THROMBOPHILIA - FACTOR V LEIDEN AND PROTHROMBIN GENE MUTATION

Thrombosis Canada
Thrombose Canada

TARGET AUDIENCE: All Canadian health care professionals.

OBJECTIVE:

- To review the frequency, clinical relevance and diagnostic testing of factor V Leiden and prothrombin mutation G20210A.
- To indicate the role of these factors in patients with thrombotic diseases, in family members, and in the general population.
- To review recommendations for treatment and management of affected individuals.

ABBREVIATIONS:

DNA	deoxyribonucleic acid
FVL	Factor V Leiden
HRT	hormone replacement therapy
OCP	oral contraceptive
VTE	venous thromboembolism

BACKGROUND:

Thrombophilias are a group of inherited conditions associated with an increased risk of developing venous thromboembolism (VTE) (see DVT diagnosis and PE guides). A point mutation of Factor V (G1691A) known as Factor V Leiden (FVL), the most frequent of the thrombophilias, has an approximate incidence of 5% in the Caucasian population. FVL may be detected by deoxyribonucleic acid (DNA) analysis. The functional consequence of the mutation is an impaired inactivation of Factor V, resulting in increased thrombin generation. The second most frequent thrombophilia is a single nucleotide substitution in the prothrombin (Factor II) molecule promoter region (G20210A), also a condition detected by DNA analysis. The point mutation functionally increases the concentration of prothrombin. In their heterozygous forms, FVL or G20210A are associated with a modest increase in VTE risk. Rare homozygous or compound heterozygous individuals have a greater VTE risk. If an individual with VTE has FVL, G20210A or both, appropriate counseling should be provided, including careful evaluation of the duration of VTE treatment, need for family screening and interventions to minimize future VTE risk. There is no association of the presence of these mutations with cardiovascular disease in the general population. There is a weak association of these mutations with late pregnancy loss; however, screening is not

recommended. Despite the thrombotic risk associated with these mutations, such individuals have a normal life-expectancy.

FAMILY – PERSONAL HISTORY OF THROMBOSIS:

FVL may be present in 20% of unselected symptomatic VTE patients, and in up to 40% of patients with a strong family history associated with familial VTE. While most individuals who are heterozygous for FVL or G20210A will not develop VTE, the overall VTE risk is mildly elevated, and compounded by increasing age, oral contraceptive (OCP) use, hormone replacement therapy (HRT), pregnancy (see Thromboprophylaxis: Pregnancy guide) and other clinical risk factors. Homozygous and compound heterozygous patients should be considered to be at higher risk of recurrent VTE. Asymptomatic first degree relatives of carriers have a 50% chance of also being carriers of the mutation. They may benefit from appropriate VTE prophylaxis at times of increased clinical VTE risk. Universal screening for these conditions is not recommended; however, testing women with a positive family history of VTE prior to OCP use may be appropriate. The role of FVL and G20210A in early pregnancy loss and pregnancy complications is not clearly established, and screening such women is not recommended.

DIAGNOSIS:

The presence of Factor V Leiden or prothrombin G20210A can be detected by DNA testing. Activated Protein C Resistance is a functional screening test for the presence of Factor V Leiden. No functional test exists to detect the presence of prothrombin G20210A. The practice of widespread thrombophilia testing is not cost-effective. The advantages and disadvantages of testing should be discussed with the patient and it should be reserved for those where results will influence clinical decision-making. A positive test result may compromise a patient's insurance eligibility status.

TREATMENT OF VTE:

The duration of VTE treatment (see Duration of Anticoagulation guide) need not be altered from usual practice in FVL and G20210A heterozygous patients with VTE. Homozygous or compound heterozygous patients are considered at significantly increased risk of recurrent VTE. All asymptomatic individuals known to have these mutations should be provided adequate thromboprophylaxis (see Thromboprophylaxis: Medical, Thromboprophylaxis: Orthopedic, Thromboprophylaxis: Surgical guides) during clinical risk periods of VTE, including the immediate post-partum period. OCP and HRT use in asymptomatic carriers is associated with a relative increase in VTE risk. The risk-benefit of OCP or HRT use should be carefully discussed. There is insufficient evidence to recommend anticoagulation prophylaxis of women with the mutations and previous pregnancy complications. The presence of heterozygous FVL or G20210A does not mandate long-term (or lifelong) anticoagulation.

PEDIATRICS:

Parental informed consent is required as testing may have long-term implications (e.g. obtaining insurance).

REFERENCES:

Bertina RM, Koeleman BP, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994;369:64-67.

Koster T, Rosendaal FR, de Ronde H, et al. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. Lancet 1993;342:1503-1506.

Poort SR, Rosendaal FR, Reitsma PH, et al. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated prothrombin levels and an increase in venous thrombosis. Blood 1996;88:3698-3703.

Segal JB, Brotman DJ, Necochea AJ, et al. Predictive value of Factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. JAMA 2009;301:2472-2485.