Clinical and Genetic Spectrums of

Paediatric Cardiomyopathy in Hong Kong

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Paediatric Cardiomyopathy

Rare (1 in 100,000)

Risk of sudden death

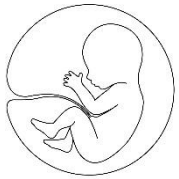
Exercise and schooling

Diagnostic challenge

Associated metabolic and neurological diseases

Management dilemmas

Reproductive decisions

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Objectives

- To analyze the clinical and genetic characteristics of cardiomyopathy of Hong Kong children
- To identify the genetype-phenotype correlations in paediatric patients with cardiomyopathy

Objectives

Methods

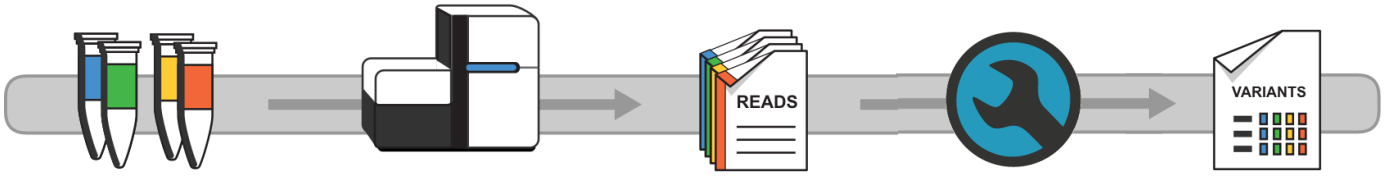
<18 years old
Primary cardiomyopathies (HCM, DCM, RCM, LVNC, ARVC)
Follow up in QMH paediatric cardiology clinic

Retrospective review of clinical records

Analyze existing genetic results (WES, gene panels or targeted testing) by genetic analyst
Perform WES for untested patients
In accordance to **ACMG guidelines**[1]
Cascade screening when indicated

**WES = whole exome sequencing*

WES Analysis Workflow



DNA extraction | Exome Capture & Sequencing | Raw Reads | Bioinformatics Pipeline | Variant interpretation

WES Data

Gene list n=138
(retrieved from ClinGen, ACMG, and other literatures)

MAF<0.001 (recommended for cardiomyopathy)
In silico prediction
Segregation analysis

LP/P

Negative

Open Exome Analysis

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ACMG PRACTICE RESOURCE | Genetics inMedicine

Corrected: Correction

Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

Ray E. Hershberger, MD[1], Michael M. Givertz, MD[2], Carolyn Y Ho, MD[3], Daniel P. Judge, MD[4], Paul F. Kantor, MD[5], Kim L. McBride, MD[6], Ana Morales, MS, LGC[1], Matthew R. G. Taylor, MD[7], Matteo Vatta, PhD[8,9,10] and Stephanie M. Ware, MD, PhD[9,11] on behalf of the ACMG Professional Practice and Guidelines Committee

Official journal of the American College of Medical Genetics and Genomics

SPECIAL ARTICLE | Genetics inMedicine

Open

Adaptation and validation of the ACMG/AMP variant classification framework for *MYH7*-associated inherited cardiomyopathies: recommendations by ClinGen's Inherited Cardiomyopathy Expert Panel

