Genetics of Cardiomyopathies
Genetics of cardiomyopathies

- Existing genetic paradigm for common forms of cardiomyopathy
- Role of genetic testing in clinical management
- Potential for new therapies
- Future challenges
“A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality.”

ESC Working Group on Myocardial Pericardial Diseases (Elliott P et al. EHJ 2007)
Classification of Cardiomyopathies

Davies M. Heart 2000;83:469-474
Key Points

• All cardiomyopathies can be inherited
• Most are autosomal dominant
• Age related penetrance is usual
• Variable clinical expression
Hypertrophic Cardiomyopathy
A systematic review and meta-analysis of genotype–phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations

Luís R Lopes, M Shafiqur Rahman, Perry M Elliott

Heart. 2013 May 14. [Epub ahead of print]
Arrhythmogenic right ventricular cardiomyopathy
Right Ventricular Dysplasia: A Report of 24 Adult Cases

Frank I. Marcus, M.D., Guy H. Fontaine, M.D., Gerard Guiraudon, M.D., Robert Frank, M.D., Jean L. Laurenceau, M.D., Christine Malergue, M.D., and Yves Grosgoeit, M.D.

Circulation 1982;2:65
Ventricular tachycardia of left bundle branch block configuration in patients with isolated right ventricular dilatation

Clinical and electrophysiological features

EDWARD ROWLAND,* WILLIAM J McKENNA,† DECLAN SUGRUE, ROBIN BARCLAY, RODNEY A FOALE, DENNIS M KRIKLER

From the Division of Cardiovascular Disease, Royal Postgraduate Medical School, Hammersmith Hospital, London

Br Heart J 1984 51: 15-24
Cardiocutaneous syndromes ("Naxos disease")

Protonarious N and Tsatsopoulou
ARVC: A Disease of Cell-to Cell Adhesion?

Plakoglobin
Desmoplakin
Plakophilin 2
Desmoglein 2
Desmocollin 2
Familial Evaluation in Arrhythmogenic Right Ventricular Cardiomyopathy
Impact of Genetics and Revised Task Force Criteria

Giovanni Quarta, MD; Alison Muir, MD, MRCP; Antonios Pantazis, MD; Petros Syrris, PhD; Katja Gehmlich, PhD; Pablo Garcia-Pavia, MD; Deirdre Ward, MBBS, MRCPI; Srijita Sen-Chowdhry, MBBS, MD (Cantab); Perry M. Elliott, MBBS, MD, FRCP; William J. McKenna, MD, DSc, FRCP

56/100 families ≥1 definite or probable mutation (6 digenic)

Circulation. 2011 Jun 14;123(23):2701-9
Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Familial disease (%)</th>
</tr>
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<tbody>
<tr>
<td>Fuster 1981</td>
<td>104</td>
<td>2</td>
</tr>
<tr>
<td>Michels 1985</td>
<td>169</td>
<td>6</td>
</tr>
<tr>
<td>Fragola 1988</td>
<td>12</td>
<td>33</td>
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<tr>
<td>Griffin 1988</td>
<td>32</td>
<td>10</td>
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<tr>
<td>Valentine 1989</td>
<td>184</td>
<td>9</td>
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<tr>
<td>Mestroni 1990</td>
<td>165</td>
<td>7</td>
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<tr>
<td>Michels 1992</td>
<td>59</td>
<td>20</td>
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<td>Zachara 1993</td>
<td>105</td>
<td>13</td>
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<td>Keeling 1995</td>
<td>40</td>
<td>25</td>
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<tr>
<td>Honda 1995</td>
<td>117</td>
<td>25</td>
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<tr>
<td>Gregori 1996</td>
<td>100</td>
<td>30</td>
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</tbody>
</table>
Genetics of DCM
Dilated Cardiomyopathy

J Am Coll Cardiol 2011;57:1641–9)
HCM
Sarcomere

DCM
Cytoskeleton
Sarcomere
Nuclear envelope...

