The Genetic Basis of Idiopathic VF

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IDIOPATHIC
/ˌɪdɪə(ʊ)ˈpaθɪk/

Adjective

Medicine

“Relating to or denoting any disease or condition which arises spontaneously or for which the cause is unknown.”
Unexplained Cardiac Arrest

- Normal Coronaries
- Normal Echocardiogram
- Non-diagnostic ECG

Exhaustive Clinical Assessment

Idiopathic VF

SC-VF (SC-TdP)
Early Repol.

SADS
Sudden Unexplained Death
Normal Post Mortem

Molecular Autopsy

12.3% of all cardiac arrest survivors

Waldmann et al EHJ 2018
Discretionary Testing

Provocative Tests
Ajmaline, Adrenaline, Ergonovine

EP Study
Induce VT, Voltage map for scar/ARVC

Genetics
Identify pathogenic variants

Initial Testing

ECG/Telemetry
Assess LVF/cardio myopathy

Echocardiogram
Coronary Assessment
Rule out CAD

Routine Testing

Exercise Test
Assess for CPVT/LQTS

High RV lead SAECG

Cardiac MRI
Detect cardiomyopathy

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Genetics
Identify pathogenic variants
Outcome of Apparently Unexplained Cardiac Arrest
Results From Investigation and Follow-Up of the Prospective Cardiac Arrest Survivors With Preserved Ejection Fraction Registry

- UCA, 59%
- Diagnosed, 41%
- CPVT, 5%
- ER, 7%
- LQTS, 9%
- Other, 2%
- Myocarditis, 2%
- BrS, 4%
- DCM, 1%
- ARVC, 7%
- SCIVF, 3%
- Coronary Spasm, 4%
## Genetic Testing in Unexplained Cardiac Arrest

<table>
<thead>
<tr>
<th>Study, year</th>
<th>n</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Genetic Testing strategy</th>
<th>Yield (P/LP)</th>
<th>VUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mellor, 2017</td>
<td>174</td>
<td>Canadian</td>
<td>CASPER</td>
<td>Variable</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>Visser, 2016</td>
<td>79</td>
<td>Belgian</td>
<td>Idiopathic VF</td>
<td>34 gene panel (+-179 gene panel if negative)</td>
<td>16% (15% + 3%)</td>
<td>24-34%</td>
</tr>
<tr>
<td>Leinonen, 2017</td>
<td>76</td>
<td>Finnish/Italian</td>
<td>Idiopathic VF</td>
<td>100 gene / 21 gene panel</td>
<td>9%</td>
<td>12%</td>
</tr>
</tbody>
</table>
Genetic Testing in the Evaluation of Unexplained Cardiac Arrest: From the CASPER (Cardiac Arrest Survivors With Preserved Ejection Fraction Registry)

- Greg Mellor, Zachary W.M. Laksman, Rafik Tadros, Jason D. Roberts, Brenda Gerull, Christopher S. Simpson, George J. Klein, Jean Champagne, Mario Talajic, Martin Gardner, Christian Steinberg, Laura Arbour, David H. Birnie, Paul Angaran, Richard Leather, Shubhayan Sanatani, Vijay S. Chauhan, Colette Seifer, Jeffrey S. Healey and Andrew D. Krahn

- 174 unexplained cardiac arrest survivors with genetic testing performed
- 17% pathogenic variant
- Prior syncope and family history of SD predictive of higher yield
Results: Implicated Genes

- SCN5A
- KCNH2
- KCNE1
- RYR2
- DSP
- DSG2
- MYBPC3
- LMNA
- KCNQ1
- CACNA1C
- KCNE2
- PKP2
- DSC2
- PLN
- TTN
Results: Phenotype negative cases

<table>
<thead>
<tr>
<th>Path.</th>
<th>VUS</th>
<th>Path. &amp; VUS</th>
<th>Path.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/79 (8%)</td>
<td>4/79 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/33 (21%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P=0.04, p<0.01

Mellor et al Circ CVG 2017
UCA Genetic Testing Conclusions

Pathogenic / Likely pathogenic in 10-15%

Channelopathy *and* Cardiomyopathy genes

VUS very common
Familial Idiopathic VF – DPP6

Alders et al 2009
Familial Idiopathic VF – DPP6

Alders et al 2009
Familial Idiopathic VF – DPP6

K⁺ channel subunit
Purkinje Fibre $I_{to}$

chromosome 7q36

ACTR3B

DPP6

PAXIP HTR5A

152.3 Mb
D7S1491

153.6 Mb
DPP6v2
$c.1-340C\rightarrow T$

153.8 Mb
D7S2546

Mean relative DPP6 expression +/- SEM

Controls
Patients

Alders et al 2009
Familial Idiopathic VF – DPP6

![Graph showing cumulative survival and age distribution with risk haplotype carriers and non-carriers.](image.png)

- Cumulative survival
- Age
- Risk haplotype carriers
- Risk haplotype non-carriers
- \( p < 0.05 \)

Postema et al 2011
Other genes implicated in IVF

- CALM1 - F90L
  - Calmodulin; involved in Ca$^{2+}$ signalling
  - Single family with multiple SUD
  - Mild QT prolongation in surviving affected individuals

- RYR2 - S4938F
  - GoF variants associated with CPVT
  - Lof variant associated with SUD at rest with no exercise-induced PVCs

- IRX3
  - Transcription factor affecting SCN5A and Cx40 expression
  - IRX3 ko mouse high risk of VF
  - 130 IVF/ERS/BrS/SQTS probands screened
    - 2 putative pathogenic variants identified

- SCN5A – S1710L
  - Also reported multiple times in Brugada Syndrome
Early Repolarisation Genetics

• The ER ECG pattern is heritable
  • OR 2.54 (1.33-4.84) if one affected parent
• No convincing monogenic cause identified

<table>
<thead>
<tr>
<th>Gene/variant</th>
<th>phenotype</th>
<th>N affected</th>
<th>Co-segregation</th>
<th>Functional Studies</th>
<th>Allele freq (gnomAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNJ8 – S422L</td>
<td>ERS/Brugada</td>
<td>5</td>
<td>No</td>
<td>Increased $I_{to}$</td>
<td>0.0016</td>
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<tr>
<td>KCND2 – D612N</td>
<td>‘Anterior J-wave’</td>
<td>1</td>
<td>No</td>
<td>Increased $I_{to}$</td>
<td>3.3x10^{-5}</td>
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<tr>
<td>CACNA1C – E850del</td>
<td>ERS</td>
<td>1</td>
<td>No</td>
<td>None</td>
<td>5.8x10^{-4}</td>
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<tr>
<td>CACNB2 – S160T</td>
<td>ERS</td>
<td>1</td>
<td>No</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>CACNB2 – R571C</td>
<td>ERS</td>
<td>1</td>
<td>No</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>CACNA2D1 – S956T</td>
<td>ERS</td>
<td>1</td>
<td>No</td>
<td>None</td>
<td>-</td>
</tr>
</tbody>
</table>
Conclusions

A minority of unexplained VF has a monogenic aetiology
Concealed arrhythmia syndromes
Short-coupled VF – DPP6

Future studies will:
Refine genotype : phenotype correlations
Explore oligo/polygenic causes of SC-VF