FANS Familial Arrhythmia Network Scotland
National Managed Clinical Network

Genetic Clinical Investigation Protocol
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1 Introduction

The Familial Arrhythmia Network Scotland helps coordinate the management of families with proven or suspected familial arrhythmia. The network comprises cardiologists, clinical geneticists and pathologists in Scotland who are involved in assessing such patients and their families.

It is provided through multidisciplinary clinical services in a variety of hospitals throughout Scotland. Patients or families may be referred to the local network clinic for assessment, specialist cardiological investigation, coordination of cascade family screening and for genetic investigation and testing.

Affected patients and affected relatives detected through cascade screening are likely to be referred back to their local cardiology, medical or paediatric services as appropriate for further management, unless the local clinician specifically requests further help or advice from the network clinic.

2 Clinical Presentation in the Index Case

2.1 Introduction

Information about the index case must be recorded in the electronic genetic record at the initial assessment. Where a relative has been referred and is not necessarily affected, it is essential to seek information about the index case to confirm the diagnosis.

2.2 Clinical findings

The index case is likely to have one or more of the following medical problems:

- Syncope
- Seizure
- Proven arrhythmia
- Suspected arrhythmia
- Sudden cardiac death
- Cardiomyopathy

Other features which may occasionally be present and indicate an underlying multisystem disorder include for example, muscle weakness and wasting, neuropathy, retinal abnormalities, hearing loss.

2.3 Cardiology Assessment

Various cardiology investigations may have been completed by cardiology prior to referral. The results should be recorded in the genetic record.

- 12 lead ECG
- Echocardiogram
- Exercise test
- 24h ECG monitor (Holter),
- cardiac MRI
- Signal averaged ECG

### 2.4 Post Mortem

Record the following information where available:

- All cardiovascular findings
- Cardiac weight
- Cardiac histology
- PM diagnosis
- Cause of death
- Toxicology (presence of drugs likely to cause arrhythmia)
- History of hypertension
- Smoking and alcohol history
- Information about previous cardiology investigations if any (ECG, echo etc)

### 2.5 Diagnosis in Index Case

Cardiology or post mortem investigation should result in a general diagnosis which may be classified as below. Each diagnostic group has a separate protocol described in the next sections.

### 3 No structural heart disease identified

Clinical investigations may refine this diagnostic group e.g. Long QT, Short QT, Brugada, CPVT. Families with ARVC may fall into this group initially. This section includes the sudden ‘Cardiac Death Protocol’ and the ‘Out of Hospital Cardiac Arrest Protocol’

### 4 Structural heart disease identified

- Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Hypertrophic
- Cardiomyopathy (HCM)
- Dilated Cardiomyopathy (DCM)

### 5 Cardiac Connective Tissue Disease

- Marfan
- Loeys Dietz
- Familial Thoracic Aortic Aneurysm
- Ehlers Danlos

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GENETIC INVESTIGATION and MANAGEMENT

3 No structural Heart Disease Identified

3.1 Sudden Cardiac Death <40 years

3.1.1 Sudden Cardiac Death Aged < 40 years

When a family is referred, the genetic work-up by the cardiac genetic nurse should include the following information:

3.1.2 Index case information:

Obtain copy of PM report or relevant findings. In particular, record:
- Circumstances of the sudden death (exercise, sleep, noise, swimming etc)
- Drugs taken by the deceased (particularly if arrhythmogenic, including OTC antihistamines).
- History of hypertension
- Evidence of vascular disease (atheroma, history of angina, myocardial infarction or stroke)
- Smoking and alcohol history
- Cardiac weight
- Cardiac histology
- PM diagnosis
- Cause of death

Check hospital case records for information about:
- Medical history,
- ECGs
- Cardiac imaging

Samples for DNA analysis should be stored from the affected individual (skeletal muscle, spleen or skin) at post mortem (check if this has been done)

3.1.3 Family history

As a minimum, a 3 generation family history should be taken from the referred family member. For all recorded relatives, this should include:
- Name, date of birth, date of death and cause of death (if deceased)
- History of cardiac events (if any)
- History of neuromuscular disorder (if any)

3.1.4 Family Investigations

All first degree relatives of the deceased and any who are symptomatic should be referred for:
- ECG, and echocardiogram
- Cardiology outpatient referral should be considered

3.1.5 Genetic testing

If the findings in the deceased or in a first degree relative suggest an underlying cause (e.g. long QT, HCM) then investigations should continue according to the disorder identified.
If a relative is shown to have one of these disorders, a sample should be taken from them for testing.

