Genetic Approach to Cardiomyopathy

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Types of Cardiomyopathy

- Hypertrophic cardiomyopathy (HCM)
- Dilated cardiomyopathy (DCM)
- Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)
- Restrictive cardiomyopathy (RCM)
- Others, e.g., left ventricular non-compaction (LVNC)

Hypertrophic Cardiomyopathy
- Fabry disease
- Friedreich's ataxia
- Noonan syndrome
- Costello syndrome
- LEOPARD syndrome
- Cardio-Facio-cutaneous syndrome
- Hunter syndrome
- Hurler syndrome
- Hurler-Scheie syndrome
- Maroteaux-Lamy syndrome
- I-cell disease
- Pompe syndrome
- Beckwith-Wiedemann syndrome
- Mitochondrial myopathy
- Cytochrome C oxidase deficiency
- Barth syndrome
- Danon disease
- Down syndrome
- Proteus syndrome
- Yunis-Varon syndrome
- Pallister-Killian mosaic syndrome
- Medium-chain acyl CoA dehydrogenase deficiency (MCAD)
- Long-chain acyl CoA dehydrogenase deficiency (LCAD)
- Multiple sulfatase deficiency

Dilated Cardiomyopathy
- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Emery-Dreifuss muscular dystrophy
- Limb Girdle muscular dystrophy
- Myotonic muscular dystrophy
- Mitochondrial myopathy
- Kearns-Sayre syndrome
- Myotubular (centronuclear) myopathy
- Nemaline myopathy
- Cytochrome C oxidase deficiency
- Barth syndrome
- Danon disease
- Fanconi anemia
- Diamond-Blackfan syndrome
- Sickle cell anemia
- Medium-chain acyl CoA dehydrogenase deficiency (MCAD)
- Long-chain acyl CoA dehydrogenase deficiency (LCAD)
- Maroteaux-Lamy syndrome
- Fabry disease

Restrictive Cardiomyopathy
- Amyloidosis
- Sarcoidosis
- Fabry disease
- Endomyocardial fibrosis
- Loffler's eosinophilic endomyocardial diseas
- Pseudoxanthoma elasticum
- Desmin myopathy
- Gaucher disease

Left Ventricular Noncompaction
- Mitochondrial myopathy
- Barth syndrome

Arrhythmogenic Right
- Ventricular Dysplasia
- Naxos disease
- Carvajal syndrome

Cardiomyopathy Associated with Systemic Diseases

Hershberger et al., J Cardiac Fail 2009

Heart Failure Society of America (HSFA) Guideline for Genetic Evaluation of Cardiomyopathy

- Family history taking
- Clinical screening in asymptomatic first-degree relatives
- Molecular genetic testing
- Genetic counseling: mendelian or complex

Recommendation for Careful Family History of ≥ 3 Generations

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmogenic right ventricular dysplasia (ARVD)	A
Left ventricular noncompaction (LVNC)	A
Restrictive cardiomyopathy (RCM)	B
Cardiomyopathies associated with extracardiac manifestations (Table 4)	A

Hershberger et al., J Cardiac Fail 2009

Clinical Screening in Asymptomatic First-Degree Relatives

a. Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmogenic right ventricular dysplasia (ARVD)	A
Left ventricular noncompaction (LVNC)	B
Restrictive cardiomyopathy (RCM)	B
Cardiomyopathies associated with extracardiac manifestations (Table 4)	A

Hershberger et al., J Cardiac Fail 2009

Clinical Screening Methods

- History
- Physical examination
- Electrocardiogram
- Echocardiogram
- Creatinine kinase (at the initial evaluation only)
- Signal-averaged electrocardiogram (SAECG) in ARVD only
- Holter monitoring in HCM, ARVD
- Exercise treadmill testing in HCM
- Magnetic resonance imaging in ARVD

