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Molecular genetic testing for thrombophilia

Introduction

Thrombophilia is an increased tendency for blood to clot and is important to diagnose because of the resulting increased risk of deep vein thrombosis and pulmonary embolism, collectively described as venous thromboembolism (VTE). Many types of thrombophilia are due to inherited defects in genes that encode components of the blood-clotting pathway. The most common genetic alterations are called Factor V (five) Leiden[1] and Prothrombin 20210[2].

Factor V Leiden is so called because it was first described in a patient from Leiden in the Netherlands. The formal genetic nomenclature for Factor V Leiden is *F5* c.1601G>A for Factor V Leiden which is predicted to cause an amino acid change of arginine to glutamine at residue 534, p.Arg534Gln. Factor V is a component of the blood-clotting pathway. Another molecule in the blood called activated protein C (APC) prevents blood clots from becoming too large by inactivating Factor V. However the Factor V Leiden genetic alteration changes the factor V protein so that it is unable to interact with APC and as a result the clotting process continues longer than usual with the increased risk of developing abnormal blood clots.

Prothrombin is a pre-protein, or inactive protein, which normally circulates in the bloodstream. If an injury occurs that damages the blood vessels it is converted to the active form called thrombin. Thrombin converts fibrinogen to its active form fibrin, the primary protein in blood clots and is involved in recruiting platelets to the developing clot. Prothrombin 20210 is a variant in the factor 2 gene and is formally referred to as *F2* c.*97G>A, it occurs downstream from the protein coding region of the gene and does not change the protein structure but causes the gene to be over active and produce too much prothrombin. Excess prothrombin in the blood increases the risk of developing abnormal blood clots.

The frequency of the factor V Leiden variant is approximately 5% in people of European origin. Carrying this variant in the heterozygous state is associated with a small increased risk (3-5 fold) of VTE. The frequency of the prothrombin 20210 is approximately 2% in Europeans and this variant is associated with an increased VTE risk of 2-3 fold[3]. People with more than one copy of either of these variants have an even greater risk of VTE. These mutations occur at lower frequencies in other ethnic groups.

Reasons for referral

Testing for genetic risk of VTE is appropriate for patients with unprovoked VTE before age 50 years, or a history of recurrent VTE or VTE during pregnancy or associated with use of oestrogen-containing oral contraceptives or hormone replacement therapy. In addition testing may be offered to first-degree adult relatives of patients with VTE before age 50 and first-degree adult relatives of individuals shown to have one of these genetic variants.

Service offered

Confirmatory diagnostic testing: molecular testing for Factor V Leiden (*F5* c.1601G>A) and Prothrombin 20210 (*F2* c.*97G>A). Genetic testing for other thrombophilia risk factors is not currently available.

Target reporting time

5 working days

References

[1]Bertina et al (1994) Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature, 369*, 64-67.

[2]Doggen et al (1998) Interaction of coagulation defects and cardiovascular risk factors: increased risk of myocardial infarction associated with factor V Leiden or Prothrombin 20210A. *Circulation, 97*, 1037-1041.

[3]Reitsma et al (2012) Mechanistic view of risk factors for venous thromboembolism. *Arterioscler Thromb Vasc Biol, 32*, 563-568.