Results

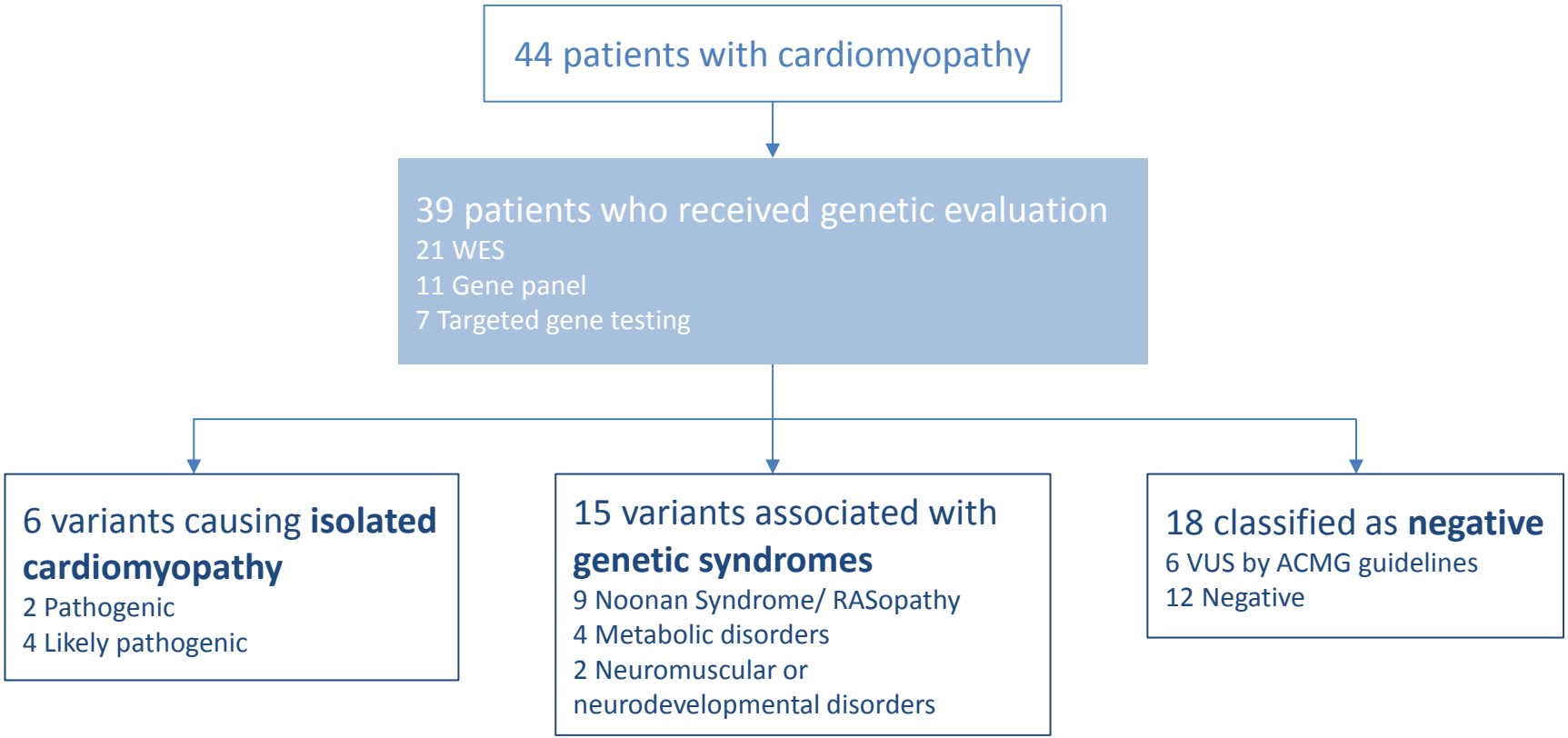
Demographic and clinical characteristics

Clinical Characteristics	No of patients (N= 44)
Demographic features	
Age at latest follow-up (years)	9.8 ±4.2
Gender (male/female)	29 (65.9%)/ 15 (34.1%)
Median follow-up duration (range) (years)	7.2 (0.3 – 16.5)
Median age at initial presentation (range) (years)	0.3 (0.0 – 14.9)
Type of Cardiomyopathy	
Hypertrophic cardiomyopathy (HCM)	19 (43.2%)
Dilated cardiomyopathy (DCM)	20 (45.5%)
Restrictive cardiomyopathy (RCM)	2 (4.5%)
Left ventricular non-compaction (LVNC)	3 (6.8%)
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	0

