THROMBOGENOMICS DNA TEST FOR A PATIENT WITH: BLEEDING OR PLATELET DISORDER

Background

Currently the diagnosis of most inherited bleeding and platelet disorders (BPD) is based on a plethora of specialised laboratory tests. The ThromboGenomics Next Generation Sequencing (NGS) test allows for the parallel sequencing of all known pathogenic genes (Tier 1 genes) in DNA samples from multiple patients. This has reduced the cost per patient tested and provide an opportunity to obtain conclusive gene-based diagnosis for patients (Simeoni I. et al, 2016, Blood).

The ThromboGenomics NGS test sequences genes associated with platelet disorders (see below - purple box) and genes associated with coagulation disorders (see below – green box).

Request a test if:

1. You suspect that your patient may have one of the bleeding and platelet disorders listed in the purple or green boxes (see below)

2. You assume a high likelihood of the condition being genetic, demonstrated by either:
    - early onset
    - other affected pedigree members*

** be mindful that genetic disease are frequently caused by de novo mutations present in the patient but absent in the parents*

DO NOT request a test if:

1. There is use of prescription or over-the-counter drugs known to be associated with bleeding or abnormal platelet phenotypes

2. There is a high likelihood of autoimmune thrombocytopenia (ITP) or other autoimmune disorders associated with low platelet count, including HIV positivity

3. There are other medical conditions known to be associated with (i) abnormal platelet count and volume, (ii) abnormal platelet function or (iii) increased risk of thrombosis:

    - Malignancies, particularly those compromising haematopoiesis
    - Bone marrow aplasia
    - TTP (Thrombotic thrombocytopenia purpura) and HUS (Haemolytic uremic syndrome)
    - Acute viral infection
    - Splenomegaly
    - Uraemia or hepatic failure
    - DIC (Disseminated intravascular coagulation)

THROMBOGENOMICS DNA TEST FOR A PATIENT WITH:
THROMBOTIC DISORDER

Background

In comparison with patients with bleeding disorders, the proportion of patients with venous thrombosis that have a genetic aetiology is far lower. The following criteria aim to select the subset of patients with thrombosis in whom a genetic cause is likely. In particular there is a rationale for having an age cut-off for testing these patients. The finding of a genetic defect in a patient whose first thrombosis occurred above the age of 40 is of doubtfull value as acquired factors are more likely to have been important in such a case. The criteria broadly follows the principles set out in the BCSH guidelines on thrombophilia testing.

The ThromboGenomics NGS test sequences genes associated with thrombotic disorders (see below – orange box).

Request a test if:

1. You assume a high likelihood of the condition being genetic, demonstrated by either:
   - First thrombotic event before 40 years of age
   - Other affected pedigree members with at least one first degree relative with thrombosis occurring before the age of 40
2. There are patients with a laboratory abnormality which may be explained by a pathogenic variant in one of the thrombotic disorder genes (see below – orange box). This includes deficiency of Protein C (PROC), Protein S (PROS) anti-thrombin (SERPINC1) and some cases of dysfibrinogenaemia.

DO NOT request a test if:

1. The first thrombotic event is after 40 years of age
2. The first thrombotic event occurs after trauma/surgical challenge
3. There are acquired thrombotic disorders, where:
   - there is evidence of anti-phospholipid antibodies (anti-β2 microglobulin), including during pregnancy
   - first thrombotic event occured after 40 years of age
   - thrombotic event occurs after trauma/surgical challenge

Platelet Disorders	Genes
ADP receptor defect	P2RY12
Amegakaryocytic thrombocytopenia with radio-ulnar synostosis	HOXA11
ARC syndrome	VPS33B; VIPAS39
Autosomal dominant thrombocytopenia 2	ANKRD26
Autosomal dominant thrombocytopenia 4	CYCS
Bernard-Soulier syndrome	GP1BA; GP1BB; GP9
Bleeding diathesis due to glycoprotein VI deficiency	GP6
Chediak–Higashi syndrome	LYST
Congenital amegakaryocytic thrombocytopenia (CAMT)	MPL
Cyclic thrombocytopenia and thrombocythemia 1	THPO
Deficiency of phospholipase A2, group IVA	PLA2G4A
Dense granule abnormalities	NBEA
Ehlers-Danlos syndrome, type I and type VIIA	CHST14, COL1A1
Familial haemophagocytic lymphohistiocytosis, type 5	STXBP2
Familial platelet disorder with predisposition to AML	RUNX1
Ghosal syndrome	TBXAS1
Glanzmann thrombasthenia	ITGA2B; ITGB3
Gray platelet syndrome	NBEAL2
Gray platelet-like syndrome	GFI1B
Hermansky–Pudlak syndrome	HPS1; AP3B1; HPS3; HPS4; HPS5; HPS6; DTNBP1; BLOC1S3; BLOC1S

Platelet Disorders	Genes
Leukocyte integrin adhesion deficiency, type III	FERMT3
Macrothrombocytopenia, Beta-tubulin 1 related	ACTN1; FLNA; TUBB1
Macrothrombocytopenia and sensorineural hearing loss	DIAPH1
May-Hegglin and other MYH9 disorders	MYH9
Myopathy associated with thrombocytopenia	GNE
Paris-Trousseau thrombocytopenia and Jacobson syndrome	FLI1
Platelet-type von Willebrand disease	GP1BA
Platelet-type bleeding disorder 18	RASGRP2
Quebec platelet disorder	PLAU
Scott syndrome	ANO6
Stormorken syndrome	STIM1; ORAI1
Thrombocytopenia and anemia	MPIG6B (C6orf25)
Thrombocytopenia and erythrokeraderma	KDSR
Thrombocytopenia and susceptibility to cancer	ETV6
Thrombocytopenia absent radius (TAR) syndrome	RBM8A
Thromboxane A2 receptor defect	TBXA2R
Wiskott-Aldrich syndrome	WAS
X-linked thrombocytopenia with dyserythropoiesis	GATA1

Coagulation Factor Disorders	Genes
Alpha 2 anti-plasmin deficiency	SERPINF2
Combined V and VIII deficiency	LMAN1; MCFD2
Factor V deficiency	F5
Factor VII deficiency	F7
Factor X deficiency	F10
Factor XI deficiency	F11
Factor XIII deficiency	F13A1; F13B
Fibrinogen deficiency	FGA; FGB; FGG
Haemophilia A	F8
Haemophilia B	F9
Multiple coagulation factor deficiency type 3	GGCX
Multiple coagulation factor deficiency type 2	VKORC1
Plasminogen Activator Inhibitor 1 deficiency	SERPINE1
Prothrombin deficiency	F2
von Willebrand disease types 2 or 3	VWF

Thrombotic Disorders	Genes
Anti-thrombin deficiency	SERPINC1
Heparin co-factor 2 deficiency	SERPIND1
Histidine-rich glycoprotein deficiency	HRG
Plasminogen deficiency	PLG
Protein C deficiency	PROC
Protein S deficiency	PROS1
Thrombomodulin deficiency	THBD
Tissue plasminogen activator deficiency	PLAT