopathy. **Methods:** A hospital-based cross-sectional descriptive study included 50 consecutives, histologically confirmed fatal cardiomyopathy cases received for medicolegal autopsy at Mandalay General Hospital from June 2020 to May 2021. Cardiomyopathy type was determined by gross and histopathological examination. DNA extracted from cardiac blood was genotyped for AXIN1 rs1805105 using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Descriptive statistics and Fisher's exact test were used. **Results:** The mean age was 46.04 ± 13.11 years; 40 cases (80%) were male. Dilated cardiomyopathy (DCM) was identified in 38 cases (76%), hypertrophic cardiomyopathy (HCM) in 11 (22%), and restrictive cardiomyopathy (RCM) in one (2%). Genotype frequencies were CT in 25 cases (50%), TT in 16 (32%), and CC in nine (18%). Among DCM cases, CT was most frequent (21/38, 55.3%), followed by TT (10/38, 26.3%) and CC (7/38, 18.4%). Genotype distribution differed descriptively across cardiomyopathy types but was not statistically significant (Fisher's exact $p = 0.124$). Genotype distribution was also not associated with sex ($p = 0.809$). **Conclusion:** AXIN1 rs1805105 variation was present in fatal cardiomyopathy cases, with the CT genotype predominating overall and in DCM. However, this small descriptive autopsy series did not demonstrate a statistically significant association between rs1805105 genotype and cardiomyopathy type. Larger case-control and multicentre studies evaluating additional variants are required.

Keywords

AXIN1, Cardiomyopathy, Dilated Cardiomyopathy, Gene Polymorphism, Medicolegal Autopsy, PCR-RFLP, Rs1805105, Sudden Cardiac Death

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1. Introduction

Sudden cardiac death is a major component of medicolegal autopsy practice. Cardiomyopathies constitute a heterogeneous group of myocardial disorders that may produce mechanical or electrical dysfunction and can lead to unexpected death [1-3]. Contemporary classifications recognize dilated, hypertrophic, restrictive, arrhythmogenic, and other phenotypes, while also distinguishing primary genetic disease from myocardial involvement secondary to systemic disorders [2, 3]. Among the principal morphological patterns, dilated cardiomyopathy is common and is frequently associated with genetic abnormalities affecting sarcomeric, cytoskeletal, nuclear-envelope, and signalling proteins [4].

The Wnt/ β -catenin pathway is central to embryonic development and contributes to cardiac specification, cardiomyocyte differentiation, hypertrophy, and remodelling [5-7]. AXIN1, located on chromosome 16p13.3, encodes a scaffold protein within the β -catenin destruction complex and acts as a negative regulator of Wnt signalling [5, 8]. Genetic variation in AXIN1 may therefore influence pathways relevant to myocardial development and disease.

Single-nucleotide polymorphisms are stable DNA sequence variations that can be used to investigate genetic susceptibility to disease [9]. Li et al. reported that two AXIN1 variants, including rs1805105, were associated with DCM in a Chinese Han case-control population. For rs1805105, carriage of the C allele was more frequent among DCM patients, and the CT genotype showed a stronger association with DCM than the TT genotype [10]. Whether a similar pattern occurs in fatal cardiomyopathy cases from Myanmar has not previously been established.

Myanmar autopsy studies have shown that cardiomyopathy is an important cause of sudden cardiac death and that DCM is the predominant morphological subtype [11, 12]. Nevertheless, morphological and routine histological findings may be nonspecific, and molecular investigation may add evidence regarding disease mechanisms and future family-oriented evaluation. The present study aimed to determine the genotype distribution of AXIN1 rs1805105 in fatal cardiomyopathy cases and to examine whether genotype distribution differed among DCM, HCM, and RCM.

2. Materials and Methods

2.1. Study Design, Setting, and Participants

This hospital-based cross-sectional descriptive study was conducted at the Police Surgeon Office, Mandalay General Hospital, and the Common Research Laboratory, University of Medicine, Mandalay. Consecutive medicolegal autopsy cases diagnosed as fatal cardiomyopathy from June 2020 through May 2021 were eligible. Decomposed bodies were excluded. A minimum sample of 45 was calculated using an

anticipated DCM proportion of 0.865, absolute precision of 0.10, and $\alpha = 0.05$ [12, 13]; 50 cases were ultimately included.

2.2. Postmortem and Histopathological Assessment

A complete postmortem examination was performed under the supervision of a senior consultant forensic surgeon. After the heart was washed, its weight and gross features were recorded. Ventricular chamber dilatation and the thickness of the left ventricular wall, interventricular septum, and right ventricular wall were assessed at the mid-ventricular level. Tissue samples from the left ventricular wall, septum, and right ventricular wall were fixed in 10% formalin, processed, stained with haematoxylin and eosin, and reviewed with a pathologist. Cases were classified as DCM, HCM, or RCM using gross and microscopic criteria [2].

