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ORIGINAL ARTICLE

MEF2C Mutation Analysis in Patients with Congenital Heart Diseases among the Tanzanian Population

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ABSTRACT

Background: Congenital heart disease (CHD) is the most common congenital anomaly worldwide and a leading cause of infant morbidity and mortality, particularly in low- and middle-income countries. Genetic factors, including mutations in cardiac transcription factor genes such as MEF2C, play a critical role in cardiac development. However, data on MEF2C gene mutations in Sub-Saharan Africa remain limited. This study aimed to determine the presence of MEF2C gene mutations among infants with CHD attending Jakaya Kikwete Cardiac Institute (JKCI), Tanzania.

Methods: A case-control study was conducted involving 62 infants with echocardiographically confirmed CHD and 101 healthy controls aged 0 to 12 months. Genomic DNA was extracted from dry blood spot samples, and polymerase chain reaction (PCR) was used to amplify exon 1 and exon 11 of the MEF2C gene. Due to resource constraints, 10 samples from cases and 10 from controls with adequate DNA quality were selected for sequencing. Sequence analysis was performed using BLAST and MEGA11 software, and the pathogenicity of identified variants was assessed using MutationTaster and Swiss-modeling tools.

Results: Among the sequenced samples, two non-synonymous MEF2C mutations were identified exclusively in CHD cases. A missense mutation (c.185T>A; p.M62K) was detected in an 8-month-old male with patent ductus arteriosus, while an insertion mutation (c.64_65insA; p.T22N) causing a frameshift and truncated protein was identified in an 8-month-old female with tetralogy of Fallot. These mutations were absent in all control samples and were predicted to be disease-causing.

Conclusion: This study identified potentially pathogenic MEF2C gene mutations among infants with CHD, suggesting a role of this gene in the disease pathogenesis. The findings highlight the importance of genetic studies in understanding CHD in low-resource settings and underscore the need for larger-scale genomic and functional studies to validate these associations.

BACKGROUND

Congenital heart disease (CHD) is a malformation in the heart's structure and/or the major great vessels due to abnormal development of the heart during embryogenesis. It is the most common and survivable type of birth defect in humans, with an estimated prevalence of 8 to 14 per 1000 newborns worldwide and accounting for about one-third of all major developmental defects,[1-3] in Sub-Saharan Africa to about 3 to 5 per 1000 live birth,[4] about 8 per 1000 live births in Tanzania.[5] The development processes of the heart involve a series of events, such as precardia cell migration from primitive streaks, the formation of heart tubes, the fusion of heart tubes, chamber formation and looping, the development of the vasculature and conducting system. The heart requires an intricate interplay between genetic factors including cardiac-specific, transcription factor, and signaling pathway genes, and environmental factors for normal development.

Approximately 1.35 million neonates are born with CHD worldwide annually, with about 1% incidence of live births.[1] Most of the minor defects resolve spontaneously, and with the development of cardiac surgeries, an increasing number of major defect survivors is reported worldwide.[1] However, in most of the low and middle-income countries, CHD poses a great number of morbidities and mortality.

Most of the major defects are shown to bring about poor quality of life,[6] as they are associated with several comorbidities such as arrhythmias,[7] congestive heart failure,[8] pulmonary hypertension,[9] increased risk of thromboembolism,[10] poor brain development,[11] infective endocarditis,[12] Eisenmenger syndrome, and sudden cardiac death.[13] Thus, CHD accounts for about 24% of all infant congenital defect-related deaths.

The genetics of CHD is highly heterogeneous,[14,15] a vast number of autosomal dominant or X-linked mutations have been identified in familial CHD.[16] Several mutations in almost 60 genes, those including coding for cardiac transcription factors, signaling molecules, chromatin modifiers, and cardiac sarcomeric proteins, have been identified.[14,17,18] Some of the genes that have been well identified and linked to CHD include the zinc finger proteins GATA4, GATA5, and GATA6,[19] the homeodomain-containing protein NKX2-5, and the T-box transcription factors TBX1, TBX5, and TBX20, HAND1, and HAND2.[20-24]

