Initial experience and results of a cardiogenetic clinic in a tertiary cardiac care center in India

Sir,

Cardiogenetic clinics have gained importance over the past two decades due to their ability to integrate genetic medicine with clinical cardiology and thereby provide comprehensive care to affected patients and their families.[1,2] A multidisciplinary team approach comprising the cardiologist, electrophysiologist, and clinical geneticist has resulted in significant changes in the management of children with inherited cardiac disorders. However, the concept of cardiogenetic clinic is not yet part of mainstream pediatric cardiology practice in developing countries. This may be attributed to the busy outpatient clinics, lack of personnel, cost constraints, and complexities of genetic testing. We share our early experience on the conduct and yield of the cardiogenetic clinic at our institute.

ESTABLISHMENT AND CONDUCT OF CARDIOGENETIC CLINIC

A cardiogenetic clinic was started in January 2015 at CARE Hospital, a tertiary cardiac care center in Hyderabad, India. Patients were recruited from the Pediatric Cardiology and Electrophysiology Departments. Eligible patients registered in the clinic included patients with (i) cardiomyopathy with one other affected family member (sibling/parent), (ii) history and electrocardiogram suggestive of channelopathy, and (iii) other cardiac disorders suspected to have a genetic basis.

A detailed clinical history, family history, electrocardiogram and echocardiogram of the patient and the family members were obtained. Pretest counseling was done by a multidisciplinary team consisting of pediatric cardiologist, electrophysiologist, and clinical and molecular geneticists. Following written informed consent, blood samples were drawn from the index patient, parents, and family members whenever feasible. DNA extracted from blood was used to perform whole-exome analysis using Agilent SureSelect (Santa Clara, CA) Human All Exome kit v5 (50 Mb). Posttest counseling was offered to the families.

GENETIC RESULTS

From January to December 2015, 26 patients were registered in the cardiogenetic clinic. Of them, 14 consented for genetic evaluation. The age of the cohort ranged from 7 months to 27 years (median 7 years; eight males). The baseline characteristics of the index patients are depicted in Table 1. A total of 56 patients, including index patients (n = 14, probands) and their family members (n = 42), were subjected to genetic testing. Significant variants (pathogenic/likely pathogenic) were detected in 7/14 probands and clinically correlating variants in known genes, whose significance is not known (variants of uncertain significance [VUS]), were detected in 4/14 probands and no significant variants in 3/14 cases [Table 2].

The cohort was classified into three groups based on the clinical diagnosis.

Group I (Cardiomyopathies)

Of the eight patients in this group, dilated cardiomyopathy (DCM) was present in six and hypertrophic cardiomyopathy (HCM) and ventricular noncompaction in one patient each. Among those with DCM, five patients had variants in genes that are known to cause cardiomyopathy. Patient 7 with asymptomatic ventricular noncompaction showed no pathogenic gene variant. Patient 8 was diagnosed to have obstructive HCM in her infancy during family screening, as her father was being treated for HCM. Her genetic report showed a heterozygous missense variation in the *MYH7* gene, which was also detected in the father. The disease had an autosomal dominant inheritance, but the clinical and echocardiographic presentation was different in the index patient. The father was diagnosed in adulthood and had nonobstructive HCM, whereas the child had obstructive HCM.

Group II (Channelopathies)

Of the five patients in this group, four were suspected to have long QT syndrome (LQTS). Two of them were found to have gene variants confirming LQTS. Patient 9, whose sibling suffered a sudden cardiac death (SCD), was found to have a missense variation in the *KCNE1* gene inherited from the mother, suggestive of LQTS 5. Patient 10, who presented with recurrent syncope, was detected to have a heterozygous missense variation in the *KCNQ1* gene, suggestive of LQTS type 1. One patient (Patient 13) had catecholaminergic polymorphic ventricular tachycardia (CPVT). He presented with a history of exertional syncope. His brother had SCD at the age of 21 years while sprinting to board a bus. A detailed pedigree chart showed that three of his maternal aunts and two maternal uncles had succumbed in their second or third decade of life,

