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Review

Hereditary thrombophilia

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Summary. Thrombophilia is a group of disorders in which blood has an increased tendency to clot. It may be caused by inherited or acquired conditions. Thrombophilia is associated with risk of deep venous thrombosis and/or venous thromboembolism. Factor V Leiden thrombophilia is the most common inherited form of thrombophilia and prothrombin-related thrombophilia is the second most common genetic form of thrombophilia, occurring in about 1.7-3% of the European and US general populations (3). Thrombophilia may have autosomal dominant, autosomal recessive or X-linked inheritance. Genetic testing is useful for confirming diagnosis and for differential diagnosis, recurrence risk evaluation and asymptomatic diagnosis in families with a known mutation. (www.actabiomedica.it)

Key words: thrombophilia, deep venous thrombosis, venous thromboembolism

Thrombophilia is a group of disorders in which blood has an increased tendency to clot. It may be caused by inherited or acquired conditions. Secondary disorders include heparin-induced thrombocytopenia, antiphospholipid antibody syndrome, neoplasia, oral contraceptive use, obesity, smoking and surgery. Primary disorders or genetic causes of thrombophilia include factor V Leiden mutation, deficiency of antithrombin III, protein C or S, histidine-rich glycoprotein deficiency and prothrombin-related thrombophilia.

Thrombophilia is associated with risk of deep venous thrombosis and/or venous thromboembolism. Sometimes the thrombosis occurs in uncommon sites, such as the splanchnic veins, cerebral veins and retinal vein, however the clinical expression of hereditary thrombophilia is variable. Some individuals never develop thrombosis, others may remain asymptomatic until adulthood and others have recurrent thromboembolism before 30 years of age.

Factor V Leiden thrombophilia is the most common inherited form of thrombophilia. The prevalence in the US and European general populations is 3-8% for one copy of the factor V Leiden mutation; about 1:5000 persons have two copies of the mutation (1). Moderate protein S deficiency is estimated to affect 1:500 individuals. Severe deficiency is rare and its prevalence is unknown (2). Moderate protein C deficiency affects about 1:500 individuals. Severe deficiency occurs in about 1:4000000 newborns (2). Prothrombin-related thrombophilia is the second most common genetic form of thrombophilia, occurring in about 1.7-3% of the European and US general populations (3). Hereditary antithrombin III deficiency has a prevalence of 1:500-5000 in the general population (4).

Clinical diagnosis is based on medical history, physical examination, laboratory data and imaging. Genetic testing is useful for confirming diagnosis, and for differential diagnosis, recurrence risk evaluation and asymptomatic diagnosis in families with a known

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mutation. Differential diagnosis should consider the above conditions and secondary causes of thrombosis.

Thrombophilia has autosomal dominant, autosomal recessive, or X-linked inheritance (Table 1). Pathogenic variants may be missense, nonsense, splicing or small indels. Large deletions/duplications have been reported in *F5, SERPINC1, PROS1, PROC, F9, FGA*, *FGB*.

MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes and MLPA to detect duplications and deletions in *F5, SERPINC1, PROS1, PROC, F9, FGA* and *FGB*. Worldwide, 78 accredited medical genetic laboratories in the EU and 27 in the US, listed in the Orphanet (5) and GTR (6) databases, respectively, offer genetic tests for thrombophilia. The guide-

Table 1. Genes associated with various forms of thrombophilia

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
F5	612309	THPH2	188055	AD	Activation of prothrombin to thrombin
F2	176930	THPH1	188050	AD	Coagulation and maintenance of vascular integrity
SERPINC1	107300	AT3D	613118	AD	Inhibition of thrombin, regulation of blood coagulation cascade
HRG	142640	THPH11	613116	AD	Adaptor protein involved in coagulation, fibrinolysis
PROS1	176880	THPH5, THPH6	612336, 614514	AD, AR	Prevention of coagulation, stimulation of fibrinolysis
SERPIND1	142360	THPH10	612356	AD	Thrombin, chymotrypsin inhibitor
PROC	612283	THPH3, THPH4	176860, 612304	AD, AR	Regulation of blood coagulation by inactivating factors Va and VIIIa
F13B	134580	Deficiency of B subunit of factor XIII	613235	AR	B subunit of factor XIII, stabilizes fibrin clots
F9	300746	THPH8	300807	XLR	Activates factor X
PLAT	173370	THPH9	612348	AD	Involved in tissue remodeling, degradation
THBD	188040	THPH12	614486	AD	Regulation of amount of thrombin
FGB	134830	Congenital dysfibrinogenemia	616004	AD	Beta component of fibrinogen. After vascular injury, fibrinogen is converted into thrombin to form fibrin (major component of blood clots)
FGG	134850	Congenital dysfibrinogenemia	616004	AD	Gamma component of fibrinogen. After vascular injury, fibrinogen is converted into thrombin to form fibrin (major component of blood clots)
HABP2	603924	THPH1	188050	AD	Role in coagulation and fibrinolysis systems
MTHFR	607093	THPH1	188050	AD	Conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate

THPH=thrombophilia; AT3D=antithrombin III deficiency; AD=autosomal dominant; AR=autosomal recessive; XLR=X-linked recessive

lines for clinical use of genetic testing are described in Genetics Home Reference (2).

Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with cardiac disorders. When a suspect of thrombophilia is present, we perform the analysis of all the genes present in this short article.

In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of ≥99% (coverage depth ≥10x).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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