ThromboGenomics

Cambridge University Hospitals NHS
NHS Foundation Trust

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 causal 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 the vast majority of patients (Simeoni et al. Blood. 2016 PMID 27084890)

The current version V2.6 of the ThromboGenomics NGS test contains 47 genes known to be causal of platelet disorders, with or without bleeding (see below - purple box) and 19 genes for 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 pruple 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 meaningful that genetic disease are frequently caused by de novo mutations present in the patient but absent from 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. High likelihood of autoimmune thrombocytopenia (ITP) or other autoimmune disorders associated with low platelet count, including HIV positivity

3. 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. In order to reduce the number of cases with a negative result following genetic analysis the following criteria aims 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.

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. Patients with a laboratory abnormality which may be explained by a oathogenic variant in one of the seven 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. First thrombotic event after 40 years of age
2. First thrombotic event occurs after trauma/surgical challenge
3. 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; VIPAS3	☐
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	☐
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	☐

Platelet Disorders	Genes	
Hermansky–Pudlak syndrome	HPS1; AP3B1; HPS3; HPS4; HPS5; HPS6; DTNBP1; BLOC1S3; BLOC1S6	☐
Leukocyte integrin adhesion deficiency, type III	FERMT3	☐
Macrothrombocytopenia	ACTN1; FLNA	☐
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 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	☐