Table 1: Demographic and clinical details of the index patients

Patient	Age (years)	Gender	Clinical diagnosis	Symptoms	Family history	Echocardiographic features	ECG	Treatment
1	9	Female	DCM	Heart failure	II consanguineous parents; one sibling death due to DCM	Dilated LV, severe MR, severe LV dysfunction	No significant changes	Antifailure medications
2	1.5	Male	DCM	Asymptomatic; screened and diagnosed when sibling was diagnosed to have DCM	III consanguineous parents; one sibling death due to DCM	Dilated LV, severe LV dysfunction	No significant changes	Antifailure medications
3	1	Female	DCM with noncompaction	Heart failure	Nonconsanguineous parents; monozygotic twin affected with DCM	LV noncompaction, moderate LV dysfunction, LVEF 40%	Biventricular hypertrophy	Antifailure medications
4	7	Male	DCM with noncompaction	Heart failure	Nonconsanguineous parents; younger sibling also has DCM with noncompaction	Dilated LV, severe MR, noncompaction of ventricles	Left atrial enlargement	Antifailure medications; underwent mitral valve repair during follow up
5	14	Female	DCM with noncompaction	Heart failure	III consanguineous parents; sibling also has DCM with noncompaction	Dilated LV, moderate MR, noncompaction of ventricles	No significant changes	Antifailure medications
6	7	Male	DCM	Heart failure	III consanguineous parents; sibling death due to DCM	Dilated LV, severe LV dysfunction, LVEF 15%, LV thrombus	Left atrial enlargement	Antifailure medications
7	11	Male	Noncompaction of ventricles with normal LV function	Asymptomatic; diagnosed when evaluated for nonspecific chest pain	Nonconsanguineous parents; sibling, mother, and maternal uncle also found to have noncompaction during family screening	Noncompaction of ventricles, no chamber dilatation, normal ventricular function	No significant changes	No medications; Follow up
8	3	Female	Hypertrophic obstructive cardiomyopathy	Asymptomatic; diagnosed when family screening was done	Nonconsanguineous parents; father has HCM	Hypertrophic LV with outflow obstruction	LV hypertrophy	On beta-blockers
9	14	Male	Suspected LQTS	Asymptomatic; screened in view of family history	Nonconsanguineous parents; sibling had SCD	Normal	Resting QTc 450 ms; QTc after adrenaline challenge test 520 ms	On beta-blockers; avoidance of QT prolonging drugs
10	11	Male	Suspected LQTS	Recurrent episodes of syncope	Nonconsanguineous parents; father has hearing loss since childhood and had few episodes of syncope in childhood	Normal	Resting QTc 540 ms on ECG	On beta-blockers; avoidance of QT prolonging drugs
11	0.6	Male	Suspected LQTS	Asymptomatic	Nonconsanguineous parents; two siblings had sudden death and mother had two miscarriages	Normal	Resting QTc 480 ms	On beta-blockers; Avoidance of QT prolonging drugs
12	1	Female	Suspected LQTS	Asymptomatic	Nonconsanguineous parents; two siblings had SCD in early infancy	Normal	Resting QTc 480 ms	On beta-blockers; avoidance of QT prolonging drugs

Contd...

Table 1: Contd...

Patient	Age (years)	Gender	Clinical diagnosis	Symptoms	Family history	Echocardiographic features	ECG	Treatment
13	27	Male	CPVT	Two episodes of syncope following exercise	Nonconsanguineous parents; three maternal aunts, two maternal uncles, and elder brother had sudden death following exercise	Normal	Normal ECG at baseline, QTc 400 ms, developed multiple ventricular ectopics on treadmill test	ICD at 19 years of age and on beta-blockers
14	0.8	Female	Methemoglobinemia	Clinical cyanosis Normal pO2	III degree Consanguineous parents	Normal	Normal	Vitamin C

DCM: Dilated cardiomyopathy, LV: Left ventricle, LVEF: Left ventricular ejection fraction, MR: Mitral regurgitation, ECG: Electrocardiogram, ICD: Implantable cardioverter-defibrillator, HCM: Hypertrophic cardiomyopathy, SCD: Sudden cardiac death, LQTS: Long QT syndrome, CPVT: Catecholaminergic polymorphic ventricular tachycardia

during some form of exercise such as running and dancing. Although his resting electrocardiogram was normal, he developed multiple ventricular ectopics on exercise stress test. Hence, a clinical diagnosis of CPVT was made and he was prophylactically treated with an implantable cardioverter-defibrillator (ICD). Later when he was enrolled in the cardiogenetic clinic, his genetic analysis confirmed the clinical diagnosis by revealing a heterozygous missense variation in the *RYR2* gene, also identified in his asymptomatic mother.

Group III (Miscellaneous)

Patient 14 presented with cyanosis due to elevated methemoglobin levels. The genetic test confirmed the diagnosis of autosomal recessive methemoglobinemia Type I and the gene variant was found in heterozygous states in both parents and paternal grandmother.

POST-TEST COUNSELING

In the DCM group, the patients with pathogenic variants were counseled about the confirmation of etiology, continuation of medications, and screening of other family members. As they planned to have future pregnancies, parents of the patient with autosomal recessive *NEXN* mutation (Patient 2) were counseled about the risk involved and need for antenatal testing. The families of patients with VUS were counseled about probable etiology and future implications. The family with ventricular noncompaction who did not have any pathogenic variant on genetic testing was advised to remain on follow-up as there was echocardiographic evidence of a familial disorder. It is well known that phenotype-positive genotype-negative cases exist in the inherited cardiac disease spectrum and that treatment decisions should not solely rely on genetic test results but should be based on comprehensive clinical assessment.