The myocyte enhancer factor 2C (MEF2C) gene is a member of the myocyte enhancer factor-2 family of MADS-box transcription factors which are expressed at high levels in various cells. The MEF2C gene plays a key role in early regulation of heart tube development, specifically the inflow tracts, chambers, and outflow tracts. MEF2C has been linked to transcriptional regulation in cardiac muscle cells.[25,26] Mutations and loss of function of the MEF2C gene in the germline led to embryonic mouse death.[27] A missense mutation was detected in a one-year-old female with a mutational prevalence of about 0.54%, and a substitution of thymine for cytosine at the first nucleotide of codon 15(c.43C>T) that predicts the transition of arginine to cysteine was discovered in a girl with DORV and VSD.[28] A non-synonymous heterozygous variant was detected in a one-year-old male with a mutational prevalence of 0.5%, and a specific substitution of cytosine for thymine at the second nucleotide of codon 38(c.113T>C), predicting a change in leucine to proline, was detected in a male with PDA and VSD who had a positive familial history of CHD.[29]

Despite the above-stated findings, mutation studies of the MEF2C gene remain scarce, and due to the genetic heterogeneity of CHD, much of information remains unknown. Africa has an overwhelming burden of CHD and a high mortality rate at a younger age due to failure of primary prevention, delay in diagnosis, and limited access to the correct intervention, yet there is a highly limited number of studies exploring the risk factors for congenital heart diseases, mostly at the molecular level.[5,30] This study aimed to determine the presence of MEF2C gene mutation among infants with congenital heart diseases attending at Jakaya Kikwete Cardiac Institute (JKCI).

METHODS

Study design and Study setting

This was a case-control study conducted among infants at the JKCI. JKCI is a national, specialized, and university teaching hospital offering cardiovascular care, training, and research services to people living within and outside Dar es Salaam. The institute has 103 beds with an average of 700 outpatients and 100 inpatients per week.

Study Population

The study involved 62 unrelated cases with CHD, including 31 males and 31 females, with mean age of 5.9 months. The recruited patients were already CHD confirmed, and they were either attending the clinic or admitted to JKCI. The study included infants with isolated congenital heart diseases and healthy infants without congenital heart diseases. Infants with other congenital syndromes presenting with CHD, such as Down's syndrome and those with other cardiomyopathies were excluded. A total of 101 unrelated healthy infants (55 males and 46 females) were enrolled as controls. The controls had no CHD history with a mean age of 6.2 months. The age of all infants (cases and controls) involved in this study range from 0 to 12 months. Because of limited funding, from each group, a total of 10 infants whose DNA had a good amplification were randomly selected and their samples were taken for sequencing (10 from cases and 10 from controls).

Cardiac phenotypic characteristics were mainly determined by echocardiography.

Sample size

The sample size was calculated using Kelsey's formula.

$$n\text{cases -Kelsey} = \frac{(z\alpha/2 + z1\text{-}\beta)^2 * p^* (1 - p) * (r+1)}{(p0 - p1)^2}$$

α The probability of type I error (significance level) is the probability of rejecting the true null hypothesis

β The probability of type II error (1 - power of the test) is the probability of failing to reject the false null hypothesis.

P_0 The proportion of cases

P_1 The proportion of controls

OR The calculated odds ratio

r The ratio of case-control (1 case/r controls)

thus $Z_{\alpha/2}$ =1.96

Z_{β} =0.84 (80%) power

OR=2

r= 2

p1= 0.08

ncases = (1.96+0.84)2 0.008(1-0.008) *(2+1)/(0.15-0.008)2 *2

ncases = 62

ncontrols = 124 (twice no of cases to increase the power of the study)

Genetic analysis of the MEF2C gene

Blood samples were obtained from the study participants through peripheral venipuncture and collected onto dry blood spot (DBS) papers. The DBS papers were then dried and carefully packaged in specialized air-tight parcels to ensure safe transfer and subsequent DNA extraction. Genomic DNA extraction was performed according to the protocol provided with the Quick-DNA miniprep kit (www.zymoreserch.com). Subsequently, the quantity and quality of the extracted DNA were assessed using a computer-based NanoDrop™ 1000 spectrophotometer from Biochrom LTD, located in Cambridge, England. The spectrophotometer measured the absorbance of the DNA sample at 260/280 nm to determine its purity and concentration.

