Clinical pathological conference, college of medicine, university of Mosul

Presented by: IHSAN MARDAN HUMOOD

Supervised by: Dr. MUNA A.KASHMOLA

Name :Rose Basheer

Age : 5 years old

Sex : Female

Address : Ba'asheqa

Chief complaint:

Loss of consciousness for 15 minutes duration.

History of present illness:

Five years old girl presented with loss of consciousness for 15 minutes, and she developed weakness of right upper and lower limbs.

History of present illness: *continue*

This condition occurred suddenly with neither history of trauma nor falling from height.

She was admitted to hospital and treated as a case of stroke.

History of present illness: *continue*

All the investigations that were done for her including CBP, RFT, LFT, S. electrolytes, U/S of the abdomen, X-ray of the chest and echocardiogram are normal for her age, CT-scan of the brain showed ischemia

History of present illness: *continue*

She received treatment of stroke, then after 2 weeks discharged from hospital.

Review of other systems:

CVS: No cyanosis, no chest pain.

RS: No SOB, no attacks of apnea.

GIT: Nothing significant.

Family history:

Negative family history of same condition.

On examination:

Nice girl, not pale, no jaundice, no purpura, no LAP.

Chest: clear, NVB.

Abdomen: soft, no palpable mass.

BP: 120/60 PR:70 Temp:37°C

On examination:

Weakness of right upper limb, sensation was intact.

No cranial nerve deficit.

1 month later after discontinuation of treatment, blood sample was drawn to do screening for thrombophilia as a predisposing factor for her condition.

Thrombophilia testing:

- Prothrombin time 14 sec.
  control 13 sec.
  INR 1.1
- Activated partial thromboplastin time
  33 sec.
  control 33 sec.

Thrombophilia testing:

	N.R
Protein C activity (ELISA):	
95 %	72-150
Protein S activity (ELISA):	
98 %	70-150
Antithrombin (Radioimmunodiffusion)	
8 mg/ml	3-12

Thrombophilia testing:

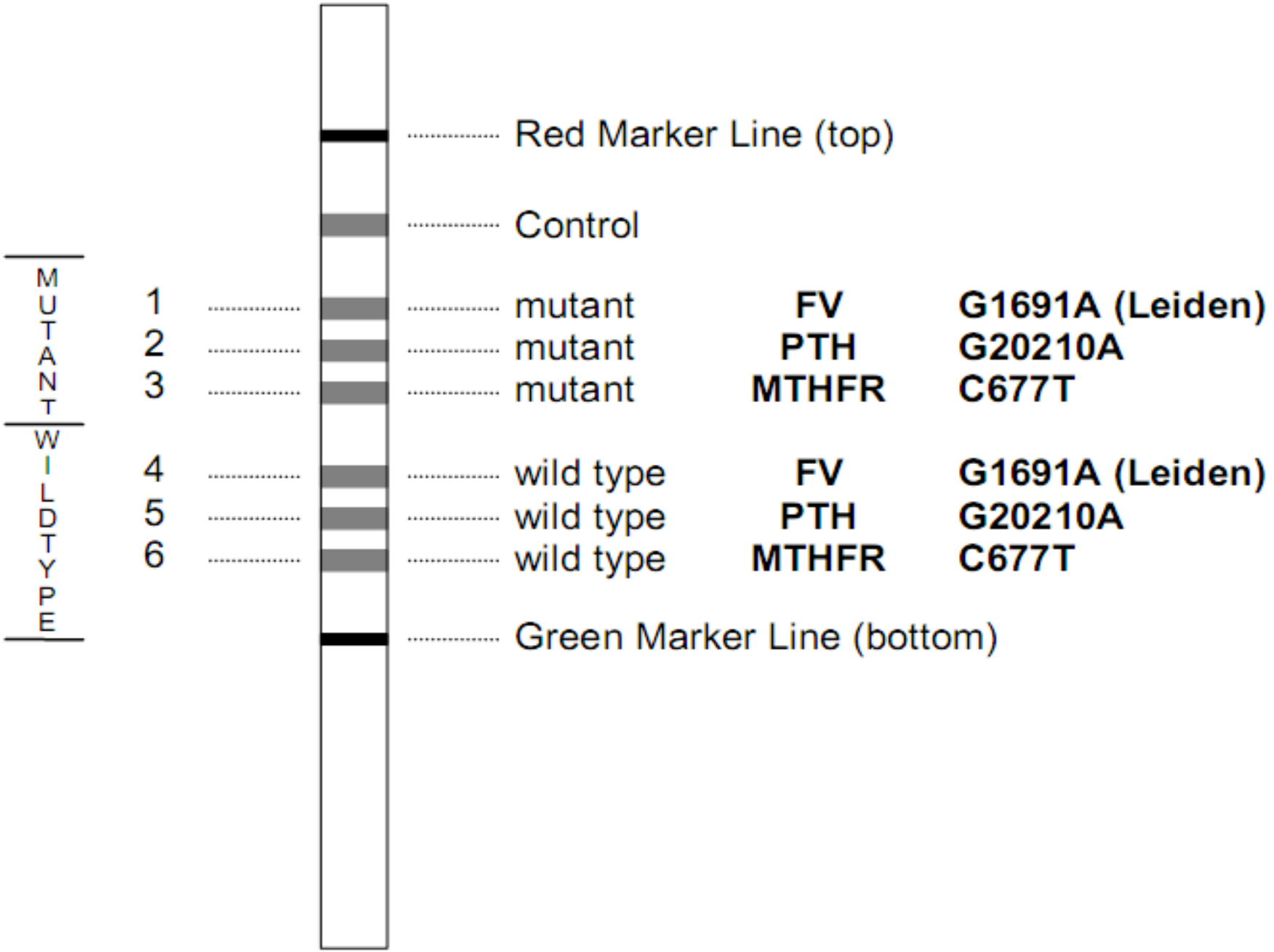
USING viena Lab kit for thrombophilia study:

- DNA extraction
- Amplification
- Reverse hybridization using specific prob for

F V leiden

Prothrombin II

MTHFR


Red Marker Line (top)
Control
MUTANT
1 mutant FV G1691A (Leiden)
2 mutant PTH G20210A
3 mutant MTHFR C677T
WILDTYPE
4 wild type FV G1691A (Leiden)
5 wild type PTH G20210A
6 wild type MTHFR C677T
Green Marker Line (bottom)

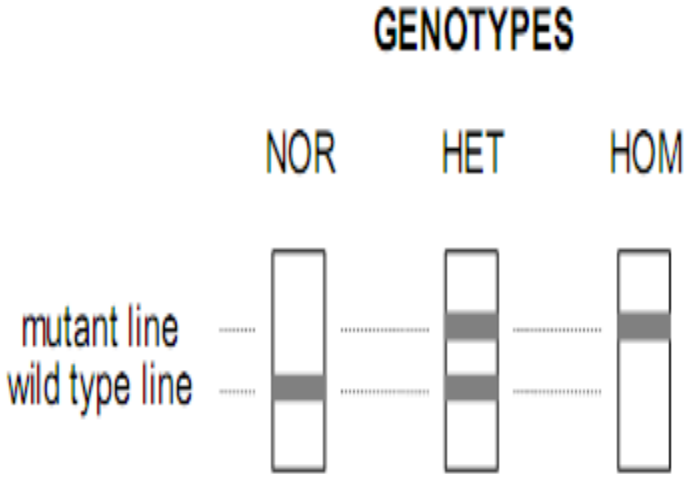
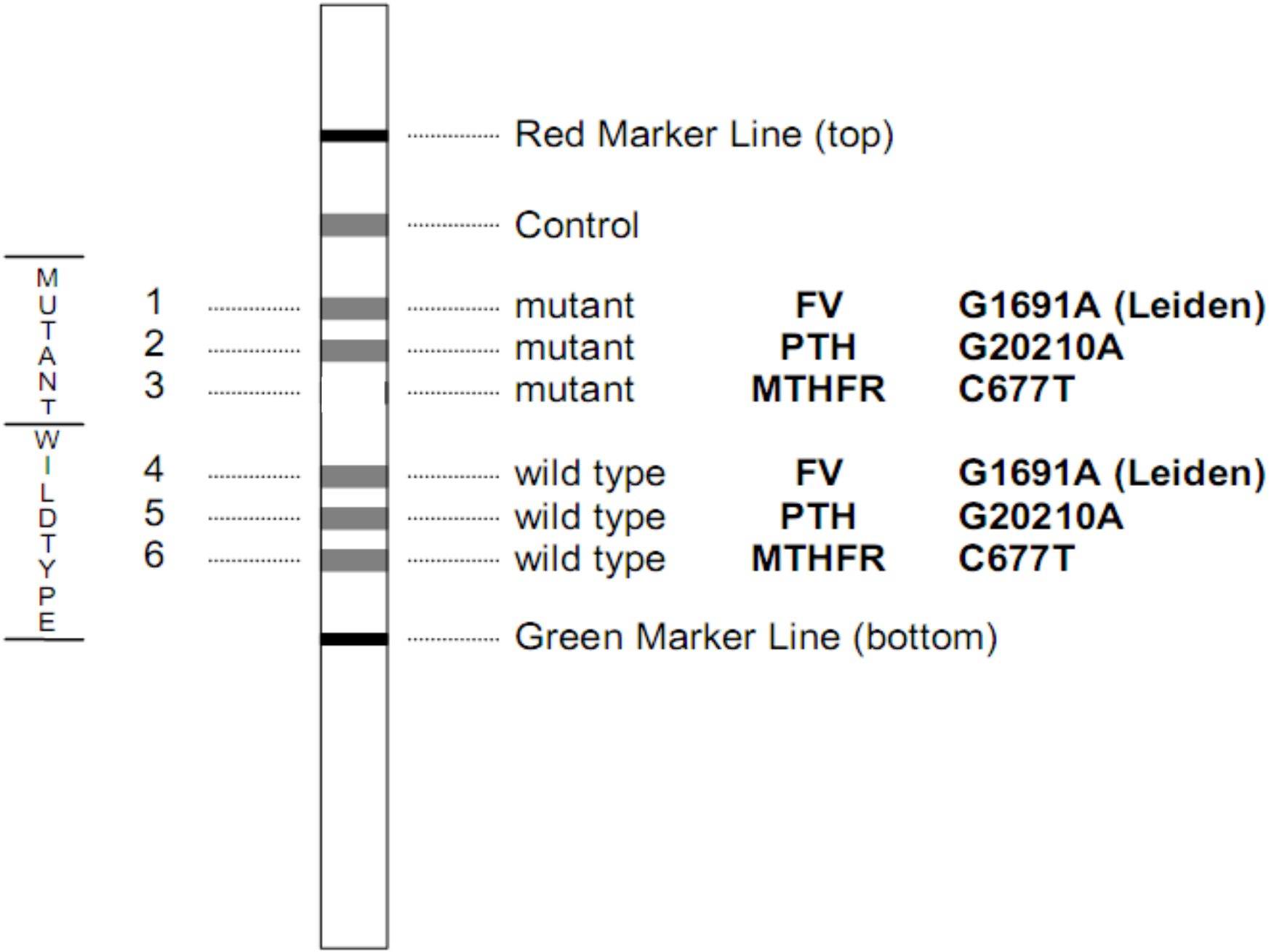


Fig. 2

	wild type line	mutant line	genotype
NOR	**positive**	negative	normal
HET	**positive**	**positive**	heterozygous
HOM	negative	**positive**	homozygous mutant


Red Marker Line (top)
Control
MUTANT
1 mutant FV G1691A (Leiden)
2 mutant PTH G20210A
3 mutant MTHFR C677T
WILDTYPE
4 wild type FV G1691A (Leiden)
5 wild type PTH G20210A
6 wild type MTHFR C677T
Green Marker Line (bottom)

THE RESULT SHOWS DOUBLE HETEROZYGOUS MUTATIONS FOR BOTH F V LEIDEN AND PROTHROMBIN GENE.

