

General background text Pharmacogenetics – Factor V Leiden

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Definitions in pharmacogenetics

The **genotype** is the hereditary information about a specific characteristic of an individual. This information is located in the genes, in the DNA that consists of nucleotides. The piece of the DNA that carries information for one specific hereditary characteristic is called a **gene**. The DNA is divided into chromosomes, which usually occur in pairs. A gene generally consists of two **alleles**; each allele is located on one of the chromosomes of a chromosome pair. People **homozygous** for an allele are those that have the same allele on both chromosomes. People **heterozygous** for an allele have different alleles on each chromosome.

The **phenotype** indicates what the final manifestation (phenotypic state) of a certain genotype is. This can involve the functionality of a protein (for example the enzyme or the receptor), but also the physical manifestation of a disease. The phenotype is a result of the genotype that a person possesses, the degree of expression of the gene in question and the combination with environmental factors such as co-medication, diet and disease conditions.

Variations can exist in a population within the DNA that encodes a protein. Variations can result in alleles that encode for proteins with no or reduced activity. The simplest form of variations are “**single-nucleotide polymorphisms**” (**SNPs**), in which a certain part of a gene differs by only one nucleotide. If a gene variation occurs in at least 1% of the population, then this is referred to as a genetic **polymorphism**. **Wild-type** is the name given to the most common active allele. There can be a number of different polymorphisms for a certain allele.

Factor V Leiden

Activated factor V is one of the blood clotting factors that play a role in the formation of thrombin and fibrin, resulting in the formation of a clot. Activated factor V is cleaved by activated protein C (APC) at amino acid Arginine 506, which inactivates factor V [1].

In the allele variant factor V Leiden (fVL), the amino acid arginine is replaced with glutamine. This causes APC-driven cleavage of activated factor V to take place about 10x more slowly. This results in the clotting cascade remaining active for longer and blood clotting to increase. This is called APC resistance (although APC resistance includes more than fVL variant alone) [1 Increased blood clotting may result in venous thromboembolism (VTE).

Oestrogen-based contraceptives may further increase the risk of VTE, likely due to acquired APC resistance [1].

Prevalence of the factor V Leiden variation

The highest incidence of the fVL variant is found in European populations and ranges from 2.0% in Germany to 7.0% in Greece. The prevalence of patients heterozygous for the fVL variant in Europe ranges from ~3% in the Netherlands and Iceland to 9% in Great Britain and 13% in Greece. The prevalence of homozygous patients is many times lower, between 0% and 1%. The incidence of the fVL variant is also lower in Asia and Africa. Approximately 5% of the white population in the United States is heterozygous for the fVL variant, compared to 2.2% of Hispanic Americans, 1.2% of African Americans and 0.5% of Asian Americans [2,3,4].

Risk of venous thromboembolism

In the absence of the fVL variant:

- Without oestrogen-based contraceptives, the absolute risk of VTE is 1:10,000;

- With oestrogen-based contraceptives, the risk of VTE is on average 2-6-fold increased [10,1], where third-generation oral contraceptives are associated with a 1.5-2-fold increased risk versus second-generation oral contraceptives [5,6,7].

Heterozygous for the fVL variant:

- Without oestrogen-based contraceptives, the relative risk of VTE is on average 6-9-fold increased versus patients without the fVL variant not using contraceptives [8, 9, 10].
- With oestrogen-based contraceptives, the relative risk of VTE associated with second-generation oral contraceptives is on average 1.3-4-fold increased [8,11] and with third-generation oral contraceptives on average 4.5-6-fold increased [6,9] versus patients with the fVL variant not using contraceptives.

The absolute risk of VTE is approximately 30-50:10,000, of which approximately 1% will involve a fatal pulmonary embolism.

Homozygous for the fVL variant:

- Without oestrogen-based contraceptives, the relative risk of VTE is on average 50-80-fold increased versus patients without the fVL variant not using contraceptives, but this is based on small patient numbers [10];
- With oestrogen-based contraceptives: the risk of VTE with contraceptive usage is not known.

Women homozygous for the fVL variant have a baseline risk of VTE high to the extent that a further increase of this risk associated with the use of oestrogen-based contraceptive is not considered acceptable. The use of oestrogen-based contraceptives is therefore not recommended [12,13,14,15].

Other risk factors of VTE:

- Other hereditary bleeding diseases such as antithrombin deficiency, protein C deficiency, protein S deficiency or factor II variations [14,16,17,18];
- Immobilisation [9,18,19];
- Surgery [9,18,19];
- Trauma [9,19];
- Age [3];
- Obesity (body mass index > 30 kg/m²) [8].

Literature

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