CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)
(OMIM 604772)

INTRODUCTION
Catecholaminergic polymorphic ventricular tachycardia or CPVT is an inherited condition characterised by bidirectional and polymorphic ventricular tachycardia and ventricular fibrillation, which predisposes to fainting or sudden death. Events usually occur during times of stress or with exercise. CPVT is a genetically heterogeneous condition. Pathogenic variants in RYR2 account for 50-60% of individuals with a clinical diagnosis of CPVT. The next highest proportion of pathogenic variants are found in CASQ2 where they are detected in 1-2% of individuals with a clinical diagnosis of CPVT. The remaining genes included on this panel (see table below) are rare causes of CPVT.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Clinical Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALM1</td>
<td>Rare[6-8]</td>
</tr>
<tr>
<td>CALM2</td>
<td>Rare[6-8]</td>
</tr>
<tr>
<td>CALM3</td>
<td>Rare[6-8]</td>
</tr>
<tr>
<td>CASQ2</td>
<td>2[6-8]</td>
</tr>
<tr>
<td>KCNJ2</td>
<td>Rare[6-8]</td>
</tr>
<tr>
<td>RYR2</td>
<td>20-60[6-8]</td>
</tr>
<tr>
<td>TRDN</td>
<td>Rare[6-8]</td>
</tr>
</tbody>
</table>

REFERRAL PROCEDURE
• Diagnostic referrals are accepted for probands with a suspected or confirmed diagnosis of CPVT.
  o Referrals are accepted from Cardiology, Clinical Genetics and Consultants from other relevant medical specialities.
  o Clinical information and details of relevant family history should be provided with all referrals either on the original request form or on a separate pre-referral form (Cardiac Arrhythmia Pre-referral form).
• Family test referrals are only accepted from Clinical Genetics specialists.
  o Referrals for affected family members (i.e. segregation analysis) must be accompanied by appropriate clinical information.
  o Referrals for unaffected family members will only be considered for variants with clear evidence for pathogenicity.
• Clinical advice is available from Dr Edward Blair, Consultant Clinical Geneticist, at the Churchill Hospital (Ed.Blair@ouh.nhs.uk).
• Further information about the test can be obtained from the laboratory (OxfordCardiac@nhs.net).

SAMPLE REQUIREMENTS
• This analysis requires 5 µg of DNA (at a minimum concentration of 30ng/µl).
• Blood samples, including post-mortem blood (provided it is not clotted) is suitable (1-5ml EDTA).
• Fresh or frozen tissue - generally spleen although other tissues are acceptable (1cm cubed)
• Formalin-fixed paraffin-embedded (FFPE) will be accepted for panel testing but poor quality of extracted DNA from these samples may mean analysis is not possible or coverage is lower than quoted. In general, Sanger gap filling is not usually possible from this material.

STRATEGY AND TECHNICAL INFORMATION
• Diagnostic Screens:
  o Gene target enrichment is undertaken using Agilent’s HaloPlex Target Enrichment System.
  o Libraries are sequenced on an Illumina MiSeq Desktop Sequencer.
  o Sequence data are analysed on a custom-designed bioinformatic pipeline.
  o Where possible, regions of interest (ROIs) in the following genes are 100% covered either by >30 reads or by Sanger sequencing: SCN5A, HCN4
  o Coverage of ROIs in the remaining genes varies, but is typically 88–100% at ≥30 reads.
  o Genomic rearrangements (large deletion/duplications) involving SCN5A are thought to be a rare cause of Brugada syndrome; a single case report of a partial deletion of the SCN5A gene causing BS has been reported in the literature.[6] If a diagnosis of Brugada syndrome is strongly suspected, MLPA dosage analysis may be undertaken as a separate test.
• Family tests- 
  o Familial variants are targeted for analysis by Sanger sequencing of the relevant exon.

TARGET REPORTING TIMES
Diagnostic screen: 60-80 working days
Family test: 10 days
MLPA Dosage Analysis: 10 days
• Please see the current price list on the Oxford Genetics laboratory Molecular genetics page


N.B. Details are correct for the date of printing only. Last updated August, 2015