**If no underlying disorder has been identified:**

- Test the index case using the full arrhythmia gene panel, and consider including cardiomyopathy genes.

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### 3 No Structural Heart Disease Identified

#### 3.2 Patient with Documented Arrhythmia or OOHCA

##### 3.2.1 Living patient who has had a proven arrhythmia including Out of Hospital Cardiac Arrest (OOHCA) survivors

When a family is referred, the genetic work-up by the cardiac genetic nurse should include the following information:

##### 3.2.2 Index case information:

Record cardiology diagnosis from letters/hospital records record the following information if available:

**Case history:**
- Precipitants of arrhythmia (exercise, sleep, noise, swimming etc)
- Drug use at time of arrhythmia (prescribed, OTC, recreational)
- Type of arrhythmia
- Current treatment (i.e. drugs, ICD)

**ECG:**
- QTc,
- Morphological abnormalities,
- Evidence of bundle branch block
- T wave appearance

**Cardiac imaging:**
- Echocardiogram
- MRI
  - (If more than one imaging modality, record details of all)

**Other investigations:**
- Exercise test
- 24 hour (Holter) ECG monitor
- Signal Averaged ECG
- Drug challenge tests

*A blood sample should be taken (with informed consent) for genetic investigation if there is no evidence of a non-genetic cause*

##### 3.2.3 Family history

As a minimum, a 3 generation family history should be taken from the
referred family member. For all recorded relatives, this should include:

- Name, date of birth, date of death and cause of death (if deceased)
- History of cardiac events (if any)
- History of neuromuscular disorder (if any)

### 3.2.4 Family Investigations

All first degree relatives and any symptomatic relative should be referred for:

- ECG
- Echocardiogram unless diagnosis is clear cut and considered unnecessary
- Cardiology outpatient referral should be considered

Symptomatic relatives, and any with abnormalities on investigation should be referred to cardiology.

### 3.2.5 Genetic Investigations

This depends on the clinical diagnosis suspected:

#### 3.2.5.1 Arrhythmia/OOHCA: Suspected/likely Long QT syndrome

Clinical summary

- History of syncope compatible with torsades de pointes, associated with stress, swimming, diving, sudden loud noise, at rest or in bed.
- 12 lead ECG shows QTc > 440 ms in males or > 460 ms in females measured in lead II or V5
- T wave morphology may be abnormal
- No history of QT prolonging drugs, evidence of hypocalcemia or hypothyroidism
- No structural abnormality on echocardiogram
- May have family history of long QT or family history compatible with ventricular arrhythmia (e.g. sudden unexpected death, normal post mortem).

Genetic testing

- Test an affected person for mutation using the Long QT gene panel.
- If these genes are normal consider testing the Brugada, CPVT and ARVC panels. A history of exercise induced VT could suggest CPVT or ARVC.

Jervell Lange Neilsen syndrome (long QT and deafness) is inherited as a recessive trait, and is normally due to the presence of two mutations in either KCNQ1 or KCNE1 or one in each.
3.2.5.2 Arrhythmia/OOHCA: Suspected/likely Short QT syndrome

Clinical summary
- As for Long QT except:
  - 12 lead ECG shows QTc <360ms in males or 370ms in females (usually < 320ms)

Genetic testing
- Test the Long QT gene panel.

3.2.5.3 Arrhythmia/OOHCA: Suspected/likely Brugada syndrome

Clinical summary
- History of syncope compatible with torsades de pointes.
- 12 lead ECG shows “Brugada” pattern (may resemble R BBB).
- No history of QT prolonging drugs, evidence of hypocalcemia or hypothyroidism
- No structural abnormality on echocardiogram
- May have family history of Brugada or family history compatible with ventricular arrhythmia (e.g. sudden unexpected death, normal post mortem).

Genetic testing
- Test the Brugada gene panel.