Inherited thrombophilia

Established
Activated protein C resistance (factor V:R506Q, V Leiden)
Protein C deficiency
Protein S deficiency
Antithrombin deficiency
Hyperhomocysteinemia
Elevated prothrombin levels (mutation G20210A)
Nonestablished as hereditary
Elevated factor VIII levels
Heparin cofactor II deficiency
Plasminogen deficiency
Elevated plasminogen inactivation inhibitor 1
Dysfibrinogenemia

Prevalence of heritable thrombophilias shown to be associated with at least a twofold increased risk of venous thrombosis in patients and controls and relative risk of a first episode of venous thrombosis.

	General population	*Consecutive patients with a first episode of venous thrombosis*	*Relative risk of venous thrombosis*
Antithrombin	0.03%	1%	10–20
Protein C deficiency	0.3%	3%	10
Protein S deficiency	0.3%	3%	?–10
FVR506Q (FV Leiden)*	4%	15%	4
*F2*G20210A*	2%	4%	2

FV R506Q (factor V Leiden)

- The gene for FV is located on chromosome 1, and contains 25 exons spanning 80 kb. FV (2196 amino acids, 330 kDa, plasma concentration of free protein 30 nmol/L) is the cofactor for activation of prothrombin by FXa in the prothrombinase complex.

FV R506Q (factor V Leiden)

- Thus thrombin generation is rate limited by FVa, and inactivation of FVa by APC attenuates thrombin generation.
- The plasma half life is 15 hours. It has no cofactor activity until cleaved by thrombin or FXa.

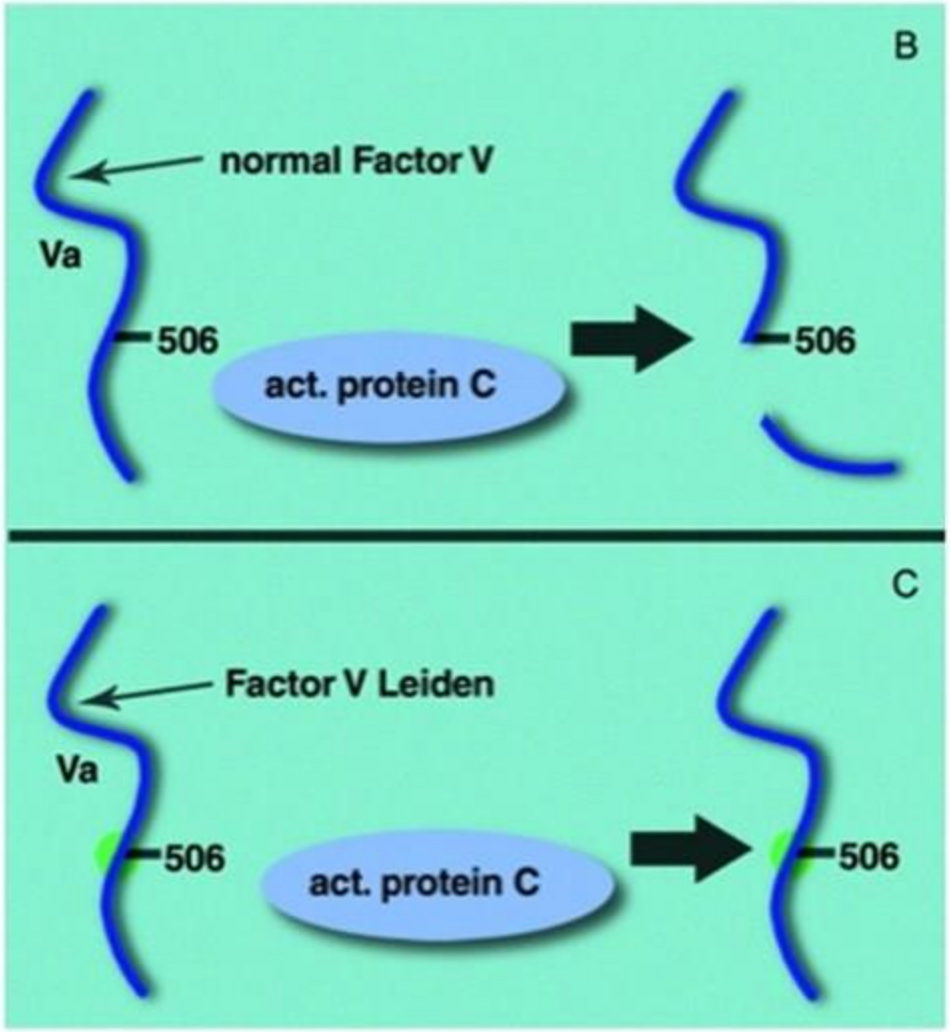
FV R506Q (factor V Leiden)

- A guanine to adenine transition at nucleotide 1691 in exon 10 of the FV gene results the FV Leiden mutation.
- Mutant FV Leiden has normal procoagulant activity but substitution of glutamine for arginine at position 506 results in slower inactivation by APC.

