Contribution of genetics for sudden death risk stratification in dilated cardiomyopathy

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I currently have, or have had over the last two years, an affiliation or financial interests or interests of any order with a company or I receive compensation or fees or research grants with a commercial company:

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- Royalty Income: none
- Ownership/Founder: none
- Intellectual Property Rights: none
- Other Financial Benefit: none
Left ventricular or biventricular systolic dysfunction and dilatation that are not explained by abnormal loading conditions or coronary artery disease.

Preclinical or Early Phase

<table>
<thead>
<tr>
<th>No cardiac expression (Mutation carrier and/or AHA positive)</th>
<th>Isolated Ventricular Dilatation (Dilation/no Hypokinesia) *^</th>
<th>Arrhythmic CM (Arrhythmias or conduction defect) *^</th>
<th>Hypokinetic Non Dilated CM (Hypokinesia/ no Dilation)</th>
<th>Dilated CM (LV Dilation + Hypokinesia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(no LV abn, no arrhythmia) ^</td>
<td>(DCM ND-NH-Mut+AHA) ^</td>
<td>(DCM D-NH, with or without mut+AHA)</td>
<td>(HNDC or DCM ND-H)</td>
<td>(DCM D-H)</td>
</tr>
</tbody>
</table>

Clinical Phase

Progressive expression of the phenotype

* Shown by two independent imaging modalities - ^mutation carrier or not; anti-heart autoantibody (AHA) positive or negative
Familial / genetic origin of DCM has been underestimated for a long time...

**Familial DCM forms after echo screening**
- 6%, retrospective study, Michels et al. AJC 1985
- 8.5% retrospective study (HTx), Valentine et al., AJC 1989
- 20% prospective study, (59 index, 315 relatives), Michels et al., NEJM 1992
- 25% prospective study, (40 index patients), Keeling et al., BHJ, 1995
- 35% prospective study, (445 index), Grünig et al., JACC 1998
- 65% prospective study, (60 index), Mestroni et al. JACC 1999

**Yield of mutation screening in DCM**
- 6%, analysis of 4 genes in 95 DCM pts, Villard et al. EHJ 2005
- 25-30% analysis of 19 genes in 73 pts, Zimmerman et al., Genet Med 2010
- +18-25%, analysis of titin (TTN) gene in 312 pts, Herman et al., NEJM 2012
- 35% analysis of 101 genes in 145 pts, Akinrinade et al., EHJ 2015
- 46-73% analysis of 84 genes in 639 pts, Haas et al., EHJ, 2015
>50 genes, variable inheritance but usually AD, proteins:

- **Cytoskeleton** (i.e. dystrophin):  
  - force transmission?

- **Nuclear membrane** (i.e. lamin A/C):  
  - membrane stabilization?  
  - transcriptional factors?

- **Sarcomere** (i.e. bêta-myosin, titin):  
  - force production?

- **Z Band** (i.e. Muscle LIM Protein):  
  - stretch sensor?

- **Ca^{2+}** metabolism (i.e. phospholamban):  
  - contraction-relaxation cycle?