3.2.4.4 Arrhythmia/OOHCA: Suspected/likely CPVT (Catecholaminergic Polymorphic VT)

Clinical summary
- History of syncope compatible with ventricular tachycardia usually associated with exercise.
- No evidence of QTc abnormality on ECG
- No evidence of cardiomyopathy on echocardiogram
- No evidence of ARVC according to agreed guidelines

Genetic testing
- Test the CPVT gene panel. If normal, consider the Long QT, Brugada and ARVC panels.

3.2.4.5 Arrhythmia/OOHCA: Cardiology investigations not diagnostic (Idiopathic VT)

Clinical summary
· Episode of VT/VF, no cause identified
· Ischaemic heart disease, drug induced arrhythmia excluded
· No evidence of QTc abnormality on ECG
· No evidence of cardiomyopathy on echocardiogram
· No evidence of ARVC according to agreed guidelines
· Family history of arrhythmia or sudden cardiac death (confirm that affected relative does not have an alternative diagnosis if possible)

Genetic testing
· Test using the full arrhythmia gene panel, and consider including cardiomyopathy genes (particularly the DCM panel).

3.2.4.6 Arrhythmia/OOHCA: Suspected/likely Bradycardia

Clinical summary
· Episodes of atrial arrhythmia or heart block

Genetic testing
· Test using the atrial/heart block panel and long QT panel.
· Test LMNA
· Consider DCM panel

3 No Structural Heart Disease Identified

3.3 Suspected Arrhythmia, not Documented

3.3.1 Suspected Arrhythmia

If arrhythmia is suspected but not documented, and there have been no serious consequences, workup should be the same but genetic testing should be discussed with a clinical geneticist.
4 Structural Heart Disease Identified

4.1 ARVC

4.1.1 Index case information

Record the evidence for the diagnosis:

Case history:
- Precipitants of arrhythmia (exercise, sleep, noise, swimming etc)
- Drug use at time of arrhythmia (prescribed, OTC, recreational)
- Type of arrhythmia
- Current treatment (ie drugs, ICD)

Cardiology investigations:
- ECG
- Signal averaged ECG
- Echocardiogram
- MRI
- Exercise test
- Drug challenge test

4.1.2 Family investigations

Investigate family history as for tachyarrhythmia

Investigate 1st degree relatives through the Familial Arrhythmia Clinic (ECG, SA ECG, 24h ECG, ETT, Echo, Consider MRI)

Refer symptomatic relatives to cardiology (e.g. syncope)

*Take a blood sample from an affected person for genetic analysis*

4.1.3 Genetic Investigations

Clinical summary
- History of syncope compatible with ventricular tachycardia. May or not be exercise induced.
- ECG, SAECG, echocardiogram, cardiac MRI suggests ARVC according to agreed criteria
- There may be a family history of ARVC or sudden cardiac death compatible with cardiac arrhythmia.

Genetic testing
- Test using ARVC panel.

If negative, consider further testing in consultation with clinical geneticist.
4 Structural Heart Disease Identified

4.2 HCM

4.2.1 Index case information

- ECG findings
- Echocardiogram (asymmetric or concentric hypertrophy)
- Exercise history
- History of hypertension
- Evidence of cardiac valve disease
- Consider neuromuscular symptoms (if present, consider Freidreich’s ataxia)

4.2.2 Family history

If family history suggests X-linked inheritance, or isolated male case (may have possibly X-linked family history of sudden death) consider Fabry’s disease.

Confirm family history of cardiomyopathy, arrhythmia or sudden cardiac death where possible.

4.2.3 Family investigations

Offer investigation of 1st degree relatives by ECG and Echocardiogram
Investigate symptomatic relatives by ECG and echocardiogram or by referral to a cardiology clinic

Take a blood sample for future mutation analysis from an affected person

If no additional features, and the above investigations are normal but there is evidence of familial transmission and younger family members at risk and request testing, consider:

4.2.4 Genetic Investigations

Clinical summary

- ECG or echocardiographic evidence of hypertrophic cardiomyopathy.
- No evidence of hypertension or valve disease considered sufficient to cause cardiac hypertrophy.
- Family history of cardiomyopathy or sudden cardiac death compatible with cardiomyopathy should be evident.
- If family history suggests X-linked inheritance, or isolated male case (may have possibly X-linked family history of sudden death) test for proteinuria in a living affected individual.
Genetic testing