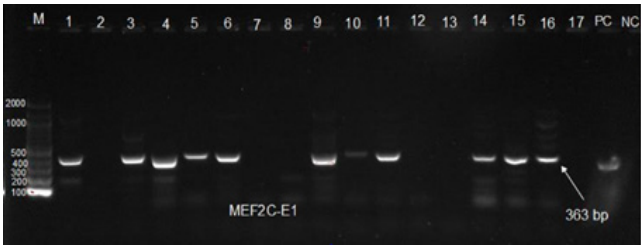
Primer design and PCR amplification of MEF2C gene (Exon 1 and Exon 11)

The referential genomic DNA sequence for the human MEF2C gene (Accession No. NM_001364339.2) was

derived from the Nucleotide database at the National Center for Biotechnology Information[31]. Using the online primer-BLAST program, primer pairs to amplify the coding exons of MEF2C (transcript variant 19) by conventional polymerase chain reaction (PCR) were designed, as shown in Table 1.

PCR was performed in a 20ul reaction volume containing 4ul of HOT FIREPol® Blend Master Mix (from Solis Biodyne, Estonia), 0.5ul of each primer (forward and reverse), 2ul of DNA template, and 13ul of molecular-grade water. PCR cycling used a pre-denaturation cycle at 95°C for 15min followed by 35 cycles of denaturation at 95°C for 30s, annealing of primers at 62°C for 30s, and extension at 72°C for 1 min. Amplicons were fractionated by electrophoresis on 1.5% agarose gel with a DNA ladder of 100bp intervals, starting from 100bp to 1500bp (from New England Biolabs, Ipswich, US) and GreenStar™ Nucleic Acid Staining Solution I (from Bioneer Corporation, South Korea) as visualization dye (Figure 1, Figure 2).

FIGURE 1: PCR Amplification of MEF2C Gene Exon 1



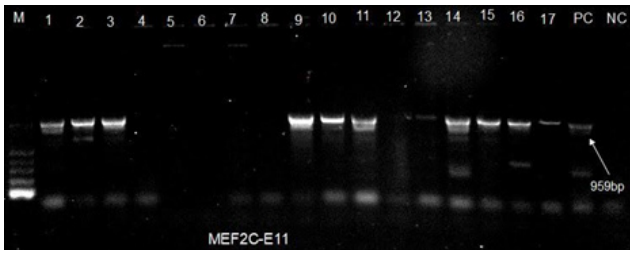
M is a 100bp Marker and Lanes 1 to 17 are the Tested Samples, PC is Positive Control and NC is Negative Control

The PCR products were purified and sequenced directly using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA) and a genetic analyzer (ABI 3730xl System from Applied Biosystems) in Macrogen, Europe (Meibergdree 57, 1105 BA, Amsterdam, Netherlands). The obtained nucleotide sequences were subjected to the Basic Local Alignment Search Tool (BLAST) to determine their identity by comparing them with other published sequences available in the GenBank database for human (taxid:9606), transcript variant 19 (NM_001364339.2). Alignment of MEF2C gene exon 1 and 11 partial nucleotide sequences with selected reference MEF2C gene nucleotide sequences from GenBank was performed using Clustal W in MEGA11 software.

Prediction of the pathogenic potential of a MEF2C variation

The causative potential of a MEF2C variation was predicted by MutationalTaster (https://www.mutationtaster.org). Swiss computational modeling was used to characterize the secondary protein structures (https://swissmodel.expasy.org).

FIGURE 2: PCR Amplification of MEF2C Gene Exon 11



M is a 100bp Marker and Lanes 1 to 17 are the Tested samples, PC is Positive Control and NC is Negative Control

Ethics approval and consent to participate

The research protocol was reviewed and approved by the institutional review board of the Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam, Tanzania (approval date – 05/03/2024, reference number - DA.282/298/01.C/2067), Following approval, administration clearance to conduct the study was obtained from Jakaya Kikwete Cardiac Institute (approval date – 26/3/2024, reference number AB.123/307/01K/21). Written informed consent was obtained from the parents/guardians of the CHD patients and the control infants before the study began.

TABLE 1: Primer Pairs used for Amplification of MEF2C Gene

Coding exon	Forward primer (5'>3')	Reverse primer (5'>3')	Product size (bp)
1	GCACACATCGTCTCCAGCTC	GGGATAGATAGACACAGTGCCG	363
11	GTATGCATTGCTGCGTGGAG	AAAGTCCAGCTTATGCCGCT	959

RESULTS

Clinical Features of the Study Participants

This study included 62 unrelated CHD patients who were randomly selected and further investigated, in contrast to 101 unrelated healthy control individuals. From the CHD patients, only samples for 10 patients were sequenced, and 10 samples from the control group were sequenced. From the group of 10 patients whose samples were sequenced, 2 cases had a positive family history of CHD. The control individuals were healthy with a negative family history of CHD and normal echocardiograms. Also, 2 sequenced infant cases were found to have MEF2C gene mutations. All participants had an echocardiogram documented (Table 2).

