F12: KIT FOR THE DETECTION OF GENETIC RISK FACTOR OF VENOUS THROMBOSIS, ICTUS AND MYOCARDIAL INFARCTION

Description

F-12 is a diagnostic kit that detects the predisposition of certain groups of patients to deep-vein thrombosis (DVT) as a result of a genetic mutation that interferes with the clotting process. DVT is a complex pathology that affects the blood clotting system. The consequences are well known and include acute myocardial infarction, pulmonary embolism and stroke.

The kit F12 allows the study of the 46C/T polymorphism of the Factor XII gene. Homozygous individuals T/T for this factor have a risk of suffering an episode of thrombosis 5 times higher than others.

Hemostasis is the stoppage of bleeding. It requires the combined activity of regulator mechanisms that limit the accumulation of platelets and fibrin in the area of the wound. Hemostatic abnormalities can lead to haemorrhaging or thrombosis.

Hypercoagulability is a state in which the patient is more predisposed to producing blood clots, which can trigger a thrombosis.

Thrombosis is the main cause of death in acute myocardial infarction, cerebrovascular accidents (stroke) and venous thrombosis (Jandl et al., 1996; Goldhaber et al., 1994).
Its prevalence is > 10%, including undiagnosed thrombotic events (Nordstrom et al., 1992).

It may be responsible for 27% of all deaths in Western societies (Murray et al., 1997).
In the United States alone, there are 2 million cases of thrombosis each year.

Thrombophilia, the genetic predisposition to thrombotic events, is a complex disease caused by genetic factors, acquired factors and the interaction of both.

It has recently been estimated that 60% of the predisposition to thrombosis is due to genetic factors (Souto et al., 2000), yet little is known about them.

Currently, only 4 genetic factors are widely accepted as molecular markers of risk of thrombosis:

- Factor V Leiden mutation
- Prothrombin mutation
- MTHFR polymorphism
- C46T polymorphism of the FXII gene

It should be noted that the presence of 2 or more of these genetic factors increases the risk of thrombosis in comparison to patients presenting only 1.

Thrombophilia is diagnosed in:

- Patients who have had a thrombotic episode and their relatives of the first degree.
- Patients who have had recurrent miscarriages.
- Patients with a family history of thrombosis who are going to be exposed to prothrombotic conditions (e.g., surgery, oral contraceptives, etc.)

Format and technique

The genetic study is performed amplifying by PCR the fragment of the gene where the polymorphism is located. The detection of the product of the amplification is done using an ELISA.

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Current situation

The technical validation of the methodology developed for the analysis of the polymorphism C46T of the Factor XII gene was done comparing it with the existing one: Factor XII Real-Time PCR and analysis by RETR (Resonance Energy to Transfer Probes) (Tirado I et al., 2003) with the technique of detection of change of nucleotide using ELISA. The validation was carried out using 122 biological samples (blood or DNA) received from the hospitals Miguel Servet and Clínico from Zaragoza and the Hospital Sant Pau from Barcelona.

Publications

Some studies have shown the involvement of the FXII C46T polymorphism in venous thrombosis (Tirado I et al., Throm. Haemost. 2004; 91: 899-904), myocardial infarction (Santamaria et al., accepted in the journal Haematologica) and stroke (Santamaria et al., accepted in the journal Stroke).

1. Tirado I et al. **Association after linkage analysis indicates that homozygosity for the 46C→T polymorphism in the F12 gene is a genetic risk factor for venous thrombosis.** Thromb Haemost. 2004 May; 91(5):899-904.

2. Santamaria A et al. **Homozygosity of the T Allele of the 46 C3T Polymorphism in the F12 Gene Is a Risk Factor for Ischemic Stroke in the Spanish Population**. Stroke 2004;35:1795-1799

3. Pérez-Montes R et al. **Deep venous thrombosis, protein S deficiency and homozygous Factor XII 46T mutation**. Eur J Pediatr (2005) 164: 591–593

4. Santamaria A et al. **Double heterozygosity for Factor V Leiden and Factor V Cambridge mutations associated with low levels of activated protein C resistance in a Spanish thrombophilic family.** Thromb Haemost 2005; 93: 1193-5. Case report.

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