SCN5A mutation associated with a novel cardiac arrhythmia disorder involving the left fascicular-Purkinje system associated with dilated cardiomyopathy.

G. Laurent ¹, S. Saal ¹, MY. Amarouch ², L. Faivre ¹, P. Charron ³, E. Baron ², JJ. Schott ², F. Kyndt ², V. Probst ², JE. Wolf ¹

(1) University Hospital of Dijon, Dijon, France
(2) INSERM UMR915, l'institut du thorax, Nantes, France
(3) AP-HP, Functional Unit of Cardiogenetic, Paris, France
Conflicts of interest

None
Purpose

- We report a large family affected by a novel autosomal dominant cardiac arrhythmia disorder.
- Uniform phenotype: incessant PVC, NSVT (“MEPT”) sometimes responsible for a transient DCM.
- Six males and 4 females over three generations were affected, with an age at diagnosis ranging from 5 to 37 years.
Electrophysiological (EP) testings were realised in 6 patients including 3D navigation systems in three of them. Precise location of the PVC firing was based on the identification of pre-systolic Purkinje potentials, early endocardial activation mapping with a QS unipolar pattern of the electrogram and concordant pace mapping.
Methods

Candidate gene approach:
Direct sequencing of Lamin A/C, ABCC9, SCN5A

Functional studies:
• Patch-clamp experiments: DNA transfected African green monkey kidney fibroblast-like cells (COS-7).
• Computational models of human left-ventricular myocytes and Purkinje cells.
Results

Symptoms:
• Palpitations, heart failure (3 patients), syncopes (2 females) and sudden death at rest (3 males at age 4 months, 29 and 45* years).
• "chaotic" surface ECGs, rare sinus or junctional beats, rate dependant polymorphic PVCs/NSVT
• DCM was diagnosed in 3 females and 1 male. In 2 females implanted with ICD, left ventricular function improved as PVC burden was dramatically reduced on Hydroquinidin (Ia) from more than 50.000/24h to <5.000/24h.
Results

EP testings:
- Incessant firings of PVC originating from various ectopic foci along the extension of the left anterior and posterior fascicles.
- One RF procedure:
  - We failed to eradicate PVC firings as the whole Purkinje tissus seemed to be involved in the firing.
<table>
<thead>
<tr>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
<th>#6</th>
<th>#7</th>
<th>#8</th>
<th>#9</th>
<th>#10</th>
<th>#11</th>
<th>#12</th>
</tr>
</thead>
<tbody>
<tr>
<td>DI</td>
<td>DII</td>
<td>DIII</td>
<td>aVR</td>
<td>aVL</td>
<td>aVF</td>
<td>V1</td>
<td>V2</td>
<td>V3</td>
<td>V4</td>
<td>V5</td>
<td>V6</td>
</tr>
</tbody>
</table>

The image shows an electrocardiogram (ECG) with leads labeled from DI to V6. Additionally, there is a 3D representation of a heart with markers indicating the proximity to EnSite surface.
c.665G>A missense mutation
Patch-clamp technique

![Graph showing availability and relative conductance vs. membrane potential.](image)
Increase in Purkinje cells excitability.
Conclusion

- Novel autosomal dominant arrythmia disorder
- Mutation p.Arg222Gln in SCN5A gene
- A net gain of function of the sodium channel
- Increase in Purkinje cells excitability
- New phenotype: “MEPT syndrome”
  - Rate dependant PVCs from the fascicular-Purkinje system
  - Sensitive to Hydroquinidine
  - Transient DCM (tachy-cardiomyopathy)
  - SCD
Thank you for your attention

ACKNOWLEDGMENTS:

- Christian De Chillou, MD, PhD; Julien Barc, PhD; Christian Dina, PhD; Geraldine Bertaux, MD, Sylvie Falcon-Eicher, MD; Olivier Barthez, MD; Christel Thauvin-Robinet, MD; Pascale Richard, MD, PhD; Alice Maltret, MD; Elisabeth Villain, MD; Jean Mérot, PhD; Rodolphe Turpault, PhD; Yves Coudière, PhD; Flavien Charpentier, PhD; Isabelle Baró, PhD; Gildas Loussouarn, PhD.

FINANTIAL SUPPORTS:

- The Fondation Leducq Trans-Atlantic Network of Excellence grant (05 CVD 01, Preventing Sudden death)
- The Association Française contre les Myopathies (n°14120)
- The Fondation pour la Recherche Médicale Programme “Vieillissement Cardiovasculaire Normal et Pathologique” (DVC20070409253).
Back up « B » plan...
Mutations in SCN5A are responsible for cardiac arrhythmias

- type-3 LQT (LQT3) [Na+ channel gain of function] lengthening of the AP
- BrS, Cardiac conduction disease (CCD) and sinus node dysfunction. [Na+ channel loss of function]
- Overlap syndromes of cardiac Na+ channelopathy
Presystolic Purkinje potential
**A**

WT, R222Q, Heterozygous

- **B**

Relative conductance (G/Gmax)

- **C**

Time to peak (ms)

- **D**

Inactivation time constant (ms)
Human ventricular model

WT

Heterozygous

Human Purkinje model

WT

Heterozygous

 Availability (I/Imax)

Relative conductance (G/Gmax)

Col 26 vs Het I/Imax ventri: -80.0000
A

Human ventricular model

cycle length: 5 s

WT

Het

cycle length: 1 s

WT

Het

cycle length: 1 s

WT

Het

cycle length: 0.5 s

WT

Het

B

Human Purkinje model

cycle length: 5 s

WT

Het

cycle length: 1 s

WT

Het

cycle length: 1 s

WT

Het

cycle length: 0.5 s

WT

Het
Sérécor 300mg LP depuis 3 jours
Experimental and simulated effects of R222Q mutation on Nav1.5 channel in COS-7 cells and single-cell models
Effects of R222Q mutation on Nav1.5 biophysical parameters.

<table>
<thead>
<tr>
<th></th>
<th>current density</th>
<th>activation</th>
<th>inactivation</th>
<th>recovery from inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>peak at −20mV</td>
<td>$V_{1/2}$</td>
<td>$k$</td>
<td>$V_{1/2}$</td>
</tr>
<tr>
<td></td>
<td>(pA/pF)</td>
<td>(mV)</td>
<td>(mV)</td>
<td>(mV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>−205.8 ± 29.3</td>
<td>−30.6 ± 2.1</td>
<td>5.7 ± 0.3</td>
<td>−79.6 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>(36)</td>
<td>(9)</td>
<td>(9)</td>
<td>(10)</td>
</tr>
<tr>
<td>heterozygous</td>
<td>−196.5 ± 17.6</td>
<td>−37.2 ± 1.6*</td>
<td>7.1 ± 0.3**</td>
<td>−82.2 ± 1*</td>
</tr>
<tr>
<td></td>
<td>(48)</td>
<td>(9)</td>
<td>(9)</td>
<td>(9)</td>
</tr>
<tr>
<td>R222Q</td>
<td>−250.4 ± 24.8</td>
<td>−42.3 ± 1.0***</td>
<td>6.5 ± 0.4</td>
<td>−84.6 ± 0.7***</td>
</tr>
<tr>
<td></td>
<td>(44)</td>
<td>(11)</td>
<td>(11)</td>
<td>(8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>