Hershberger et al., J Cardiac Fail 2009

Clinical Screening Intervals

Cardiomyopathy Phenotype	Interval if genetic testing is negative and/or if clinical family screening is negative	Screening interval if a mutation is present	Level of Evidence
Hypertrophic	Every 3 years until 30 years of age, except yearly during puberty; after 30 years, if symptoms develop	Every 3 years until 30 years of age, except yearly during puberty; every 5 years thereafter.	B
Dilated	Every 3–5 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	B
ARVD/C	Every 3–5 years after age 10	Yearly after age 10 to 50 years of age.	C
LVNC	Every 3 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	C
Restrictive	Every 3–5 years beginning in adulthood	Yearly in childhood; every 1–3 years in adults.	C

Hershberger et al., J Cardiac Fail 2009

Consideration of Genetic Testing

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	B
Arrhythmogenic right ventricular dysplasia (ARVD)	A
Left ventricular noncompaction (LVNC)	C
Restrictive cardiomyopathy (RCM)	C
Cardiomyopathies associated with other extracardiac manifestations	A

Hershberger et al., J Cardiac Fail 2009

Specific Genes Available for Screening

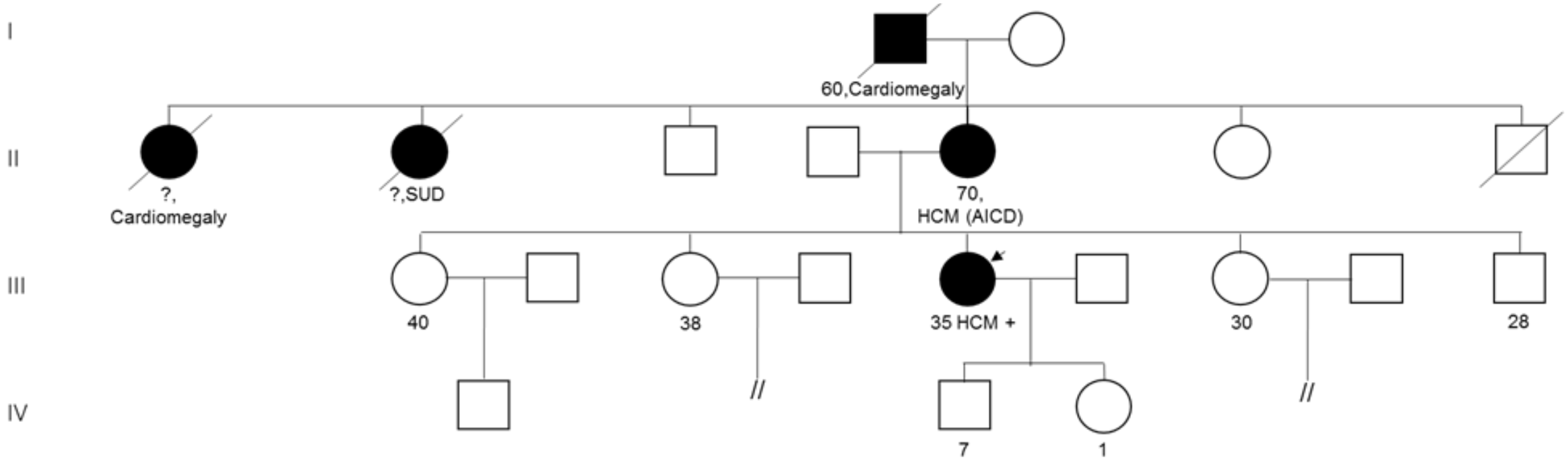
Cardiomyopathy Phenotype	Gene Tests Available*	Yield of Positive Results
HCM	MYH7, MYBPC3, TNNT2 TNNI3, TPMI, ACTC, MYL2, MYL3.	MYH7, MYBPC3 each account for 30%–40% of mutations, TNNT2 for 10%–20%. Genetic cause can be identified in 35%–45% overall; up to 60%–65% when the family history is positive.
DCM	LMNA, MYH7, TNNT2, SCN5A, DES, MYBPC3, TNNI3, TPMI, ACTC, PLN, LDB3 and TAZ.	5.5%, 4.2%, 2.9%, for LMNA, MYH7, and TNNT2, respectively. All data are from research cohorts.
ARVD	DSP, PKP2, DSG2, DSC2	6%–16%, 11%–43%, 12%–40%, for DSP, PKP2, and DSG2, respectively
LVNC	Uncertain—see discussion	Uncertain—see discussion
RCM	Uncertain—see discussion	Uncertain—see discussion