2.3. DNA Extraction and AXIN1 Genotyping

Three millilitres of blood were collected from a cardiac chamber into an EDTA tube and stored at -20°C . Genomic DNA was extracted from 300 μL of blood using a silica-membrane genomic DNA mini kit. DNA quantity and purity were assessed spectrophotometrically; extraction was repeated when the yield was below 20 ng or the A260/A280 ratio was outside 1.8-2.0.

A 245-base-pair region containing AXIN1 rs1805105 was amplified using the forward primer 5'-CTGGATAC-CTGCCGACCTTA-3' and reverse primer 5'-AC-CTTCCCTGGCTTGTTCT-3' [10]. The 10- μL reaction contained 0.6 μL genomic DNA, 5 μL Taq PCR master mix, 0.15 μL of each primer, and 4.1 μL nuclease-free water. Cycling comprised initial denaturation at 94°C for 4 minutes; 34 cycles of 94°C for 30 seconds, 66°C for 30 seconds, and 72°C for 30 seconds; and final extension at 72°C for 10 minutes.

PCR products were verified by 3% agarose-gel electrophoresis. For RFLP analysis, 5 μL of PCR product was digested with FokI at 37°C for one hour and resolved on a 4% agarose gel. The CC genotype produced an uncut 245-bp band; TT produced 186- and 59-bp fragments; and CT produced 245-, 186-, and 59-bp fragments.

2.4. Statistical Analysis

Data were entered in Microsoft Excel and analysed using SPSS version 23.0. Categorical data are reported as frequencies and percentages; age is reported as mean $\pm$ standard deviation. Differences in genotype distribution by sex and cardiomyopathy type were assessed using Fisher's exact test because of small expected cell counts. A two-sided p value below 0.05 was considered statistically significant.

2.5. Ethical Considerations

The study was approved by the Ethical Review Committee of the University of Medicine, Mandalay. Written informed consent was obtained from a relative or next of kin after explanation of the purpose and procedures. Participation was voluntary and did not alter the routine postmortem examination. Identifiers were replaced with codes, specimens were used only for the approved research, and confidentiality was maintained.

3. Results

3.1. Demographic and Morphological Characteristics

All 50 enrolled cases were histologically confirmed as cardiomyopathy. Ages ranged from 18 to 73 years, with a mean of 46.04 ± 13.11 years. Twenty-two cases (44%) were aged 21-40 years and 18 (36%) were aged 41-60 years; thus, 80% occurred between 21 and 60 years. Forty cases (80%) were male, giving a male-to-female ratio of 4: 1.

Table 1. Demographic characteristics of fatal cardiomyopathy cases ($n = 50$).

Characteristic	Category	n (%)
Age group	<20 years	1 (2.0)
	21-40 years	22 (44.0)
	41-60 years	18 (36.0)
	61-80 years	9 (18.0)
Sex	Male	40 (80.0)
	Female	10 (20.0)

DCM was the most common subtype (38 cases, 76%), followed by HCM (11 cases, 22%) and RCM (one case, 2%). DCM occurred across all age categories, whereas HCM was confined to the 21-60-year age range in this series. Male predominance was observed for both DCM and HCM.

Table 2. Cardiomyopathy type by sex ($n = 50$).

Cardiomyopathy type	Male, n	Female, n	Total, n (%)
Dilated cardiomyopathy	29	9	38 (76.0)
Hypertrophic cardiomyopathy	10	1	11 (22.0)
Restrictive cardiomyopathy	1	0	1 (2.0)

Cardiomyopathy type	Male, n	Female, n	Total, n (%)
Total	40	10	50 (100.0)

3.2. AXIN1 Rs1805105 Genotype Distribution

The heterozygous CT genotype was most frequent, occurring in 25 cases (50%). TT was identified in 16 cases (32%), and CC in nine (18%). Genotype distribution did not differ significantly by sex (Fisher's exact $p = 0.809$).

Table 3. AXIN1 rs1805105 genotype distribution by sex.

Genotype	Male, n (%)	Female, n (%)	Total, n (%)
TT	12 (75.0)	4 (25.0)	16 (32.0)
CT	20 (80.0)	5 (20.0)	25 (50.0)
CC	8 (88.9)	1 (11.1)	9 (18.0)
Total	40 (80.0)	10 (20.0)	50 (100.0)

3.3. Genotype Distribution by Cardiomyopathy Type

Among the 38 DCM cases, CT was the predominant genotype (21 cases, 55.3%), followed by TT (10, 26.3%) and CC (seven, 18.4%). Among 11 HCM cases, TT was most frequent (six, 54.5%), followed by CT (four, 36.4%) and CC (one, 9.1%). The single RCM case had the CC genotype. The overall genotype distribution across cardiomyopathy types was not statistically significant (Fisher's exact $p = 0.124$).

