

## Molecular Biology

### **Factor V Leiden gene mutations.**

Activated protein C (APC) is a serine protease with potent anti-coagulant properties. During normal haemostasis, APC limits clot formation by inactivation of factors Va and VIIIa. It has been shown that APC resistance is associated with a risk of deep vein thrombosis (DVT). This resistance is mostly due to a single point mutation in Factor V Leiden (FVL) gene mutation at position 1691 G to A, that codes for factor V, produces **Arg506Gln**. This mutation prevents the optimal inactivation of activated factor V by APC and become a genetic risk factor DVT. Some studies also suggested an association between F5L gene mutation and late pregnancy complications.

### **Prothrombin gene mutations.**

Another candidate for the hereditary factor for DVT is a mutation in the prothrombin gene. Prothrombin is a precursor of the serine protease thrombin a key enzyme in the processes of haemostasis and thrombosis. It has been found that in the 3'-UT (untranslated) region of the gene there is a G to A substitution at nucleotide position 20210. This G20210A allele is associated with higher plasma prothrombin levels in subjects and it is a mild risk factor for thrombotic events.

### **JAK2 (V617F) mutations.**

This test identifies the clonal V617F JAK2 activating mutation present in many myeloproliferative disorders (MPD), particularly in more than 70% of the PV. The three main disorders are polycythemia vera (PV), essential thrombocytopenia (ET) and idiopathic myelofibrosis (IMF). As this is an acquired somatic point mutation at the level of multipotent haematopoietic stem cell, it is characterised by increased blood cell production, particularly increased production of erythroid and myeloid cells.

### **HFE gene mutations.**

Hereditary haemochromatosis (HH) is a genetic disease associated with progressive iron overload in a variety of organs, and is common in Caucasians. Two mutations are tested, a substitution of cysteine for tyrosine at amino acid 282 (C282Y, nucleotide 845) and histidine for aspartate at amino acid 63 (H63D, nucleotide 187). Over 90% of UK hereditary haemochromatosis patients are homozygous for the C282Y mutation and H63D mutation is a mild risk factor for HH.

### **HLA B27 allele status.**

Ankylosing spondylitis (AS) is a condition characterised by ossification of the spinal ligaments and stiffness of sacro-iliac joints and it is known to be strongly associated with HLA class I specificity B27. This test is not diagnostic because 7% of the Caucasian population have HLA B27 positive allele but not AS, however the absence of HLA B27 virtually excludes AS.

### **MTHFR gene mutations.**

A common polymorphism in the *methylenetetrahydrofolate reductase* (MTHFR) gene, where a cytosine at nucleotide 677 is replaced by a thymine (677C→T), is associated with reduced enzyme activity and thermolability of MTHFR. Elevated plasma homocysteine level has been reported in patients homozygous to this mutation

and it has been identified as a risk factor for cerebrovascular, peripheral vascular and coronary heart disease.