- **Other**

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**Table 2: Genes associated with DCMs**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Estimated prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTN</td>
<td>20</td>
</tr>
<tr>
<td>MYH7</td>
<td>4–7</td>
</tr>
<tr>
<td>LMNA</td>
<td>2–6</td>
</tr>
<tr>
<td>SCN5A</td>
<td>2–3</td>
</tr>
<tr>
<td>TNN13</td>
<td>2–3</td>
</tr>
<tr>
<td>LDB3</td>
<td>1–3</td>
</tr>
<tr>
<td>PLN</td>
<td>1–3</td>
</tr>
<tr>
<td>TNN12</td>
<td>1–3</td>
</tr>
<tr>
<td>TNNC1</td>
<td>Rare</td>
</tr>
<tr>
<td>TAZ</td>
<td>Rare</td>
</tr>
<tr>
<td>CRRP3</td>
<td>Rare</td>
</tr>
<tr>
<td>DES</td>
<td>Rare</td>
</tr>
<tr>
<td>ACTN2</td>
<td>Rare</td>
</tr>
<tr>
<td>ANKRD1</td>
<td>Rare</td>
</tr>
<tr>
<td>ABCC9</td>
<td>Rare</td>
</tr>
<tr>
<td>TPM1</td>
<td>Rare</td>
</tr>
<tr>
<td>FMDM</td>
<td>Rare</td>
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<tr>
<td>VCL</td>
<td>Rare</td>
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<tr>
<td>EMD</td>
<td>Rare</td>
</tr>
<tr>
<td>MYOZ1</td>
<td>Rare</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Rare</td>
</tr>
<tr>
<td>BAG3</td>
<td>Rare</td>
</tr>
<tr>
<td>ABCC9</td>
<td>Rare</td>
</tr>
<tr>
<td>LAMP2</td>
<td>Rare</td>
</tr>
<tr>
<td>EYA4</td>
<td>Rare</td>
</tr>
<tr>
<td>TEMO</td>
<td>Rare</td>
</tr>
<tr>
<td>PSEN1</td>
<td>Rare</td>
</tr>
<tr>
<td>PSEN2</td>
<td>Rare</td>
</tr>
<tr>
<td>SGCD</td>
<td>Rare</td>
</tr>
</tbody>
</table>

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Chen J, Chien KR. J Clin Invest 1999

Impact of genetic knowledge in risk stratification of DCM
Revised concept on familial DCM

**Prognosis and phenotype-genotype correlations**

*High risk of sudden cardiac death / ventricular arrhythmia for some genes*

**High risk of SCD / VA associated with**

**Phospholamban (PLB) mutations**

*Van der Zwaag, EJHF 2012;14(11):1199*

**High risk of SCD / VA associated with**

**Filamin C (FLNC) mutations**

*Ortiz-Genga, JACC 2016;68(22):2440-2451*
Revised concept on DCM

**Prognosis and phenotype-genotype correlations**

*prognosis of DCM related to Lamin A/C mutation*

- LMNA (lamin A/C) gene mutations
- Autosomal dominant inheritance

**Specific phenotype:**
- early AV block / sinus dysfunction and/or SV or V arrhythmia
- DCM
- +/- skeletal myopathy

Fatkin et al., NEJM 1999;341:1715
Revised concept on DCM

**Prognosis and phenotype-genotype correlations**

*prognosis of DCM related to Lamin A/C mutation*

- LMNA (lamin A/C) gene mutations
- Autosomal dominant inheritance

- Meta-analysis of 299 LMNA mutation carriers
- Progressive ↑ dysrhythmia (CD or arrhythmia): 92% after 30 y.
- ↑ PM implantation: 44% after 30 y.
- ↑ Heart Failure: 64% after 50 y.

Specific phenotype:
- early AV block / sinus dysfunction and/or SV or V arrhythmia
- DCM
- +/- skeletal myopathy

Fatkin et al., NEJM 1999;341:1715

Van Berlo et al., J Mol Med 2005;83:79
Revised concept on DCM

Prognosis and phenotype-genotype correlations

**prognosis of DCM related to Lamin A/C mutation**

Natural history of DCM patients
(12 LMNA mutations vs 93 pts) Taylor JACC 2003;41:771

- Analysis of survival in DCM patients
  - LMNA mutation carriers (N = 12)
  - DCM without LMNA mutation (N=93)
- Event free (D+Htx) survival at 45 y.: 45% vs 89%

Genotype-phenotype in 8000 DCM patients
Kayvanpour Clin Res Cardiol 2017 Feb;106(2):127

LMNA gene associated with:
- Highest rate of conduction disease (73%)
- Highest rate of ventricular arrhythmia (50%)
- Highest rate of heart transplant (27%)
Prediction of ventricular arrhythmia in LMNA carriers and management
Risk Factors for Malignant Ventricular Arrhythmias in Lamin A/C Mutation Carriers
A European Cohort Study