Send blood spot (Guthrie card) for alpha galactosidase assay (Fabry’s disease) Test using HCM gene panel

4 Structural Heart Disease Identified

4.3 DCM< 50

4.3.1 Index case information

- History of breathlessness with findings of left ventricular failure, including echocardiographic features of dilated cardiomyopathy

- There may be a history of syncope or pre-syncope compatible with tachy or brady arrhythmia, or evidence of arrhythmia on ECG investigation

- The following conditions should be excluded:
  - Ischaemic heart disease (angiography)
  - Hypertension
  - Skeletal muscle disease (neurology/genetics evaluation, CPK)
  - Excess alcohol consumption (history and biochemical evidence)
  - Exposure to cardiotoxic drugs (history)
  - Haemochromatosis (ferritin/genotyping)

- A metabolic evaluation for mitochondrial disorder should be considered if there is a history of diabetes, deafness, retinitis pigmentosa, skeletal muscle disease, growth retardation or cognitive disorder.

4.3.2 Family History

A Family history of cardiomyopathy or sudden cardiac death compatible with cardiomyopathy should be evident.

4.3.3 Family investigations

First degree relatives should be offered at least one ECG and echocardiogram

Repeat assessments should be discussed with a clinical geneticist or genetic cardiologist

Investigate symptomatic relatives by ECG and echocardiogram or by referral to a cardiology clinic

*Take a blood sample for future mutation analysis from an affected person*

4.3.4 Genetic investigations

Family history compatible with autosomal dominant inheritance
- Test using DCM panel (Edinburgh) and DCM subpanel of the Arrhythmia Gene Panel

Family history compatible with X-linked inheritance

- Test dystrophin
- In children, consider Barth syndrome, test paediatric cardiomyopathy panel

5 Cardiac Connective Tissue Disorders

5.1 Marfan, Loeys Dietz, Ehlers Danlos

- Marfan syndrome should be diagnosed using the Ghent Nosology according to the Scottish Guidelines and Care Pathway
- Consider taking a blood sample for FBN1/TGFBR1/TGFBR2 mutation testing in cases which fall short of the Ghent criteria by one system, or have a systemic score > 4
- If Ehlers-Danlos syndrome Arterial Variant (formerly Type 4) is suspected, test COL3A1
- If these tests are negative, or there are insufficient additional clinical findings outside the arterial system to suggest a “syndrome” diagnosis, test using a TAAD (Thoracic Aortic Aneurysm and Dissection) panel.

6 Hyperlipidemia

6.1 Familial Hyperlipidemia

6.1.1 Index case

Genetic investigation of an index case including LDLR mutation and deletion screening, ApoB (p.R3527Q) and PCSK9 (p.D374Y) should be considered if the Simon Broom Criteria suggest a definite or probable diagnosis of familial hypercholesterolemia:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>a</td>
<td>Total cholesterol concentration above 7.5 mmol/liter in adults or a total cholesterol concentration above 6.7 mmol/liter in children aged less than 16 years, or</td>
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<tr>
<td>b</td>
<td>Low density lipoprotein cholesterol concentration above 4.9 mmol/liter in adults or above 4.0 mmol/liter in children</td>
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<tr>
<td>c</td>
<td>Tendinous xanthomata in the patient or a first-degree relative</td>
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<tr>
<td>d</td>
<td>DNA-based evidence of mutation in the LDLR or APOB gene</td>
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<td>e</td>
<td>Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree</td>
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</table>
Family history of raised total cholesterol concentration above 7.5 mmol/liter in a first- or second-degree relative

**Diagnosis**
- A "definite" FH† diagnosis requires either criteria a and b or criterion c
- A "probable" FH diagnosis requires either criteria a and d or criteria a and e

### 6.1.2 Family investigations

Cascade screening using genetic testing and blood lipids should be offered to first degree relatives when a mutation has been detected in the index case.

Cascade screening using blood lipids should be offered to first degree relatives if no mutation has been detected.

Statin treatment should be considered for all affected individuals identified.

### 7 Other

#### 7.1 Coagulopathy

##### 7.1.1 Index case

Coagulopathies are an occasional cause of sudden death and may therefore be identified in families referred to the familial arrhythmia service.

The investigation and management of this group of disorders is outwith the scope of this document, and should be considered in conjunction with colleagues from Haematology.