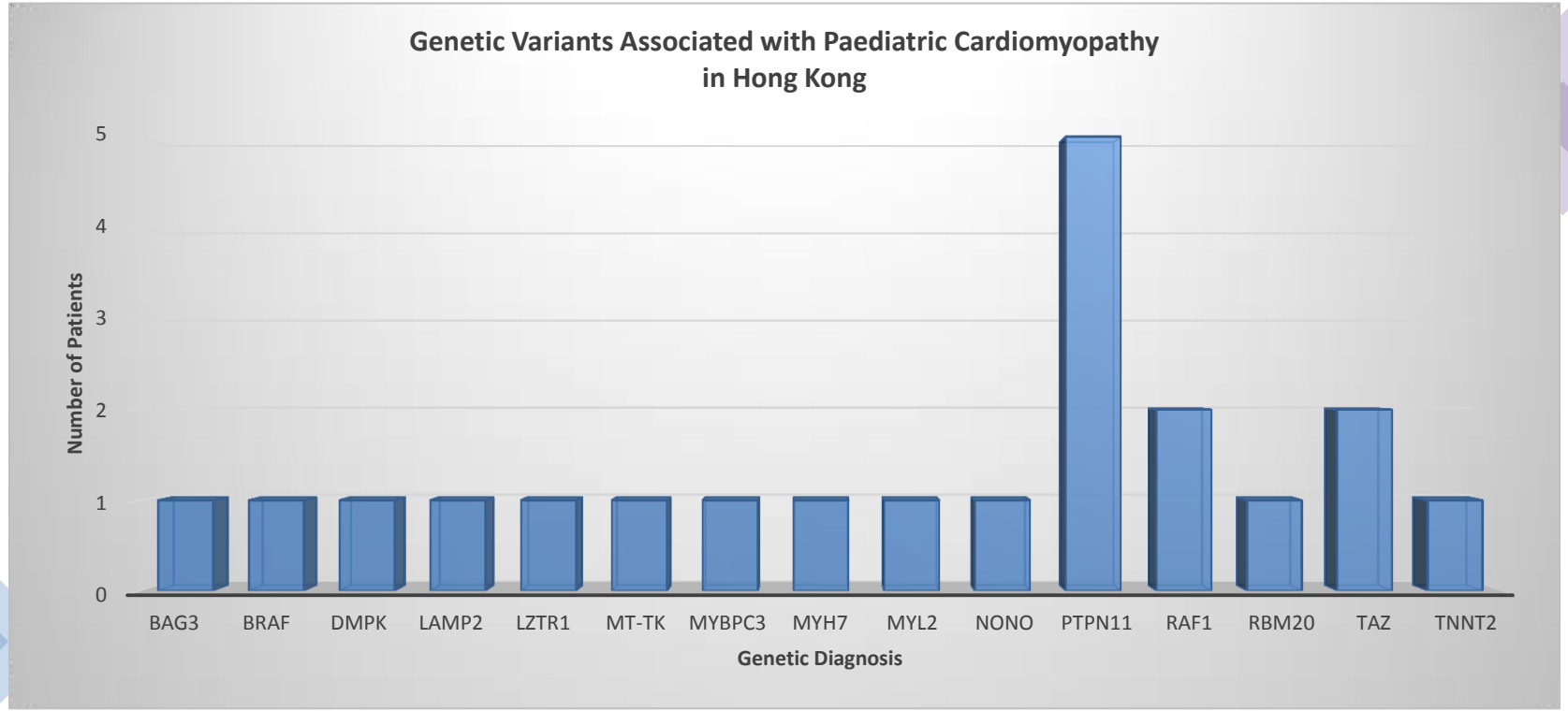
The Clinical Spectrum

Clinical Characteristics	No of patients (N= 44)
NYHA Class 3 or above	3 (6.8%)
History of arrhythmia	6 (13.6%)
Atrial tachyarrhythmia	3 (6.8%)
Ventricular tachyarrhythmia	3 (6.8%)
ICD/ CRT-D implantation	4 (9.1%)
Mechanical circulatory support	5 (11.4%)
Active	3 (6.8%)
Previous	2 (4.5%)
Listing for heart transplantation	4 (9.1%)
Received heart transplantation	2 (4.5%)

Findings of Genetic Evaluation

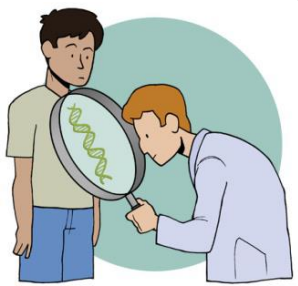


The Genetic Spectrum



Genotype-phenotype Correlations

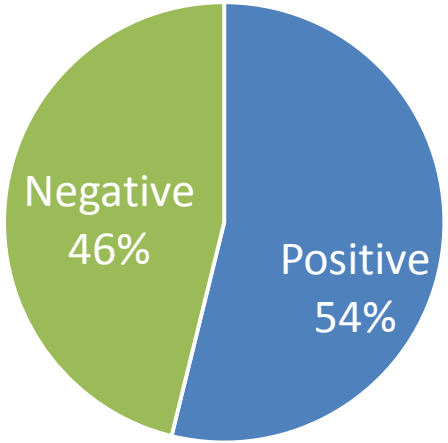
	Gene Positive (*n*= 21)	Gene Negative (*n*= 18)	*p*
Male sex	13 (61.9%)	13 (72.2%)	0.73
Age at initial presentation (years)	2.1 ±4.2	2.9 ±4.2	0.53
Type of Cardiomyopathy	12 HCM 6 DCM 0 RCM 3 LVNC	6 HCM 10 DCM 2 RCM 0 LVNC	0.36
Syndromic/ extracardiac manifestations	11 (52.4%)	1 (5.6%)	0.002
NYHA class 3 or above	0	2 (11.1%)	0.21
History of Arrhythmia	1 (4.8%)	4 (22.2%)	0.16
ICD/ CRT-D implanted	1 (4.8%)	3 (16.7%)	0.32
Indicated for Device	1 (4.8%)	3 (16.7%)	0.32
Indicated for HTx	1 (4.8%)	3 (16.7%)	0.32



