Scottish Muscle Network

A Guide for Anaesthetists: Genetic Testing in Malignant Hyperthermia in Scotland

Within Scotland, access to genetic testing for Malignant Hyperthermia (MH) and access to 'In Vitro Contracture Testing' (IVCT) is by referral to the local Clinical Genetics Department as per the Managed Clinical (Scottish Muscle) Network Pathway[1].

Malignant Hyperthermia (MH) & Genetics

- The inheritance pattern of MH is considered autosomal dominant so each first degree relative (parent, sibling, child) of a person at risk of MH, has a 50% (1 in 2) chance of inheriting the genetic predisposition.
- In an MH family, all blood relatives are potentially at risk until testing has been undertaken.
- Genetic variants in three genes have to date been associated with MH: RYR1, CACNA1S, STAC3.
- The most common gene variants are in the RYR1 gene that encodes the skeletal muscle sarcoplasmic reticulum calcium release channel.

Limitations of Genetic Testing in MH

- The exact genetic variant underlying the MH is identified in around half of individuals presenting to the genetic clinic[2].
- It is likely that other, as yet uncharacterized, genetic causes exist.
- An individual's genetic information may also change over time as more is understood about that gene.
- Genetic testing alone will not always confirm MHS and cannot be used to exclude MHS
- If someone in a family with a known causative MH gene variant has a genetic test and is negative for that variant, this does not exclude an MH risk for that individual. Studies show there is a residual risk of up to 10% in such cases[2]. This means gene negative family members in an MH family should still be offered an IVCT. This is counterintuitive to mainstream genetic testing for other conditions where a negative result usually reduces an individual's risk to the general population risk of that condition. See Summary scenarios below for an example.

Key information to give to Affected Cases - Individuals who have had a confirmed MH reaction and are being referred to Clinical Genetics

- An alert card should be carried by an affected individual. These are available from the Scottish Muscle Network.
- An electronic alert should be placed on Trakcare and the GP asked to place a KIS alert.
- At the Genetics clinic, the MH Clinical geneticist will fully discuss options for further testing prior to consenting for genetic testing.
- If appropriate, a blood test will be offered, and DNA tested to look for sequence variants in the MH genes.
- If a disease-causing genetic alteration is identified:
  - This confirms Malignant Hyperthermia Susceptibility (MHS) for this individual.
  - This test can then be offered to other blood relatives to further define their MH risk (see below)
- If a disease-causing gene alteration is NOT identified (including variants of unknown clinical significance – 'VUSs'):
  - Patient still should be considered Malignant Hyperthermia Susceptible (MHS) and referred for IVCT
  - No genetic blood test is available to relatives.
  - All blood relatives should be considered MHS.
  - All blood relatives should be offered an IVCT – see below.

Key information for Family Members of an individual who has had an MH reaction and family member is referred to Genetics

- Consider as MHS until results of further testing are collated.
- As much information as possible will be required about the family member who had the MH reaction.
- If possible, please ask patient to bring to Genetics clinic:
  - Genetic testing results (ideally a copy of the affected family member's genetic report, their IVCT test, or, at least, that individual's consent to access their results).
- If a disease-causing genetic variant has been identified in the individual with MH;
  - A blood test can be offered to family members to look for this gene alteration.
  - If a family member **has** inherited this alteration, they are considered MHS and will be issued with an alert card, electronic alerts placed on Trak and KIS.
  - If a family member has **NOT** inherited the familial gene alteration, current European Guidelines suggest this individual is potentially still MHS because there is a history of MH reaction in the family and there are reports of families with >1 gene variant underlying the MH

Susceptibility[2]. These family members should carry an alert card and consider an IVCT.

- If a disease-causing genetic alteration has **NOT** been identified in the individual with MH reaction;
  - A genetic blood test is not available to relatives
  - All blood relatives are considered MHS and should carry an alert card.
  - An IVCT test would be required to give further information (see below).

The In Vitro Contracture test (IVCT)

- May be offered where genetic testing has not been helpful in excluding MH Susceptibility.
- Only available in the National MH Centre, located in St James's Hospital, Leeds.
- Involves overnight stay in Leeds for Scottish patients.
- Thigh muscle biopsy carried out under femoral nerve block.
- IVCT is then interpreted alongside full clinical picture by MH Team in Leeds and reported to referrer.
- False positives and negatives are possible.

Summary of Scenarios where a patient may be considered MHS:

- Affected case – MH episode occurred during anaesthesia & patient tests positive for a pathogenic gene variant
- Affected case – MH episode occurred during anaesthesia, patient test positive on IVCT
  - Possibly no identifiable gene variant (14-23%)[2]
- Family history cases – Patient hasn't had MH episode but tests positive for pathogenic gene variant which is known to be carried by a relative who has had MH.
- Family history cases – Patient hasn't had MH and is **negative** for pathogenic gene variant in family **BUT** positive on IVCT or has refused IVCT.
  - Up to 10% of cases >1 pathogenic gene variant potentially involved in pathogenesis of MH[2].
  - Whilst gene / IVCT pending or if individual declines IVCT, person remains MHS and should be managed as such.

Clinical Genetics Departments

Northern Scotland (main base Aberdeen)
Dr Alison Ross, Consultant in Clinical Genetics
Tel: 01224 552120
(Aberdeenshire, Moray, Highland, Western & Northern Isles)

Tayside (main base Dundee)
Dr Catherine McWilliam, Consultant in Clinical Genetics
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West of Scotland (main base Glasgow)
Dr Cheryl Longman, Consultant in Clinical Genetics
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South East Scotland (main base Edinburgh)
Dr Elaine Fletcher, Consultant in Clinical Genetics,
Tel: 0131 537 1116
(Lothian, West Lothian, Borders, Fife)

References:

1) Scottish Muscle Network - Managed Clinical Network Pathways
Affected Cases Pathway
Family History Pathway

2) Miller DM et al. Genetic epidemiology of malignant hyperthermia in the UK. *British Journal of Anaesthesia,* 121 (4): 944-952, 2018.