Hershberger et al., J Cardiac Fail 2009

Genetic Counseling

- Mendelian for family with strong family and mutation detected
  - 50% chance for autosomal dominant
  - 25% chance for autosomal recessive if both parents are carriers
- Complex disease counseling for others
  - Genetics combined with environmental factors

Lessons from Hypertrophic Cardiomyopathy



Heterozygous p.Gln508* in MYBPC3

Phusanti et al., *in press*

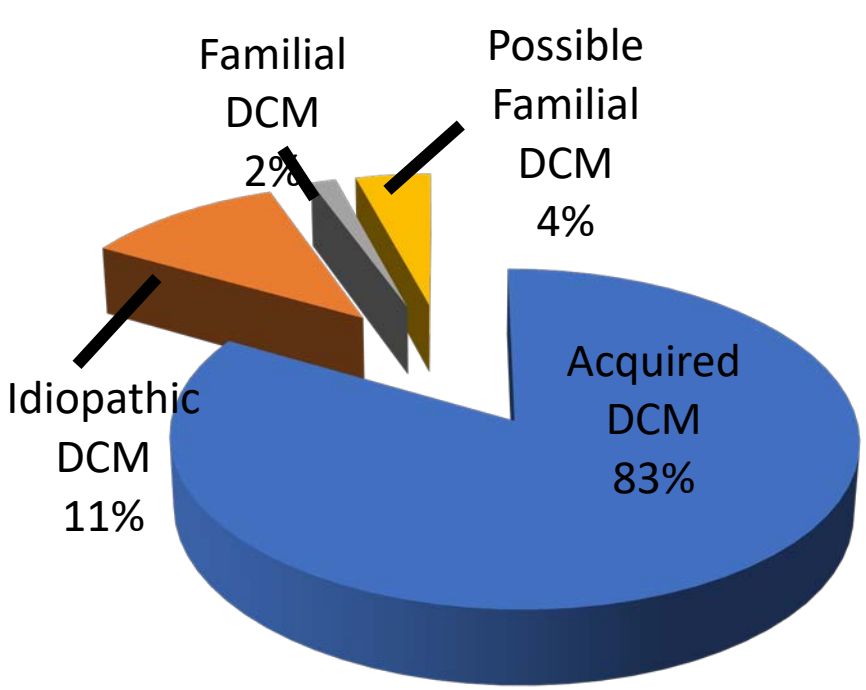
Guidelines for Clinical Screening of Healthy Family Members with Physical Examination, Echocardiography, and Electrocardiogram (ECG)

Age	Screening Guideline
<12 years	Optional but recommended, particularly if any of the following are present: Family history of early HCM-related death, early development of LVH, or other adverse complications Competitive athlete in intense training program Symptoms Other clinical findings that suggest early LVH
12-18 years	Repeat evaluation every 12-18 months
>18-21 years	Repeat evaluation approximately every 3-5 years or in response to any change in symptoms Tailor evaluation if the family has late-onset LVH or HCM-related complications