Identification of a MEF2C mutation

Finding 1: Sequence analysis of the MEF2C gene led to the identification of a non-synonymous mutation in a male infant, 8 months old with Patent ductus arteriosus. Specifically, a substitution of adenine for guanine at position 185 (c. 185T>A) was predicted to result in the change of methionine amino acid at position 62 into lysine (p.M62K) (Figure 3). The mutation was not found in other cases and controls.

Finding 2: Sequence analysis of the MEF2C gene also led to the identification of a non-synonymous mutation in an 8-month-old female patient with Tetralogy of Fallot. Specifically, an insertion of adenine at position 65 (c.64_65insA), which predicted amino acid alteration at position 22 from threonine to asparagine (p.T22N), frameshift, splice site changes, and a truncated protein (Figure 4).

TABLE 2: Sociodemographic Characteristics of the Study Participants

Characteristic	Cases		Controls	
	Frequency (n=62)	Proportion (%)	Frequency (n=101)	Proportion (%)
Age (months)				
Below or equal to 6	39	62.9	68	67.3
Above 6	23	37.1	33	32.7
Sex				
Male	31	50	55	54.5
Female	31	50	46	45.5
Residence				
Lake zone	10	16.1		
Coastal zone	35	56.4		
Central zone	2	3.2		
Southern zone	5	8.1		
Northern zone	6	9.7		
Zanzibar	4	6.5		
Education level				
No education	5	8.1	4	3.9
Primary education	24	38.7	33	32.7
Secondary education	22	35.5	43	42.6
Collage education	11	17.7	21	20.8

FIGURE 3: Predicted Sequence – Wild-type, Mutated Amino Acid Sequence and the Respective Predicted Structures

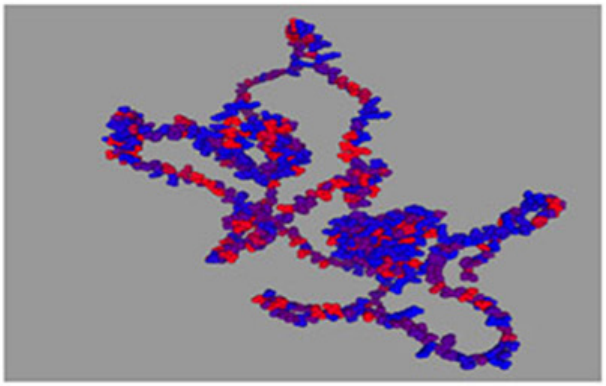
A] Predicted sequence – wild-type amino acid sequence

MGRKKIQITR IMDERNRQVT FTKRKFGLMK KAYELSVLCD CEIALIIFNS TNKLFQYAST
DMDKVLLKYT EYNEPHESRT NSDIVETLRK KGLNGCDSPD PDADDSVGHS PESEDKYRKI
NEDIDLMISR QRLCAVPPPN FEMPVSIPVS SHNSLVYSNP VSSLGNPNLL…

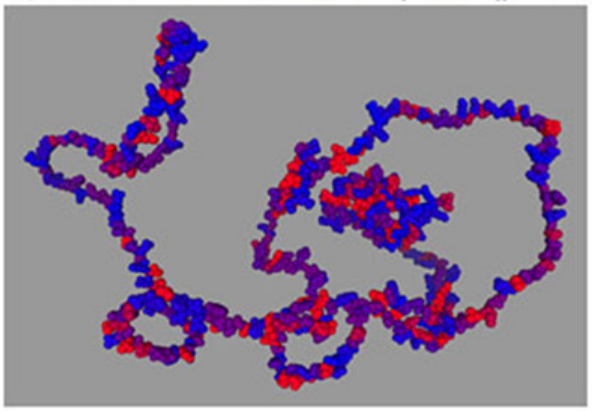
B] Predicted sequence – mutated amino acid (p.M62K)

MGRKKIQITR IMDERNRQVT FTKRKFGLMK KAYELSVLCD CEIALIIFNS TNKLFQYAST
DKDKVLLKYT EYNEPHESRT NSDIVETLRK KGLNGCDSPD PDADDSVGHS PESEDKYRKI
NEDIDLMISR QRLCAVPPPN FEMPVSIPVS SHNSLVYSNP VSSLGNPNLL PLAHPSLQRN.

