A Comprehensive Next Generation Sequencing Service for Inherited Cardiac Conditions

A review of the first three years of implementation

James Eden
Clinical Scientist
Genomic Diagnostics Laboratory
Manchester Centre for Genomic Medicine
Inherited cardiac arrhythmias (channelopathies)

- **BrS**
  - Normal ECG
  - BrS ECG

- **CPVT**
  - Normal ECG
  - CPVT ECG

- **LQTS**
  - Normal ECG
  - LQTS ECG

**Inherited cardiomyopathies**

- Normal
- Septal HCM
- Apical HCM with LVH
- DCM
- ARVC

Giudicessi & Ackerman (2010). Nature Reviews Cardiology 9

Wilde (2013). Nature Reviews Cardiology 10
Aortopathies

Isselbacher (2005). Circulation 111

Schwartz Principles of Surgery 10th Edition

Normal aorta

Aortic dissection
The Importance of Cardiac Genetic Testing

- Predisposition to cardiac arrest/sudden cardiac death at a young age

- 600,000 people in the UK are at risk of an inherited cardiac condition or an inherited form of coronary heart disease (BHF)

- Identifying causative mutation:
  - Predictive testing
  - Protective treatments
    - β blockers
    - Implantable Cardioverter Defibrillator (ICD)
  - Cardiac surveillance (ECG/ECHO/MRI)
  - Awareness of environmental risk factors (exercise, stress, diet)
  - Coming to terms with sudden death of a relative
Manchester Cardiac Gene Panel

☐ Aortopathy
☐ ARVC
☐ Brugada syndrome
☐ CPVT
☐ Dilated cardiomyopathy
☐ Hypertrophic cardiomyopathy
☐ Long QT syndrome
Manchester Cardiac Gene Panel

- Aortopathy
- ARVC
- Brugada syndrome
- CPVT
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Long QT syndrome

Genes:
- KCNE2
- KCNJ5
- KCNH2
- KCNQ1
- AKAP9
- SCN5A
- CACNA1C
- SCN4B
- KCNJ2
- SNTA1
- KCNE1
- ANK2
Manchester Cardiac Gene Panel

- Aortopathy
- ARVC
- Brugada syndrome
- CPVT
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Long QT syndrome

Gene Symbols:
- TRDN
- KCNE2
- KCNJ5
- CALM1
- KCNH2
- KCNQ1
- AKAP9
- SCN5A
- CACNA1C
- SCN4B
- RYR2
- KCNJ2
- SNTA1
- CASQ2
- KCNE1
- ANK2
Manchester Cardiac Gene Panel

- Aortopathy
- ARVC
- Brugada syndrome
- CPVT
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Long QT syndrome

Gene Symbols:
- HCN4
- KCNJ2
- KCNE2
- CALM1
- TRDN
- KCNH2
- KCNQ1
- AKAP9
- KCNE3
- SCN5A
- RYR2
- ABCC9
- CACNA1C
- SCN4B
- CACNA2D1
- SNTA1
- SCN1B
- CASQ2
- SCN10A
- TRPM4
- GPD1L
- KCNNE1
- ANK2
Manchester Cardiac Gene Panel

- Aortopathy
- ARVC
- Brugada syndrome
- CPVT
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Long QT syndrome
Manchester Cardiac Gene Panel

- Aortopathy
- ARVC
- Brugada syndrome
- CPVT
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Long QT syndrome
Manchester Cardiac Gene Panel

- Aortopathy
- ARVC
- Brugada syndrome
- CPVT
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Long QT syndrome
Challenges of Cardiac Genetic Testing

• Consistency of variant interpretation and reporting
  – Dominantly inherited missense variants
  – TTN

• Limited clinical symptoms

• Variable penetrance

• Apparent absence of cosegregation
  – ?oligogenic cause → modifiers, functional polymorphisms
Multidisciplinary teamwork
The Cardiac MDT meeting
MDT review

- ECG
- Exercise Tests
- Cardiac Imaging
- Genetic Testing
- Clinical History
- Family History
- Counselling issues
Clinical and Genetic Diagnosis
Clinical and Genetic Diagnosis

- Initiation of cascade testing
- Treatment and surveillance options

- Re-investigation of phenotype
- Re-testing by other subpanels
- Recruitment to studies e.g. 100KGP
- Cosegregation analysis
- Availability of functional studies
Cardiac subpanels requested

Total = 1517

- Aortopathy: 355
- Brugada syndrome: 35
- CPVT: 93
- Long QT syndrome: 85
- ARVC: 59
- DCM: 145
- HCM: 412
- Combined cardiomyopathy: 127
- Combined arrhythmia: 89
- 'Molecular Autopsy': 98
- Failed: 19

Total = 1517
Overall detection rate

- Class 5: Clearly pathogenic (31, 2%)
- Class 4: Likely to be pathogenic (271, 18%)
- Class 3: Unknown significance (VUS) (273, 18%)
- No pathogenic mutation identified (923, 62%)

Total = 1498
Analysis of copy number variation (CNV)

FBN1 exons 46-48 heterozygous deletion
FBN1 exons 56-58 duplication (3 copies)

Consistent with a diagnosis of Marfan syndrome
Future improvements to cardiac testing

- Re-evaluation of gene panel
- Data sharing between centres → phenotype and genotype
- Implementation of variant analysis guidelines (ACMG)
- Quantitative guidelines for cosegregation
Acknowledgements

Manchester Heart Centre
Dr Luigi Venetucci
Prof Bernard Keavney
Dr Mani Motwani
Prof Bernard Clarke
Prof Clifford Garratt
Dr Helen Dormand
Dr Omar Asghar

Genomic Diagnostics Laboratory
Simon Ramsden
Helene Schlecht
Lesley Heptinstall
Sanjeev Bhaskar

Clinical Genetics Service
Prof Bill Newman
Dr Kay Metcalfe
Natalie Moreton
Dr Claire Bailey
Sarah Bennett

University of Manchester
Jill Urquhart
James O’Sullivan
Jamie Ellingford

james.eden@cmft.nhs.uk