Table 4. Association between AXIN1 rs1805105 genotype and cardiomyopathy type.

Type	CC, n (%)	CT, n (%)	TT, n (%)	Total
DCM	7 (18.4)	21 (55.3)	10 (26.3)	38
HCM	1 (9.1)	4 (36.4)	6 (54.5)	11
RCM	1 (100.0)	0 (0.0)	0 (0.0)	1

Counting two alleles per individual, DCM cases contributed 35 C alleles and 41 T alleles; HCM cases contributed six C and 16 T alleles; and the single RCM case contributed two C alleles. These descriptive counts should not be interpreted as evidence of risk because the study did not include a non-cardiomyopathy control group.

Table 5. *AXIN1 rs1805105 allele counts by cardiomyopathy type.*

Type	C allele, n (%)	T allele, n (%)	Total alleles
DCM	35 (46.1)	41 (53.9)	76
HCM	6 (27.3)	16 (72.7)	22
RCM	2 (100.0)	0 (0.0)	2
Overall	43 (43.0)	57 (57.0)	100

4. Discussion

4.1. Principal Findings

This study provides initial evidence on *AXIN1* rs1805105 variation among histologically confirmed fatal cardiomyopathy cases in a Myanmar medicolegal autopsy setting. Three findings are central. First, DCM accounted for approximately three quarters of cases. Second, the CT genotype was the most frequent genotype overall and among DCM cases. Third, neither cardiomyopathy type nor sex showed a statistically significant association with genotype distribution. The data therefore describe the occurrence of rs1805105 variants but do not establish that the variant causes or increases susceptibility to fatal cardiomyopathy.

4.2. Demographic Pattern and Cardiomyopathy Types

The mean age of 46 years indicates that fatal cardiomyopathy affected a relatively young and middle-aged population. Eighty percent of cases were between 21 and 60 years, and males constituted 80% of the series. Earlier autopsy studies in Myanmar likewise reported male predominance and identified cardiomyopathy most often in young or middle adulthood [11, 12]. International studies have also shown sex differences across cardiomyopathy phenotypes, although the magnitude and direction vary with genotype, phenotype, referral pattern, hormones, and sociocultural exposures [14].

DCM was the dominant phenotype in the present study. This agrees with the retrospective autopsy study from Mandalay General Hospital and with clinical descriptions of DCM as a common cardiomyopathy phenotype [4, 12]. The distribution differs from some population registries, illustrating that an autopsy-based sample represents fatal cases referred for medicolegal investigation rather than the full spectrum of living patients with cardiomyopathy. Consequently, the observed proportions should not be interpreted as population prevalence.

4.3. *AXIN1* Rs1805105 and Dilated Cardiomyopathy

The predominance of the CT genotype among DCM cases

is directionally similar to the report by Li et al., in which CT was more frequent among DCM patients than controls and C-allele carriers had increased odds of DCM [10]. However, the present findings did not reach statistical significance. Several design differences are important: the earlier study used 340 DCM patients and 430 healthy controls, whereas the present study included only 50 fatal cardiomyopathy cases distributed across three phenotypes and had no healthy or non-cardiomyopathy comparison group.

The biological rationale for studying *AXIN1* remains plausible. *AXIN1* regulates β -catenin turnover, while Wnt/ β -catenin signalling has stage-dependent effects on cardiogenesis and contributes to adult cardiac hypertrophy and remodeling [5-8]. Nevertheless, biological plausibility does not substitute for an adequately powered association design. The rs1805105 variant is synonymous, and any contribution to disease may reflect linkage with another functional variant, regulation of expression or splicing, interaction with other genes, or population-specific linkage disequilibrium. Functional studies would be required to determine mechanism.

4.4. Forensic and Clinical Implications

Molecular analysis can complement, but should not replace, comprehensive autopsy and histopathological examination. In sudden unexplained or cardiomyopathy-related death, a molecular diagnosis may clarify aetiology and can have implications for surviving relatives. However, a common polymorphism identified in a descriptive series should not be reported as a pathogenic cause without validated evidence. Current practice increasingly favours targeted or panel-based analysis of established cardiomyopathy genes, careful variant classification, and clinical genetic evaluation of relatives when indicated [15].

The present PCR-RFLP method offers a relatively accessible approach for studying a predefined variant in a resource-constrained setting. Future work should add matched controls, expand the number of cardiomyopathy-associated variants, document family history, and integrate pathological phenotype with molecular findings. Multicentre recruitment would improve precision and permit meaningful subgroup analysis.