C] Predicted structure - wild-type protein



D] Predicted structure - mutated protein (p.M62K)



E] Conservation protein level for non-synonymous changes

conservation protein level for non-synonymous changes	species	match	gene	aa alignment
	Human			62 TNKLFQYASTDMDKVLLKYTEYNE
	mutated	not conserved		62 DKDKVLLKYTEYN
	Ptroglodytes	all identical	ENSPTRG00000024214	62 DMDKVLLKYTEYN
	Mmulatta	all identical	ENSMMUG00000019836	62 DMDKVLLKYTEYN
	Fcatus	all identical	ENSFCAG00000011595	44 TNKLFQYASTDMDKVLLKYTEYN
	Mmusculus	all identical	ENSMUSG00000005583	62 DMDKVLLKYTEYN
	Ggallus	all identical	ENSGALG00000014645	62 DMDKVLLKYTEYN
	Trubripes	all identical	ENSTRUG00000000877	62 DMDKVLLKYTEYN
	Drerio	all identical	ENSDARG00000002418	62 DMDKVLLKYTEYN
	Dmelanogaster	all identical	FBgn0011656	62 DMDRVLLKYTEYN
	Celegans	all identical	W10D5.1	62 DMDKVLLKYTEYN
	Xtropicalis	all identical	ENSXETG00000007038	51 TNKLFQYASTDMDKVLLKYTE

FIGURE 4: Predicted sequence – wild-type, mutated amino acid sequence and the respective predicted structures (Finding 2)

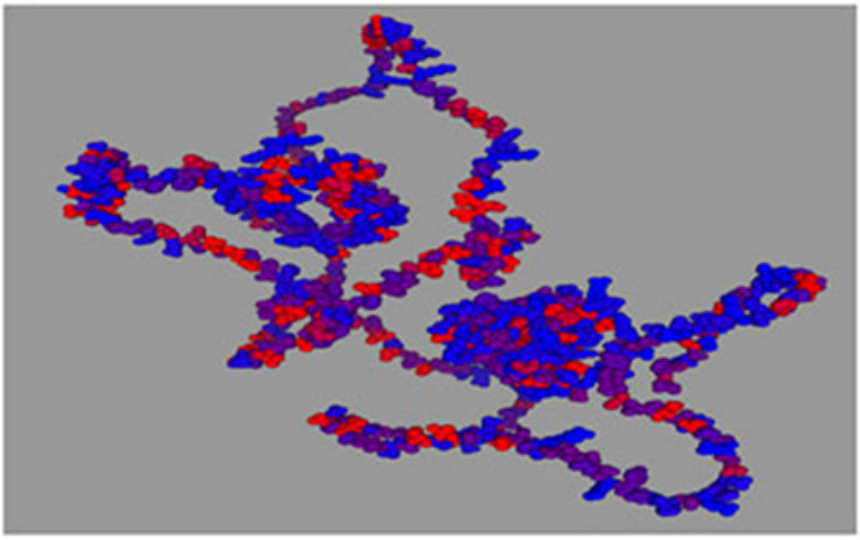
A] Predicted sequence - wild-type protein

MGRKKIQITR IMDERNRQVT FTKRKFGLMK KAYELSVLCD CEIALIIFNS TNKLFQYAST...

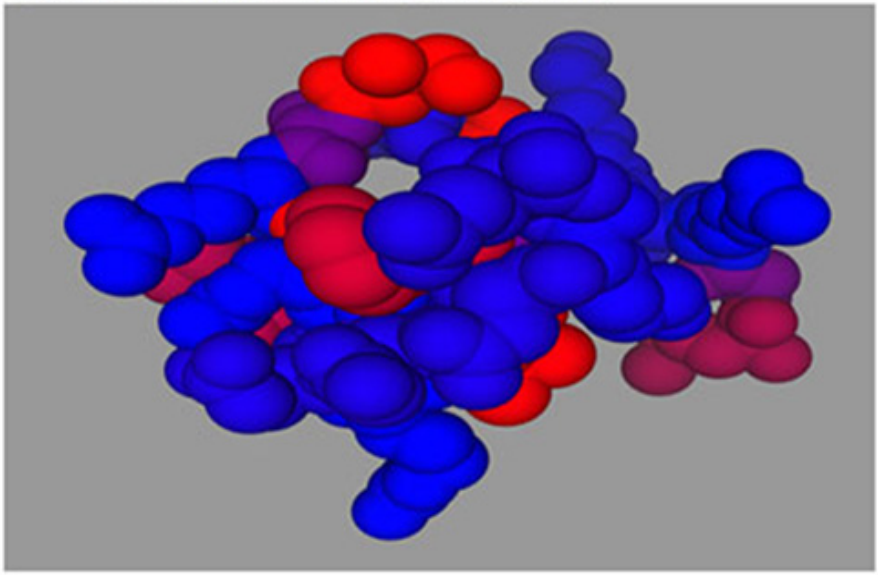
B] Predicted sequence - mutated protein(p.T22N)

