Spotting the clues for diagnosing dilated arrhythmogenic cardiomyopathies

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Barts Heart Centre
Died aged 31 playing football; previous collapse 1 week prior.
Mother of Proband (1): DP aged 73
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- Asymptomatic; NYHA 1
- **PMH**: Hypothyroidism, Type 2 DM, HTN, Permanent AF
- **ETT**: Exercise induced ‘salvo’
- **Holter**: Perm. AF, mean HR 100bpm, 802 VE/hour
Died aged 31 playing football; previous collapse 1 week prior
Half-sister of Proband (2): AM aged 43

- Asymptomatic; NYHA Class 1. No medications
- **ECG**: SR, Normal ECG
- **SAECG**: Positive for late potentials.
- **TTE**: Normal Biventricular Size / Function; Normal Valves
- **Holter**: 10,040 polymorphic VE (9.8% of total QRS complexes).
Died aged 31 playing football; previous collapse 1 week prior
Niece of Proband (3): PM aged 19

- Asymptomatic; NYHA Class 1. No medications
- **SAECG**: Negative for late potentials
- **CPEX**: NAD
- **TTE**: Normal Biventricular Size + Function; no RWMA, Normal valve function
- **24 hours Holter**: Sinus rhythm with HR 47-139bpm. Minimal VE’s.
Died aged 31 playing football; previous collapse 1 week prior

Red flags?
Niece of Proband (3): PM aged 19

March 2017:

-presented local hospital with erratic heart beat and chest tightness after flu ‘prodrome’. Diagnosed myocarditis; had BCT at 100bpm. TnT 3000
Arrhythmogenic Cardiomyopathy

Red Flags:

- Frequent Ventricular Ectopy / Non-Sustained VT
  - Especially with mild LV systolic dysfunction
- FH of Sudden Cardiac Death
- Conduction Disease
- Extensive Scar on cardiac MRI (incl. circumferential pattern)
Arrhythmogenic Cardiomyopathy

**Genetics:**
- LAMIN A/C
- Filamin C
- RBM20
- BAG3
- SCN5A
- Desmoplakin

**Acquired:**
- Myocarditis
- Sarcoidosis
RESULT: CARRIER

The FLNC variant previously identified in the index case of this family was found in the present study.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Result</th>
<th>Pathogenicity</th>
<th>Population frequency</th>
<th>Number of references</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLNC</td>
<td>NP_001449.3:p.Arg991*</td>
<td>Heterozygosis</td>
<td>Very likely to be pathogenic or disease-causing ++</td>
<td>Mutation (not found in controls)</td>
<td>2</td>
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<tr>
<td></td>
<td>NM_001458.4:c.2971C&gt;T</td>
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<td>NC_000007.13:g.128484099C&gt;T</td>
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Clinical interpretation

Radical variants in the FLNC gene have been associated with a particular form of dilated arrhythmogenic cardiomyopathy with predominantly left ventricle involvement. Intramyocardial fibrosis, ventricular dilatation, and family history of sudden death are the most common associated features. Such variants cosegregated with the disease in multiple families, with very high penetrance after the age of 40.

We recommend the inclusion of this variant in the familial screening. Carrier status can be used as predictive of disease.
Lessons from the clinic...

- Not all dilated cardiomyopathies are the same.
- ACM should trigger thoughts of LMNA, FLNC and other potential genetic aetiologies – these may affect prognosis and clinical management.
- Genetics play an increasingly important in guiding clinical outcomes.
- **Look for the clues:** High VE count; extensive LGE on CMRI (often disproportionate to degree of LVSD); SCD in the family.
Truncating FLNC Mutation Produces an Abnormal Protein

Alteration of Intercalated Disks and Costameres Weakens Myocytes' Adhesion

Dilated/Arrhythmogenic Cardiomyopathies

- Left Ventricular Dilation and Systolic Dysfunction with Myocardial Fibrosis
- Ventricular Arrhythmias
- Familial Sudden Cardiac Death

Ortiz-Genga et al. (2016)
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THANK YOU!