ARVC
Desmosome
WHY OFFER GENOTYPING?
Why Offer Genotyping?

– Confirmation of Diagnosis?
– Management?
– Screening/management of family?
Cardiomyopathy is a **clinical** diagnosis

- ECG/Echo
- Cardiomyopathy
- CMR
  - Biopsy
  - Genetics
  - Blood screen
Cardiomyopathies

- HCM
- DCM
- ARVC
- RCM
- Unclassified

Familial/Genetic
- Unidentified gene defect

Non-familial/Non-genetic
- Disease sub-type*
- Idiopathic
- Disease sub-type*

### Table 1: Examples of different diseases that cause cardiomyopathies

<table>
<thead>
<tr>
<th>Hom</th>
<th>DCM</th>
<th>ARVC</th>
<th>RCM</th>
<th>Undiagnosed</th>
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</thead>
<tbody>
<tr>
<td>Familial</td>
<td>Familial, unknown gene</td>
<td>Familial, unknown gene</td>
<td>Familial, unknown gene</td>
<td>Familial, unknown gene</td>
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<tr>
<td></td>
<td>Sarcomeric protein mutations (see HCM)</td>
<td>Intercalated disc protein mutations</td>
<td>Sarcomeric protein mutations</td>
<td>Sarcomeric protein mutations</td>
</tr>
<tr>
<td></td>
<td>B-myosin heavy chain</td>
<td>Plakoglobin</td>
<td>Muscle LIM protein</td>
<td>Tropomodulin</td>
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<tr>
<td></td>
<td>Cardiac troponin I</td>
<td>Desmoplakin</td>
<td>TCAP</td>
<td>Plakophilin 2</td>
</tr>
<tr>
<td></td>
<td>Troponin-T</td>
<td>Cardiac troponin I</td>
<td>Cytoskeletal genes</td>
<td>Desmoglin 2</td>
</tr>
<tr>
<td></td>
<td>α-tropomyosin</td>
<td>Dystrophin</td>
<td>Metavinculin</td>
<td>Desmoscinol 2</td>
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<tr>
<td></td>
<td>Essential myosin light chain</td>
<td>Desmin</td>
<td>Sarcoglycan complex</td>
<td>Cardiac sarcoendocrine</td>
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<tr>
<td></td>
<td>Regulatory myosin light chain</td>
<td>Epicardin</td>
<td>CRMP4</td>
<td>receptor (flyR2)</td>
</tr>
<tr>
<td></td>
<td>Cardiac actin</td>
<td>Nuclear membrane</td>
<td></td>
<td>Transforming growth factor β3 (TGFβ3)</td>
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<tr>
<td></td>
<td>α-myosin heavy chain</td>
<td>Lamin A/C</td>
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<tr>
<td></td>
<td>Titin</td>
<td>Emerin</td>
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<td></td>
<td>Troponin C</td>
<td>Mildly dilated CM</td>
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<td></td>
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<tr>
<td></td>
<td>Muscle LIM protein</td>
<td>Intercalated disc protein mutations (see ARVC)</td>
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<td></td>
<td>Glycogen storage disease (e.g. Pompe;</td>
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<td></td>
<td>PINK2, Forbes', Danon)</td>
<td>Mitochondrial cytopathy</td>
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<tr>
<td></td>
<td>Lyssosomal storage diseases (e.g.</td>
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<tr>
<td></td>
<td>Anderson-Fabry, Hurler's)</td>
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<td></td>
<td>Disorders of fatty acid metabolism</td>
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<tr>
<td></td>
<td>Carnitine deficiency</td>
<td></td>
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<td></td>
<td>Phosphorylase B kinase deficiency</td>
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<tr>
<td></td>
<td>Mitochondrial cardiomyopathies</td>
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<tr>
<td></td>
<td>Syndromic HCM</td>
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<tr>
<td></td>
<td>Noonan's syndrome</td>
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<tr>
<td></td>
<td>LEOPARD syndrome</td>
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<td></td>
<td>Friedreich's ataxia</td>
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<td></td>
<td>Beckwith-Wiedemann syndrome</td>
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<td></td>
<td>Swyer's syndrome</td>
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<tr>
<td></td>
<td>Other</td>
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<tr>
<td></td>
<td>Phospholamban promoter</td>
<td></td>
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<tr>
<td></td>
<td>Familial amyloid</td>
<td></td>
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<tr>
<td></td>
<td>Obesity</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Infants of diabetic mothers</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Athletic training</td>
<td></td>
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<tr>
<td></td>
<td>Amyloid (AL/pretalbumin)</td>
<td></td>
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<tr>
<td></td>
<td>Myocarditis (Infective/toxic/immune)</td>
<td>Inflammation?</td>
<td>Amyloid (AL/pretalbumin)</td>
<td>Tako Tsubo</td>
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<tr>
<td></td>
<td>Kawasaki disease</td>
<td></td>
<td>Scleroderma</td>
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<tr>
<td></td>
<td>Dilated cardiomyopathy (Churg Strauss syndrome)</td>
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<td>Endomyocardial fibrosis</td>
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<td></td>
<td>Viral persistence</td>
<td></td>
<td>Hyperreinophous syndrome</td>
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<tr>
<td></td>
<td>Drugs</td>
<td></td>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td></td>
<td>Chromosomal cause</td>
<td></td>
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<tr>
<td></td>
<td>Endocrine</td>
<td></td>
<td>Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nutritional — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia</td>
<td></td>
<td>Cardiomyopathy heart disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
<td></td>
<td>Metastatic cancers</td>
<td></td>
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<tr>
<td></td>
<td>Tachycardio-myopathy</td>
<td></td>
<td>Radiation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Drugs (anthracyclines)</td>
<td></td>
</tr>
</tbody>
</table>