In Group II, the families with pathogenic mutations were advised continuation of medications and screening of other family members. The two patients without an underlying mutation were weaned off beta-blockers. The patient with CPVT was reluctant to undergo ICD battery replacement, as there were no documented shocks for 10 years. Confirmation of CPVT on genetic testing re-emphasized the requirement of ICD as there was a risk of SCD.

Thus, genetic testing had diagnostic, prognostic, and therapeutic implications in our cohort.

CLINICAL IMPLICATIONS OF CARDIOGENETIC CLINICS

The recent advances in the field of genomic medicine have unraveled the heritable nature of several cardiac diseases. In LQTS, genetic testing not only confirms the diagnosis but also guides the pharmacological management. While beta-blockers are the first line of treatment in LQTS, mexiletine is the drug of choice for LQTS 3. Genetic testing helps identify carriers of disease, who could be offered targeted therapy to modify disease onset or progression. For example, *MYBPC3* mutation carriers of HCM were found to be more responsive to disease-modifying treatment with diltiazem than *MYH7* mutation carriers, in a double-blind trial.[3] The genotype-positive/phenotype-negative carriers with a family history of DCM can be followed up regularly and monitored with echocardiographic global longitudinal strain for early evidence of ventricular function impairment.

Establishment of cardiogenetic clinics in tertiary care centers can help in systematic evaluation of inherited cardiac diseases, paving the way for appropriate diagnosis and management of the index patient as well as cascade screening of asymptomatic family members.

Table 2: Details of the variants detected following the genetic analysis by next-generation sequencing and their clinical relevance

Patient number (number of family members screened)	Clinical diagnosis	Genetic analysis result-in the proband		Segregation of the variant(s) among the family members	Inheritance	Relevance (ACMG classification)
		Gene name	Amino acid change			
1 (*n*=2)	Dilated cardiomyopathy	TNNT2 (exon 10)	Arg141Gn (homozygous)	Same variant detected in heterozygous state in the unaffected father and maternal grandmother	AR	This significant variant in troponin domain has been reported previously with familial cardiomyopathy *(likely pathogenic)*
2 (*n*=3)	Dilated cardiomyopathy	NEXN (exon 12)	Glu528del (homozygous)	Same variant detected in heterozygous state in asymptomatic father, mother and unaffected sibling	AR	The variant has been reported previously with dilated cardiomyopathy *(likely pathogenic)*
3 (*n*=2)	Dilated cardiomyopathy	NEXN (exon 13)	Glu572LysfsTer2 (heterozygous)	Both the variants were detected in heterozygous state in the monozygotic asymptomatic sister and absent in the unaffected mother	AD	Frameshift variant affecting highly conserved immunoglobin domain. Mutations in this gene causes dilated cardiomyopathy *(likely pathogenic)*
		MYH7 (exon 13)	Gly414Arg (heterozygous)			Rare missense variant at conserved codon at the myosin head; motor domain. *(uncertain significance)*
4 (*n*=2)	Dilated cardiomyopathy with noncompaction	DES (exon 4)	Tyr296His (heterozygous)	Detected in the heterozygous state in the asymptomatic father and maternal grandmother	AD (?incomplete penetrance)	Rare missense variant. Incomplete penetrance reported with mutations in this gene. *(uncertain significance)*
5 (*n*=3)	Dilated cardiomyopathy with noncompaction	PRDM16 (exon 9)	Arg759Trp (heterozygous)	Detected in the heterozygous state in the affected sister and unaffected father; absent in the unaffected mother	AD	Rare missense variant. Mutations in this gene known to cause ventricular noncompaction and dilated cardiomyopathy *(uncertain significance)*
6 (*n*=4)	Dilated cardiomyopathy	RAF1 (exon 11)	Ser244Arg (homozygous)	Detected in the heterozygous state in the unaffected sibling, mother, maternal uncle and was not present in the maternal grandmother	AR	Rare conserved missense variant, autosomal dominant dilated cardiomyopathy is associated with this gene *(uncertain significance)*
7 (*n*=8)	Ventricular noncompaction	NA	NA	NA	NA	No pathogenic variant detected
8 (*n*=2)	Hypertrophic obstructive cardiomyopathy	MYH7 (exon 23)	Glu903Lys (heterozygous)	Detected in heterozygous state in the affected father and absent in the unaffected mother	AD	This significant variant has been reported previously to cause HCM *(likely pathogenic)*
9 (*n*=2)	Suspected LQTS	ECE1 (Exon 8)	Gln321Ter (heterozygous)	Detected in heterozygous state in the asymptomatic father and absent in the unaffected mother	AD (?incomplete penetrance)	Loss of function variants in this gene has been associated with cardiac defects and SIDS. *(uncertain significance)*

Contd...