Key Findings

Diagnostic Yield was 54%

Disease-causing variants identified in QMH Paediatric Cardiomyopathy Cohort



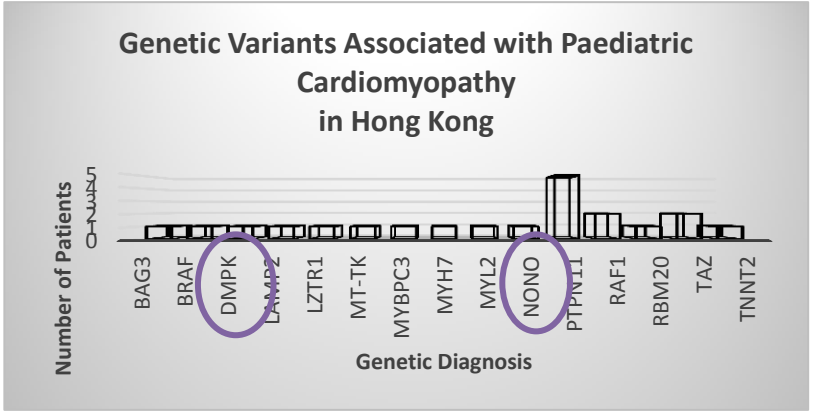
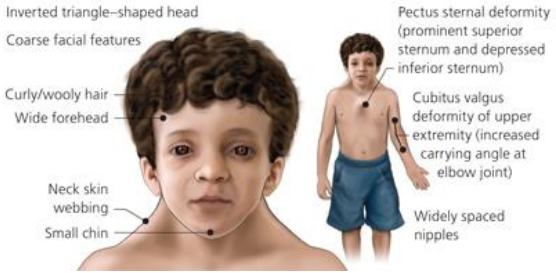


Table 3. Selected Genes in Association With Cardiomyopathy

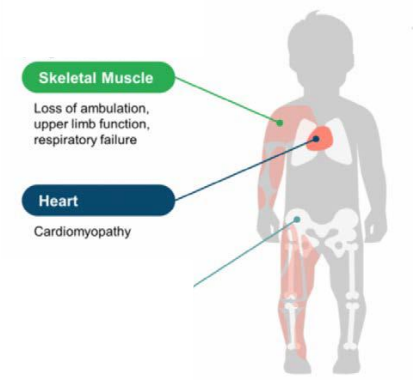
Cardiomyopathy	Core Genes*	Estimates of Genetic Testing Diagnostic Yield	ACMG Secondary Findings Gene List	Metabolic Causes of Cardiomyopathy	Examples of Genetic Syndromes
HCM	*MYH7, MYBPC3, TNNT2, TNNC1, TNNI3, TPM1, MYL2, MYL3, ACTC1, ACTN2, CSRP3, PLN, TTR, PRKAG2, LAMP2, GLA*	30%–60%	*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA*	*GAA* (Pompe); Mitochondrial disease genes	RASopathies (eg, Noonan syndrome, others); Friedreich ataxia
DCM	*TTN*,† *LMNA, MYH7, TNNT2, BAG3, RBM20, TNNC1, TNNI3, TPM1, SCN5A, PLN.* For testing, all HCM and ARVC genes are recommended to be included.	10%–40%		Mitochondrial disease genes	Muscular dystrophies; Alström syndrome
ARVC	*DES, DSC2, DSG2, DSP, JUP, LMNA, PKP2, PLN, RYR2, SCN5A, TMEM43, TTN*†; consider full DCM panel	10%–50%	PKP2, DSP, DSC2, TMEM43, DSG2, RYR2 SCN5A		Naxos syndrome; Carvajal syndrome
RCM	Consider HCM or DCM gene panel	10%–60%			
LVNC	Use the gene panel for the cardiomyopathy identified in association with the LVNC phenotype	Unknown		Mitochondrial disease genes, including *TAZ* in Barth syndrome	1p36 deletion syndrome; RASopathies

Recommended Gene Selection according to HFSA 2018 guideline

Rare or novel genetic variants that are not included in existing gene panels were identified



Am Fam Physician. 2014 Jan



Presence of syndromic/ extracardiac manifestations were associated with positive genetic findings

Take Home Messages

Genetic testing is recommended for paediatric patients with cardiomyopathy

Although gene panels are still the mainstay of genetic testing , whole exome sequence is powerful to identify rare or novel variants in special circumstances

Patients with syndromic/ extracardiac manifestations are more likely to have an identified genetic variant

References

1. Hershberger, Ray E., et al. “Genetic Evaluation of Cardiomyopathy: a Clinical Practice Resource of the American College of Medical Genetics and Genomics (ACMG).” *Genetics in Medicine*, vol. 20, no. 9, 2018, pp. 899–909.
2. Wilkinson, James D., et al. “The Pediatric Cardiomyopathy Registry and Heart Failure: Key Results from the First 15 Years.” *Heart Failure Clinics*, vol. 6, no. 4, 2010, pp. 401–413.

Thank You

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