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.
DOES A (GENETIC) DIAGNOSIS ALTER MANAGEMENT?
Genetic “guided” therapies in cardiomyopathy

- Pompe ERT
- Anderson-Fabry Disease ERT
- ATTR Amyloid Diflunisal, stabilisers, Tx…
Lamin AC
Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers

A European Cohort Study

(J Am Coll Cardiol 2012;59:493–500)

NSVT, LVEF 45%, male

+ non-missense mutations (ins-del/truncating or mutations affecting splicing)
Management of laminopathies

- Anti-failure therapy
- Anticoagulation
- ICD when bradycardia/AVB/ventricular arrhythmia
- Transplantation
Will it help the family?
(Predictive/Cascade Testing)
Reasons for PT in HCM

- **Prevention of Complications**
  - Sudden Death
  - Stroke
  - (Heart failure)

- **Psychosocial**
  - select career, sports activities
  - relieve uncertainty
  - time to adjust
  - Family “well being” – anxious parents etc
Economic

A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy

Jodie Ingles,1,2 Julie McGaughran,3,4 Paul A Scuffham,5 John Atherton,4,6 Christopher Semsarian1,2,7

Ingles J et al. Heart. 2012 Apr;98(8) 625-30

DNA testing for hypertrophic cardiomyopathy: a cost-effectiveness model

Sarah Wordsworth1*, José Leal1, Edward Blair2,3, Rosa Legood4, Kate Thomson5, Anneke Seller5, Jenny Taylor6, and Hugh Watkins3


Euro 587 per quality-adjusted life-year gained,
Euro 9509 per additional life-year gained

The incremental cost per life year saved was Euro 14 397
MUTATION GUIDED THERAPY?
Gene transfer: Viral Vectors
Duchenne Muscular Dystrophy

Gowers Sign

Using hands to push on legs to stand

shoulders and arms are held back awkwardly when walking

swayback

weak butt muscles (hip straighteners)

Knees may bend back to take weight.