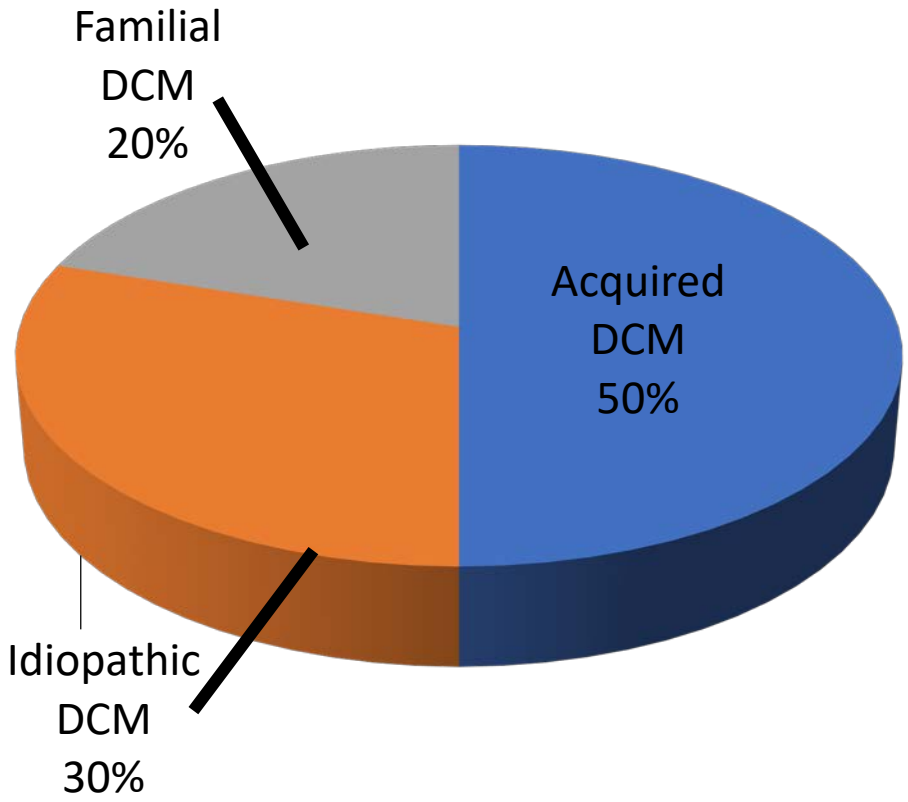
Maron BJ, Cardiac Rev 2002

Lessons from Dilated Cardiomyopathy

Srisukh, et al., 2014*



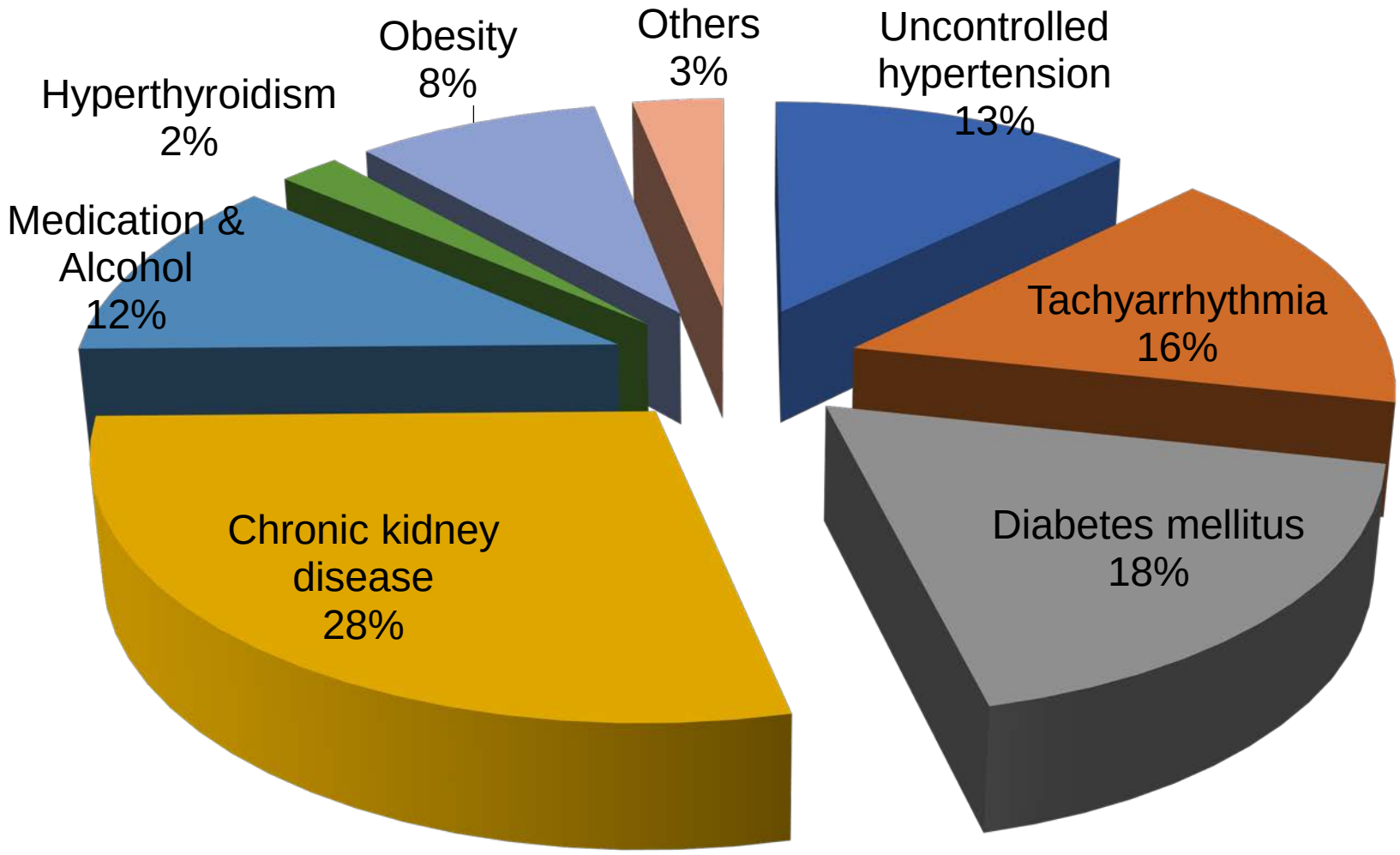
Global studies**



*Srisukh Etiologies of Dilated Cardiomyopathy in Patients Manifested with Congestive Heart Failure in Ramathibodi Hospital, Ramathibodi medical journal Vol 37. No.4;November 2014

**Update 2011: clinical and genetic issues in familial dilated cardiomyopathy.
J Am Coll Cardiol. 2011 Apr 19;57(16):1641-9

Etiologies of acquired DCM in Ramathibodi Hospital



Srisukh S, MD., Trachoo O, MD., Ph.D., Tangchareon T, MD. Etiologies of Dilated Cardiomyopathy in Patients Manifested with Congestive Heart Failure in Ramathibodi Hospital, Department of Medicine, Ramathibodi medical journal Vol 37. No.4;November – December 2014.