Table 2: Contd...

Patient number (number of family members screened)	Clinical diagnosis	Genetic analysis result-in the proband		Segregation of the variant(s) among the family members	Inheritance	Relevance (ACMG classification)
		Gene name	Amino acid change			
		KCNE1 (exon 3)	Arg36His (heterozygous)	Detected in heterozygous state in the asymptomatic mother and absent in the unaffected father	AD	The observed variant has been reported with LQTS *(uncertain significance)*
10 (*n*=1)	Suspected LQTS	KCNQ1 (exon 7)	Gly314Ser (heterozygous)	Detected in heterozygous state in the unaffected father	AD	The observed variant lies in the ion transport domain, has been reported with LQTS *(likely pathogenic)*
		STRC (intron 24)	5' splice variant (heterozygous)	Detected in homozygous state in the father who has hearing loss	AR (affected father)	The observed variant has been reported with autosomal recessive deafness *(pathogenic)*
11 (*n*=2)	Suspected LQTS	NA	NA	NA	NA	No pathogenic variant detected
12 (*n*=2)	Suspected LQTS	NA	NA	NA	NA	No pathogenic variant detected
13 (*n*=2)	CPVT	RYR2 (exon 3)	Ser72Tyr (heterozygous)	Present in heterozygous state in unaffected mother and absent in unaffected father	AD	The observed variant lies in the ligand binding domain of the receptor. Mutations in this domain are reported with CPVT-1 *(likely pathogenic)*
14 (*n*=7)	Methemoglobinemia	CYB5R3 (exon 4)	p.Ile118_ Asp119del (homozygous)	Present in heterozygous state in the unaffected mother, father, paternal grandmother, and was absent in the brother, maternal grandmother, maternal uncle and paternal grandfather	AR	The variant lies in the oxidoreductase FAD-binding domain, wherein mutations have been reported with severe form of the disorder methemoglobinemia Type I *(likely pathogenic)*

*The Annotations in the table are based on human Genome reference- Grch37/hg19. AD: Autosomal dominant, AR: Autosomal recessive, ACMG: American College of Medical Genetics and Genomics, HCM: Hypertrophic cardiomyopathy, LQTS: Long QT syndrome, CPVT: Catecholaminergic polymorphic ventricular tachycardia, NA: Not applicable, SIDS: Sudden Infant Death Syndrome, FAD: Flavin Adenine Dinucleotide

Financial support and sponsorship

This study received funding from MedGenome Labs Ltd, Bengaluru, India.

Conflicts of interest

There are no conflicts of interest.

Saileela Rajan[1], Priya Chockalingam[2], Nageswara Rao Koneti[3], Thenral S Geetha[4], Sanghamitra Mishra[4], Calambur Narasimhan[5]

[1]Department of Pediatric Cardiology, MIOT Centre for Children's Cardiac Care, MIOT Hospitals, Chennai, Tamil Nadu, India, [2]Cardiac Wellness Institute, Chennai, Tamil Nadu, India, [3]Department of Pediatric Cardiology, Rainbow Children's Heart Institute, Hyderabad, Telangana, India, [4]MedGenome Labs Ltd., Bengaluru, Karnataka, India, [5]Department of Cardiology, Division of Cardiac Electrophysiology, AIG Hospital, Hyderabad, Telangana, India.

E-mail: drsaileelarajan@gmail.com

Submitted: 16-Jun-2021 **Revised:** 11-Jul-2021

Accepted: 18-Jul-2021 **Published:** 26-Aug-2021

REFERENCES

1. Kodde J, Hofman N, Reichert CL, van Langen IM, Willde AA. Cardio-genetic counseling in a non-university hospital. Neth Heart J 2007;15:412-4.
2. Hofman N, Tan HL, Alders M, Kolder I, de Haij S, Mannens MM, *et al.* Yield of molecular and clinical testing for arrhythmia syndromes: Report of 15 years' experience. Circulation 2013;128:1513-21.
3. Ho CY, Lakdawala NK, Cirino AL, Lipshultz SE, Sparks E, Abbasi SA, *et al.* Diltiazem treatment for pre-clinical hypertrophic cardiomyopathy sarcomere mutation carriers: A pilot randomized trial to modify disease expression. JACC Heart Fail 2015;3:180-8.

Access this article online

Quick Response Code:

Website: www.annalspc.com

DOI: 10.4103/apc.apc_123_21

How to cite this article: Rajan S, Chockalingam P, Koneti NR, Geetha TS, Mishra S, Narasimhan C. Initial experience and results of a cardiogenetic clinic in a tertiary cardiac care center in India. Ann Pediatr Card 2021;14:443-8.