MGRKKIQITR IMDERNRQVT FNKEEIWVDE EGL.|.

C] Predicted structure - wild-type protein



D] Predicted structure – mutated protein (p.T22N)



DISCUSSION

This study aimed to determine the presence of MEF2C gene mutation among infants with congenital heart diseases attending at Jakaya Kikwete Cardiac Institute. Non-synonymous mutations in the MEF2C gene were discovered in the patient with Tetralogy of Fallot and Patent ductus arteriosus. These mutations were absent in all 10 controls. Structural analyses demonstrated that the mutated proteins were disease-causing, with splice-site changes, and the amino acid sequences were not conserved across species. These mutations were neither found in ExAC nor 1000G.

Four members of the MEF2 family are found in vertebrates including MEF2A, MEF2B, MEF2C, and MEF2D. MEF2B and MEF2C are first activated in the cardiogenic mesoderm at approximately day 7.5, then on embryonic day 8.5, the MEF2C transcripts in somites along with the begin of myocyte differentiation of myotomes. [32] MEF2C is widely expressed in many types of cells to regulate tissue-specific gene expression during the eukaryotic embryonic period, including cardiac muscles, skeletal, neural, chondroid, immune, and endothelial cells. In humans, MEF2C maps on chromosome 5q14.3, it contains five key structural domains, including MADS, MEF2, transcriptional activation domain 1 (TAD1), Transcriptional activation domain 2 (TAD2), and nuclear localization signal (NLS).[32]

The highly conserved MADS domain at the amino terminus of MEF2C consists of 56 amino acids, and its main role is to mediate DNA interactions with co-factors.

The MEF2 domain is adjoining the MADS domain and comprises 30 highly conserved amino acids. In combination with the MADS domain, the MEF2 domain plays an important role in mediating dimerization and DNA binding. The TAD1 and TAD2 domains function as the transcriptional activators, while the NLS domain is located at the Carboxyl-terminus of MEF2C, which is responsible for the nuclear translocation of the protein. [32] The MEF2C gene plays a key role in early regulation of heart tube development, specifically the inflow tracts, chambers, and outflow tracts.

Notably, previous studies identified related mutations in more than 60 genes, including those encoding cardiac transcription factors to CHD in humans. In mice, target deletion of the MEF2C gene caused severe cardiac structural abnormalities and embryonic lethality in homozygous mutants due to the failure of the heart tube to undergo looping and the absence of the right ventricular region of the heart.[27] Quao and colleagues identified a heterozygous mutation (c.113T>C equivalent to p.L38P) in the MEF2C gene in a family with PDA and VSD and PS.[29] As well and Lu and fellows identified a heterozygous mutation (c.43C>T equivalent to p.R15C) in a family with DORV and VSD.[28]

This study provides an insight into molecular mechanisms underpinning CHD and signifies the likely implications of genetic counseling in MEF2C-related CHD.

Study strengths and limitations

The study was able to identify two non-synonymous mutations that may be linked to CHD, and bring insight into the possible risk factors for the disease in a low-resource setting. However, the sample size was small due to limited funds which greatly limits the possibility of detecting other possible mutations.

CONCLUSION AND RECOMMENDATION

This study provides insight into the molecular mechanisms underlying CHD and highlights the likely implications of genetic counselling in MEF2C-related CHD. Understanding how these mutations contribute to the pathogenesis of CHDs may provide valuable insights for future research and therapeutic approaches.

Based on these findings, we recommend more studies with a larger sample size on sequencing, performing whole exome sequencing and functional studies to associate mutations with congenital heart diseases.

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