Summary of genetic variants found in patients diagnosed with idiopathic and familial DCM in Ramathibodi Hospital

ID	Sex	Age (years)	Family history	Genes	mRNA	protein	Zygosity	Classification
001	F	54	Pos	*TTN*	c.71731C>T	p.arg23911*	Het	Likely pathogenic
002	M	58	Pos	*TTN* *DMD*	c.9323A>G c.163G>A	p.Arg3585Cys p.Asn756Ser	Het Hem	VUS VUS
003	F	50	Neg	*SCN5A*	c.3575G>A	p.Arg1192Gln	Het	Known Pathogenic
004	M	57	Neg	*SCN5A*	c.3575G>A	p.Arg1192Gln	Het	Known Pathogenic
005	M	37	Neg	*LDB3*	c.1903G>A	p.Trp388Arg	Het	Likely pathogenic
006	M	57	Neg	*PSEN2* *LDB3*	C.640G>T C.493C>T	p.Val214Leu p.Arg165Trp	Het Het	VUS VUS
007	F	43	Neg	*TTN*	c.1423G>A	p.Ser3373Asn	Het	VUS
008	M	74	Neg	No variant found	N/A	N/A	N/A	N/A
009	M	56	Neg	No variant found	N/A	N/A	N/A	N/A

Mukdadilok et al., *in press*

Thank you for your attention