thick lower leg muscles (the 'muscle' is mostly fat, and not strong)

tight heel cord (contracture); child may walk on toes

Weak muscles in front of leg cause 'foot drop' and tiptoe contractures.

belly sticks out due to weak belly muscles (child is poor at sit-ups)

thin, weak thighs (especially front part)

poor balance; falls often

awkward, clumsy if walking
Fig. 4 Molecular characteristics of BMD. a Relative frequencies of different DMD mutations in the BMD patient population. b Distribution of mutations along the DMD gene. Deletions (blue) and duplications (red) are mapped in the upper part of the figure. Arrows indicate point mutations (Nonsense mutations in pink, small insertions/deletions in green, splicing mutations in black)
Gene Transfer: DMD

Human Molecular Genetics, 2011, Vol. 20,
Exon Skipping

**A**

Duchenne muscular dystrophy

- Pre-mRNA: Deletion of exon 50
  - 48 - 49 - 50 - 51 - 52
- Splicing
- mRNA: Reading frame disrupted
  - 48 - 49 - 51 - 52
- Translation stops prematurely
- Protein: truncated/unstable non-functional dystrophin

**Exon skipping approach**

- Pre-mRNA: AO masks exon 51
  - 48 - 49 - 50 - 51 - 52
- Skipping of exon 51
- mRNA: Reading frame restored
  - 48 - 49 - 52
- Translation continues
- Protein: internally deleted but functional dystrophin
# Myotonic Dystrophy

## Systemic involvement in DM1

<table>
<thead>
<tr>
<th>System</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Cataract</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>Diabetes, Thyroid dysfunction, Hypogonadism</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Dysphagia, Constipation, Gallbladder stones, Pseudo-obstruction</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Cognitive impairment, Mental retardation, Attentive disorders</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
</tr>
</tbody>
</table>
Genetics

DM1 Chromosome
19q 13.3
DM Protein kinase (DMPK)

DM2 Chromosome
3q21
Zn Finger 9

Science 2001: 293:816-17
RNA Toxicity

HUMAN GENE THERAPY 24:499–507 (May 2013)
RNA Toxicity: DM1
NOVEL THERAPIES IN SARCOMERE DISEASE
Spudich JA. Biophysical Journal Volume 106 March 2014 1236–1249
“Down-stream” targets

- Cross-bridge kinetics
- Calcium sensitivity & cycling
- Signalling pathways and protein degradation
- Cardiomyocyte-fibroblast cross-talk
- Energetics
- Gene therapy
Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients With Advanced Heart Failure

The CUPID 2 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b)
Key Message

- Aetiology and pathogenesis are critical in the development of new therapies
FUTURE CHALLENGES
The INHERITANCE Next-Generation Sequencing Study: A Comprehensive Atlas of the Genetics of Human Dilated Cardiomyopathy

Jan Haas1,2, Karen S. Frese1,2, Barbara Peil1, Wanda Kloos1, Andreas Keller1, Rouven Nietsch1,2, Zhu Feng1, Sabine Müller1, Elham Kayvanpour1,2, Britta Vogel1, Farbod Sedaghat-Hamedani1,2, Wei-Keat Lim1, Xiaohong Zhao1, Dmitriy Fradkin1, Doreen Köhler1, Simon Fischer1, Jennifer Franke1, Sabine Marquart1,2, Ioana Barb1,2, Ali Amir1,2, Philipp Ehlermann1, Derliz Mereles1,2, Tanja Weis1,2, Andreas Kremer1, Vanessa King1, Emil Wirsz1,2, Richard Isnard1,2, Michel Komajda1, Diego Garcia-Giustini1, Martin Ortiz-Genga1, Marisa Crespo-Leiro1,1,1, Anders Waldenstrom1, Martino Bolognesi1, Riccardo Bellazzi1,2, Stellan Mörner1,6, Justo Lorenzo Bermejo1, Lorenzo Monserrat1,1,1,1, Eric Villard1,6, Jens Mogensen1, Yigal Pinto1, Philippe Charron1, Perry Elliott1, Eloisa Arbustini1, Hugo A. Katus1,2, Benjamin Meder1,2,8

Table 2: Multiple mutations affecting single patients.

