Bristol Genetics Laboratory

North Bristol NHS Trust

Congenital Amegakaryocytic Thrombocytopenia (CAMT)

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Sample Required:
Adult: 5mls blood in EDTA
Paediatric: at least 1ml EDTA (preferably >2ml)

Prenatal testing MUST be arranged with the laboratory well in advance.

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 test, family history, address and POSTCODE, NHS number, referring clinician and unit/hospital.

Consent and DNA 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 unless consent for this is specifically denied.

Stored samples may be used for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

Clinical Background and Genetics

- Congenital amegakaryocytic thrombocytopenia (CAMT: OMIM# 604498) is a rare autosomal recessive bone marrow failure syndrome characterised by severe thrombocytopenia from birth, absent or decreased numbers of megakaryocytes in the bone marrow and low platelet counts.
- Development of pancytopenia in later childhood is common. CAMT patients often develop complete bone marrow failure and have poor prognosis without definitive treatment with allogeneic stem cell transplant.
- CAMT is caused by autosomal recessive mutations in the *MPL* gene.
- The UK prevalence is unknown, however it is estimated that 10-15 new diagnoses are made annually.
- CAMT is clinically difficult to distinguish from other disorders with similar presentations including other heritable non-syndromic thrombocytopenia and bone-marrow failure syndromes and from other acquired causes of these presentations.
- The 12 exon *MPL* gene (1p34) encodes the thrombopoietin (TPO) receptor which is the main regulator of megakaryocyte proliferation and differentiation.
- AR mutations in *MPL* have also been reported in patients presenting with tri-lineage bone marrow failure (aplastic anaemia) (Walne *et al* (2012) Haematol 97(4):524).
- Early and definitive diagnosis through *MPL* gene sequencing enables early intervention improving prognosis.

Referrals

- **Diagnostic referrals** are accepted from Consultant Haematologists and Clinical Geneticists with the following criteria:
  - Pedigree compatible with autosomal recessive inheritance.
  - Patient with persistent thrombocytopenia or bone marrow failure.
  - Absent or markedly reduced megakaryocytes in marrow or multi-lineage marrow aplasia or hypoplasia.
  - Absence of syndromic features associated with other heritable thrombocytopenias.
- **Carrier Testing:** Testing of parental samples is offered once the mutations have been identified in the affected patient.
- **Cascade testing** for familial mutations can be undertaken on close adult relatives and siblings where HLA compatibility is indicated.
- **Prenatal diagnosis** is available if the pathogenic familial *MPL* mutations have been identified. Please contact the laboratory to disc

Routine mutation analysis of the *MPL* gene is performed by sanger sequencing.

The *MPL* gene is also included in a 45 gene panel for inherited bone marrow failure syndromes which uses Next Generation Sequencing (NGS). This panel also includes the genes *GATA1, RBM8A, RUNX1* and *WAS* which are associated with Thrombocytopenia. Please contact the laboratory for further information on this service.

Target reporting Time

Full Gene Screen	56 days
Familial Mutation Testing	14 days
Prenatal Diagnosis	3 days

Quality: This laboratory participates in the following external quality assurance schemes which cover the technique and strategies used for this service: EMQN Sanger DNA sequencing scheme (since the pilot scheme was introduced in 2002) and UKNEQAS Pathogenicity of sequence variants interpretation only scheme (pilot scheme introduced in 2012).

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