Bristol Genetics Laboratory

North Bristol NHS Trust

Inherited Bone Marrow Failure Syndromes Gene Panel

Contact details:
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Sample Required:
Adult: 3-4mls blood in EDTA
Paediatric: at least 1ml EDTA (preferably >2ml)
DNA: 2µg total

Samples should be accompanied by a FULLY completed request form (available 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:
Genetic testing requires consent. It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.

This is a gene panel test using next generation sequencing. It contains genes associated with inherited bone marrow failure syndromes and their differential diagnoses. Included in the test are cancer susceptibility genes including *BRCA2*. There is therefore a possibility of incidental findings. Results obtained may have implications for the wider family. Results may also include variants of unknown clinical significance requiring further family studies to determine their significance. The interpretation provided is based on the available information at the date of issue; it may change if further evidence becomes available.

DNA is stored from all patients unless consent for this is specifically denied. Stored samples may be used anonymously for quality assurance and development purposes for this assay.

Clinical Background and Genetics

- The Inherited Bone Marrow Failure Syndromes are a group of rare inherited diseases with varying defects in the production of red blood cells, white blood cells and/or platelets, leading to low blood counts.
- An IBMFS should be considered for patients with cytopenias due to failure of production affecting one or more blood cell lines. Indications for a genetic etiology may be obtained through family history (marrow failure, MDS, leukemia, or solid tumors) and from characteristic physical findings such as skin or skeletal anomalies or through imaging techniques such as renal or pancreatic ultrasound.
- More than 25% of paediatric patients and approximately 10% of young adults who present with aplastic anaemia have an inherited aetiology.
- Patients with some of the IBMFS are at risk for developing both blood and solid malignancies. Many of these patients also have typical changes in their physical appearance and dysfunction in multiple organ systems apart from the bone marrow.
- A full list of genes and disorders included in the panel is on page 2.

Service offered

- 45 genes are sequenced using a custom designed Agilent SureSelect Target Enrichment method; sequencing is performed on an Illumina MiSeq. Analysis is performed using an open source in-house developed pipeline (alignment: BWA; alignment modification and variant calling: GATK; variant annotation: Annovar).
- All variants that are potentially pathogenic are reported and variants relevant to the patients phenotype are confirmed by Sanger sequencing

Referrals

- Diagnostic referrals are accepted from Consultant Clinical Geneticists, Consultant Paediatricians and Consultant Oncologists.
- It is essential that the referring clinician provides the clinical information and consent required in the pre-test proforma (page 3) or relevant clinical letter of referral.

Quality

- BGL participates in the appropriate technical EQA schemes for Sanger and next generation sequencing.

Target reporting Time (2016/2017)

- Gene panel testing 16 weeks
- Cascade tests 14 days

- Please contact the laboratory for up-to-date prices.
- For more information please contact the laboratory and for clinical advice please contact Dr Colin Steward, Consultant in BMT, Genetic and Metabolic Disease, Royal Hospital for Children, Bristol. Tel: 0117 342 0245. E-mail: colin.steward@uhbristol.nhs.uk

References

1. Tsangaris, E. et al. Genetic analysis of inherited bone marrow failure syndromes from one prospective, comprehensive and population-based cohort and identification of novel mutations. *J. Med. Genet.* 48, 618–28 (2011).
2. Alter B.P. Diagnosis, genetics and Management of Inherited Bone Marrow Failure Syndromes. *Hematology* Am Soc Hematol Educ Program. 29-39 (2007)

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Suspected Genetic Bone Marrow Failure NGS Panel Pro forma

Patient Name:		Consultant Name:	
Patient postcode:		Hospital Address:	
Date of Birth:			
Sex:			
NHS Number			
Hospital Number:			

Diamond-Blackfan Anaemia
RPL5
RPS7
RPS10
RPL11
RPS17
RPS19
RPS24
RPS26
RPL35A
GATA1

Natural killer cell and glucocorticoid deficiency with DNA repair defect
MCM4

Shwachman-Diamond Syndrome
SBDS

Dyskeratosis Congenita
DKC1
CTC1
NHP2
NOP10
RTEL1
TERC
TERT
TINF2
WRAP53

Myelodysplastic Syndrome
SRP72
GATA2

Neutropenia
ELANE (ELN2)
GFI1
HAX1
G6PC3
WAS

Fanconi Anaemia
FANCA
FANCB
FANCC
BRCA2 (FANCD1)
FANCD2
FANCE
FANCF
FANCG
FANCI
BRIP1 (FANCJ)
FANCL
PALB2 (FANCN)
RAD51C (FANCO)
SLX4 (FANCP)

Thrombocytopenia
GATA1
MPL
RBM8A
RUNX1
WAS

Please indicate suspected clinical diagnosis:

Disorder	Tick
Congenital Amegakaryocytic Thrombocytopenia (CAMT)	
Dendritic cell, Monocyte, B and NK lymphoid deficiency (DCML)	
Diamond-Blackfan Anaemia (DBA)	
Dyskeratosis Congenita (DKC), Dominant	
Dyskeratosis Congenita (DKC), Recessive	
Dyskeratosis Congenita (DKC), X-Linked	
Emberger syndrome	

Familial Platelet Disorder with Associated Myeloid Malignancy (FPD/AML)	
Fanconi Anaemia	
Hoyeraal-Hreidarsson syndrome	
Idiopathic Cytopenia	
MonoMAC syndrome	
Natural killer cell and glucocorticoid deficiency with DNA repair defect	
Neutropenia, Chronic Idiopathic	
Neutropenia, Cyclical	
Neutropenia, Severe Congenital	
Revesz Syndrome	
Short telomeres	
Shwachman-Diamond Syndrome	
Thrombocytopenia Absent Radius Syndrome	
Thrombocytopenia, X-linked (with or without dyserythropoietic anaemia)	
Wiskott-Aldrich Syndrome	

Please detail the clinical features of this patient, including relevant haematology results:

Please note this NGS panel test includes cancer predisposition genes including *BRCA2*. Analysis may reveal information regarding cancer susceptibility that may have implications for this patient and other family members. It is laboratory policy to report all clinically relevant findings. Please sign below to indicate that informed consent has been obtained prior to testing. Testing will not be undertaken if this form is not signed by the referring clinician.

Signed _____

Print _____

Position _____