<table>
<thead>
<tr>
<th>Number of mutations</th>
<th>HGMD1 variant pos Patients, (%)</th>
<th>Category Ib-III2 variant pos Patients, (%)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>345 (54.0%)</td>
<td>171 (26.7%)</td>
</tr>
<tr>
<td>≥1</td>
<td>294 (46.0%)</td>
<td>468 (73.2%)</td>
</tr>
<tr>
<td>≥2</td>
<td>82 (12.8%)</td>
<td>243 (38.0%)</td>
</tr>
<tr>
<td>≥3</td>
<td>14 (2.2%)</td>
<td>82 (12.8%)</td>
</tr>
<tr>
<td>≥4</td>
<td>2 (0.3%)</td>
<td>16 (2.5%)</td>
</tr>
</tbody>
</table>

1 = category Ib. 2 = either category Ib or category II or category III.
Genetic complexity in hypertrophic cardiomyopathy revealed by high-throughput sequencing

Luis R. Lopes,¹ Anna Zekavati,² Petros Syrris,¹ Mike Hubank,² Claudia Giambartolomei,³ Chrysoula Dalageorgou,¹ Sharon Jenkins,¹ William McKenna,¹ Uk10k Consortium,⁴ Vincent Plagnol,³ Perry M Elliott¹

- **243 (48%)**: 173 distinct rare variants in the 8 sarcomeric protein genes most commonly associated with HCM

- **317 (63%)**: 278 rare variants in genes previously associated with HCM

Genotype-phenotype associations:
NON SARCOMERE genes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Gene</th>
<th>Gene-positive</th>
<th>Gene-negative</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA diameter (mm)</td>
<td>SCNSA</td>
<td>47.7±6.4</td>
<td>44.1±7.7</td>
<td>0.033</td>
</tr>
<tr>
<td>Moderate-severe diastolic dysfunction</td>
<td>SCNSA</td>
<td>45%</td>
<td>27.2%</td>
<td>0.035</td>
</tr>
<tr>
<td>LVOT gradient (mmHg)</td>
<td>SCNSA</td>
<td>62.4±57.5</td>
<td>32.9±40.6</td>
<td>0.035</td>
</tr>
<tr>
<td>LVOTO (&gt;30 mmHg)</td>
<td>SCNSA</td>
<td>65%</td>
<td>34.8%</td>
<td>0.008</td>
</tr>
<tr>
<td>MLVWT &gt;30mm</td>
<td>ANK2</td>
<td>10.9%</td>
<td>2%</td>
<td>0.003</td>
</tr>
<tr>
<td>MLVWT (mm)</td>
<td>ANK2</td>
<td>20.1±6.2</td>
<td>18.5±4.2</td>
<td>0.024</td>
</tr>
<tr>
<td>LV dilation (LVED &gt;55mm)</td>
<td>PKP2</td>
<td>13.3%</td>
<td>4.2%</td>
<td>0.022</td>
</tr>
<tr>
<td>Systolic dysfunction</td>
<td>PKP2</td>
<td>17.2%</td>
<td>2.9%</td>
<td>0.001</td>
</tr>
<tr>
<td>(fractional shortening &lt;25%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSVT (baseline)</td>
<td>PLN</td>
<td>100%</td>
<td>25.4%</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>ANK2</td>
<td>45.5%</td>
<td>24%</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Severe hypertrophy ANK2
Left Atrium SCN5A
Diastolic dysfunction SCN5A
LVEF PKP2
LVed PKP2

Lopes et al. Heart. 2015 Feb 15;101(4):294-301
Kathiresan et al. Cell 2012
Figure 2 The contributions of ‘omics’ and systems biology to the practice of PPPM.