FV R506Q (factor V Leiden)

- The FVR506Q mutation is present in about 4% of the white population and about 15% of unselected consecutive patients with a first venous thrombosis.
- The prevalence is highest in northern Europeans.

Figure 7-2 A, Sites of action of the natural anticoagulants; B, method of inactivation of factor V; and C, demonstration of the inability of activated protein C, to inactive factor Va when the factor V Leiden mutation is present



Moll, S. et al. ASH-SAP 2010;2010:179-215

FV R506Q (factor V Leiden)

- The population baseline risk of thrombosis is about 1 per 10000 per year under the age of 40.
- If a woman used a COC it would increase about fourfold to about 4 per 10000 per year.
- For a woman with the factor V Leiden mutation, her baseline risk of thrombosis would be about 1 per 2000 per year under the age of 40, If this woman were to take a COC, her absolute risk would increase from 1 per 2000 to 1 in 300, a risk that is increased about sevenfold for her but which is 35 - fold greater than the population baseline risk.

F2 G 20210 A (Prothrombin)

- The gene for prothrombin is located on chromosome 2 and contains 14 exons spanning 21 kb.
- Prothrombin is a vitamin K - dependent protein synthesized in the liver (579 amino acids, 72 kDa, plasma concentration 2μmol/L).

F2 G 20210 A

- Prothrombin is the zymogen precursor of thrombin.
- The prevalence of the F2 G20210A mutation is about 2% of whites.
- A single nucleotide change, guanine to adenine at position 20210 of the prothrombin gene (F2G20210A), is -

F2 G 20210 A

-associated with elevated plasma prothrombin levels and an increased risk of venous thrombosis.

- The mutation increases the plasma level of prothrombin by about 30% but the mechanism has not been explained.

F2 G 20210 A

- No specific clotting test for the presence of the mutation has been described and diagnosis depends on detection of the genetic mutation by DNA analysis.

Homocysteine Hyperhomocysteinaemia may be caused by genetic abnormalities (homozygous cystathionine β-synthase deficiency and homozygous deficiency of methylenetetrahydrofolate reductase) result in congenital homocysteinuria associated with an increased risk of both arterial and venous thrombosis as well as premature atherosclerosis and mental retardation, epilepsy, and skeletal and eye problems. Half of patients present with venous or arterial thrombosis before the age of 30 years.

Other natural anticoagulants

- Tissue factor pathway inhibitor (TFPI) is an inhibitor of FXa and tissue factor bound FVIIa.
- Protein Z is a vitamin K – dependent protein that circulates in complex with PZI (protein Z dependent protease inhibitor) and catalyses the inhibition of FXa.
- Heparin cofactor II, a serpin with a similar structure –function relationship to antithrombin, inhibits thrombin when activated by glycosaminoglycans.

Other procoagulant factors

- Increased FVIII levels are associated with an increased risk of both venous and arterial thrombosis.
- Elevated FIX and FXI levels are also associated with venous thrombosis risk.
- There is equivocal evidence for a causal relationship between fibrinogen levels and venous thrombosis.
- Dysfibrinogenaemia has been found in less than 1% of patients with a history of venous thromboembolism.

Other procoagulant factors

- It was previously thought that deficiency of FXII was a risk factor for venous thromboembolism but subsequent investigation strongly indicates that this is unlikely.
- A polymorphism in the FXIII gene (FXIIIV341L) is significantly less common in patients with coronary heart disease than in control subjects and a protective effect for venous thromboembolism has been reported.

THANK YOU VERY MUCH
FOR YOUR ATTENDANCE