SCOTTISH MUSCLE NETWORK

Gene variants of uncertain significance and copy number variants in the DMD gene –
Guidance for phenotyping and family studies in clinical genetics

NOTE
This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined based on all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Phenotyping of male Duchenne Muscular Dystrophy (DMD) variant of uncertain significance (VUS) carriers in segregation studies

Families should be seen by a Clinical Geneticist. History should include exercise related cramp/myalgia, rhabdomyolysis, symptoms suggestive of weakness, and cardiomyopathy.

Examination should include muscle strength and bulk.

Creatine kinase (CK) should be measured in the proband.

Where the VUS is an incidental finding in an asymptomatic person, or where the proband does not have muscle weakness (e.g., rhabdomyolysis, strong males with cardiomyopathy) phenotyping additional variant carrying males in the family is suggested. Where these are not available, multiple CK measurements in the proband may be more informative than a single measurement.

Uncertain cases can be discussed with Clinical Geneticists with a neuromuscular interest in each Regional Genetic Centre (Elaine Fletcher, Alison Ross, Catherine McWilliam, Cheryl Longman) and discussed within the SMN Genetic Diagnostic Subgroup prior to potential review by or with Neurology, and consideration of muscle biopsy and MRI.

CK interpretation

CK is always raised in Duchenne MD. CK below 1000 IU/L in a male excludes Duchenne MD with a high level of certainty, except in preterm babies. It does not exclude Becker MD.

CK is usually raised in weak males with dystrophinopathy.

CK may be normal in strong males with dystrophinopathy, usually in the upper normal range.

In females, raised CK suggests though doesn’t prove pathogenicity, but a single normal CK in a female is of little help.

Guidance on additional dystrophinopathy investigations

Regional neuropathology service biopsy evaluation

Muscle biopsy could be considered in both males and females. Histology and immunohistochemistry may reveal definitive abnormalities in morphology and/or dystrophin and/or utrophin and/or dystrophin associated proteins.

Biopsy analysis will diagnose or exclude Duchenne MD in males and DMD carrier status in females. In weak males affected by Becker MD, local biopsy is very likely to be abnormal. Normal studies do not exclude a dystrophinopathy.

Additional muscle biopsy studies

If a biopsy is performed, immunoblotting should also be performed. This is available through the Newcastle Muscle Immunoanalysis Unit (MIU), Institute of Genetic Medicine, University of Newcastle upon Tyne, International Centre for Life, Central Parkway, Newcastle upon Tyne, United Kingdom, NE1 3BZ.

Immunoblotting assesses dystrophin molecular weight. Patients with abnormal molecular weight dystrophin in muscle should be considered at risk of becoming affected by dystrophinopathy though this could be a mild phenotype.

Abundance of dystrophin is assessed on immunoblotting but is not quantitative and apparently normal levels do not exclude a mild dystrophinopathy.

Muscle MRI might document subtle muscle involvement in strong individuals, supportive of variant pathogenicity, though muscle MRI appearance is not highly specific.