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Aeilko H. Zwinderman, MS, PhD,§ Philippe Charron, MD, PhD,‡‡‡ Yigal M. Pinto, MD, PhD,*†

- **MVA (n=48):** 11 resuscitations, 28 appropriate ICD therapy (8%/y in PP), 14 SCD
- **4 Predictors of MVA** (multivariate analysis):
  - **nsVT** HR 4.4 (95% CI: 1.9-10.4)
  - **LV EF < 45%** HR 4.4 (95% CI: 2.0-8.0)
  - **Male gender** HR 2.9 (95% CI: 1.2-7.0)
  - **Ins/del/nonsense/splice site mutation** HR 2.5 (95% CI: 1.4-4.5)

≥ 2 RF → propose ICD

van Rijjsingen J Am Coll Cardiol 2012
N= 122 LMNA carriers

Predictors of sVA (multivariate):
- Male sex (HR 3.1, p=0.01)
- Non missense mutation (HR 2.5, p=0.03)
- LVEF<50% (HR 3.4, p=0.004)

Ventricular arrhythmia (sVT/VF): 34 ±5% at 7 years
Device implanted in 48% during FY (7 y.)
Other predictors of VA in LMNA carriers

- 94 Italian mutation carriers, FU: 57 months
  - 2 independent RF for sudden death:
    - type of mutation (splice site mutations)
    - history of competitive sports
      - Pasotti et al. J Am Coll Cardiol 2008;52:1250

- 47 French mutations carriers
  - 1 RF for sudden death:
    - significant conduction disorders
    (hazard ratio 5.20; 95% confidence interval 1.14-23.53; P = 0.03)
Implications for practical management of DCM in daily practice

Diagnostic work up in DCM:

(6) Cardiac screening with echocardiography and ECG is recommended in all first degree-relatives of an index patient with DCM, irrespective of family history.

(7) Genetic testing is recommended in the presence of a familial form of DCM or in sporadic DCM with clinical clues suggestive of a particular/rare genetic disease (such as atrio-ventricular block or CK elevation).

Aetiology directed management:

Recommendation 6:

• When a definite causative LMNA mutation is identified, early indication for primary prevention by ICD implantation should be considered (guided by the risk factors as detailed elsewhere).
Conclusions

- Familial/genetic origin is frequent in DCM
  - At least 1/3 of DCM are familial forms
  - Yield of mutation screening: 20-30% with Sanger → 45-75% with NGS
  - Genetic testing is recommended in the presence of a familial form of DCM OR in sporadic DCM with clinical clues suggestive of a particular/rare genetic disease

- Some genes are associated with higher risk of SCD in DCM, especially LMNA gene (lamin A/C)
  - When should you suspect Lamin A/C gene mutations? If a particular phenotype (including conduction defect, SV and V arrhythmia, dilated cardiomyopathy, sometimes muscular dystrophy)
  - Why should you identify LMNA mutations? Because of high mortality, particular cardiac expression, early sport restriction, early PM and ICD implantation (LVEF <45 %, nsVT, male gender and non-missense LMNA mutation), genetic counselling

www.cardiogen.aphp.fr
Sources d’information

- **Centre de référence Maladies rares** (Paris),
  label Plan Maladies rares n°1:
  - Centre de référence pour les *maladies cardiaques héréditaires*,
  Coordinateur du centre: philippe.charron@aphp.fr
  Paris multi-site: A. Paré, Bichat, HEGP, Necker, R. Debré, Pitié-Salpêtrière
  - 22 Centres de compétence en région

- **Filière nationale de santé CARDIOGEN**, label Plan Maladies rares n°2, coordinateur: Ph Charron
  [www.filiere-cardiogen.fr](http://www.filiere-cardiogen.fr)