4.5. Strengths and Limitations

Strengths include consecutive recruitment, systematic medicolegal examination, histopathological confirmation of cardiomyopathy type, and a clearly defined molecular assay. The work also provides locally generated genetic data in a setting where such evidence is limited.

Several limitations constrain interpretation. The sample was small, particularly for HCM and RCM, producing sparse contingency-table cells and low statistical power. There was no control group, so genotype frequencies cannot be used to estimate susceptibility or causal risk. Consecutive sampling

from one hospital limits generalisability and may overrepresent particular demographic or referral patterns. Only one AXIN1 polymorphism was examined, while cardiomyopathy is genetically heterogeneous. Potential confounders, comorbid diseases, ancestry, family history, and other pathogenic variants were not evaluated. Finally, allele observations within individuals are not statistically independent, and the descriptive allele table was therefore not used for a separate association test.

5. Conclusions

In this series of 50 histologically confirmed fatal cardiomyopathy cases, DCM was the predominant phenotype and AXIN1 rs1805105 CT was the most frequent genotype. Genotype distribution was not significantly associated with cardiomyopathy type or sex. The study supports the feasibility of molecular investigation in medicolegal autopsy practice but does not establish rs1805105 as a risk marker for fatal cardiomyopathy in Myanmar. Larger, controlled, multicentre studies incorporating broader cardiomyopathy gene panels and functional interpretation are needed.

Abbreviations

AXIN1	Axis Inhibition Protein 1
DCM	Dilated Cardiomyopathy
DNA	Deoxyribonucleic Acid
EDTA	Ethylenediaminetetraacetic Acid
HCM	Hypertrophic Cardiomyopathy
PCR-	Polymerase Chain Reaction-restriction
RFLP	Fragment Length Polymorphism
RCM	Restrictive Cardiomyopathy
SNP	Single-Nucleotide Polymorphism

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Author Contributions

Myo Zaw Thu: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft

Ye Phyo Aung: Conceptualization, Validation, Writing – original draft

Thet Hnin San: Conceptualization, Methodology, Supervision, Validation

Chan Myae Thein: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing

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Data Availability Statement

The data supporting the findings are contained in the original doctoral thesis and may be available from the author subject to ethical and institutional requirements.

Conflicts of Interest

The authors declare no conflicts of interest.

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Biography



Myo Zaw Thu is an Assistant Lecturer in the Department of Forensic Medicine at the Defence Services Medical Academy, Myanmar. He received his MBBS degree in 2006, MMedSc (Medical Jurisprudence) in 2013, Doctorate of Medical Science (Medical Jurisprudence) in 2023, and Diploma in Medical Education in 2025. He actively contributes to undergraduate and postgraduate medical education. His research interests include forensic science, medical ethics, and medical education.



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Thet Hnin San is an Associate Professor in the Department of Pathology, University of Medicine, Taunggyi, Myanmar. She got Bachelor of Medicine and Bachelor of Surgery (M.B., B.S.) degree from the University of Medicine, Magway, in 2006, followed by a Master of Medical Science (M.Med. Sc.) in Pathology in 2013 and a Doctor of Philosophy (Ph.D.) in Pathology in 2017 from the University of Medicine, Mandalay. She got a Diploma in Medical Education (Dip.Med.Ed.) from the University of Public Health, Yangon in 2025. Her professional interests include Diagnostic pathology, Histopathology, Hematopathology, and Medical Education.



Chan Myae Thein is Professor and Head of Department of Forensic Medicine, University of Medicine 2, Yangon, Myanmar. He also serves as Police Surgeon of North Okkalapa General Hospital, Yangon. He graduated his MBBS degree from University of Medicine, Mandalay, Myanmar. He got his Master of Medical Science (M.Med.Sc) degree, Doctor of Medical Science (Dr.Med.Sc) degrees specialized on Forensic Medicine and Diploma of Communication and Medical Ethics (D.C.M.E) from University of Medicine 2, Yangon. He had the Diploma of Medical Education (Dip.Med.Ed) conferred from University of Public Health, Yangon. He focuses on teaching of Forensic Medicine, Medical Ethics and Professionalism, Research Ethics to undergraduate and post-graduate students. His research interest is related to Forensic related research. He is also a member of Academic board of post-graduate studies and Ethics Research Committee of University of Medicine 2, Yangon. He serves as a member of Clinical Management Committees of central Hospitals of Yangon.

Research Field

Ye Phyo Aung: Medical and Health Sciences, Medical Education, Clinical Research

Myo Zaw Thu: Medical and Health Sciences, Medical Education, Clinical Research

Thet Hnin San: Medical and Health Sciences, Medical Education, Clinical Research

Chan Myae Thein: Medical and Health Sciences, Medical Education, Clinical Research