Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

Medium Chain Acyl-Coenzyme A Dehydrogenase Deficiency (MCADD)

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Sample Required

See Sample requirements page at www.nbt.nhs.uk/genetics for full details

- Paediatric: at least 1ml EDTA (preferably >2ml)
- Guthrie card or other tissue sample be may relevant in some cases (contact lab).

Prenatal testing MUST be discussed with the laboratory, prior to the taking of any samples.

Samples should be accompanied by a FULLY completed request form (available as download at www.nbt.nhs.uk/genetics or from the laboratory).

Please include details of the test required, family history, address and POSTCODE, NHS number, referring clinician and centre.

Consent and Storage:

All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

DNA is stored from **ALL** patients undergoing DNA testing, unless consent for this is specifically denied.

Stored material from all referrals may be retained for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

Clinical Background and Genetics

- The autosomal recessive disorder, MCADD, is a defect of fatty acid β-oxidation due to deficiency of the enzyme medium-chain acyl-CoA dehydrogenase.
- This enzyme is required for the metabolism of medium-chain fatty acids and is necessary to enable the body to use its own fat reserves to produce energy in periods of fasting / stress. Deficiency of medium-chain acyl-CoA dehydrogenase causes a block in the medium-chain length step of fat oxidation.
- This leads to a build-up of medium-chain fatty acids, in particular octanoylcarnitine (C8) and its metabolites and results in inefficient breakdown of fat.
- MCAD deficiency is typically characterised by hypoketotic hypoglycemia, vomiting and lethargy triggered by a common illness in a previously healthy child. This may lead to coma and death. Liver disease may also be present.
- Typical presentation is between 3 and 24 months of age, though later presentation into adulthood is possible.
- Prognosis is good once a diagnosis is established and dietary treatment started.
- Diagnosis of MCADD in neonates is carried out biochemically through the population neonatal screening programme by detection of raised octanoylcarnitines in bloodspots. Diagnosis requires the integrated interpretation of multiple biochemical analyses such as detecting acylcarnitines and urine organic acids.
- The *ACADM* gene is located at 1p31 and has 12 coding exons. Most of the pathogenic variants reported are family specific. c.985A>G p.(Lys329Glu) is the most common disease-causing pathogenic variant of the *ACADM* gene and leads to an unstable protein. This pathogenic variant accounts for approximately 90% of *ACADM* pathogenic alleles in the UK affected population (Seddon *et al.*, 1997, Clin Chem 43:436-442), and approximately 75-82% of *ACADM* pathogenic alleles in the UK newborn screen-positive population (Oerton *et al.,* 2011, J Med Screen 18 (4): 173-181 & local data).
- The incidence of MCADD in the UK is between ~1/10,000-1/20,000, with a carrier frequency of between 1/37-1/70 (depending on whether assessed through genetic testing on Guthrie cards or via clinical presentation).

Service Offered

- Pathogenic variant analysis of the *ACADM* c.985A>G (p.Lys329Glu) only (see below*)

Referrals

Referrals for c.985A>G p.(Lys329Glu) analysis are accepted in the following scenarios:

- A clinical diagnosis of MCADD
- Presumptive positives on MCADD newborn screening
- Asymptomatic siblings of a MCADD patient
- Parents of a child with MCADD
- Adult relatives of a child with MCADD or MCADD carrier.
- Population risk partner of a known MCADD carrier

*If a biochemical diagnosis of MCADD has been made, further genetic analysis of the entire *ACADM* gene could be considered in patients in whom only one copy of the c.985A>G p.(Lys329Glu) pathogenic variant has been detected. Such analysis would be carried out by forwarding an aliquot of stored DNA to a specialist laboratory.

Clinical Advice: If clinical discussion is required, we would recommend contact with Dr Germaine Pierre, Paediatric Metabolic Consultant, Bristol Children's Hospital, (Tel: 0117 342 8513).

Biochemistry/ Newborn screening Lab contacts: Clinical Chemistry, Southmead Hospital (Tel: 0117 414 8426)

Target reporting Times

Level 1: c.985A>G p.(Lys329Glu) pathogenic variant analysis	42 days
Level 2: Urgent diagnostic c.985A>G p.(Lys329Glu) analysis	4 days

Quality

BGL participates in the GENQA MCADD Bloodspot and MCADD full scheme for this service.

Indicative Costs

Please contact the laboratory for up to date prices.

Information document No.33 Version 11
Active date of this version: 07/03/2020
DETAILS CORRECT AT DATE OF PRINTING ONLY
Approved by: Rebecca Whittington