General background text Pharmacogenetics - CYP3A5

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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.

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 for the DNA that encodes for 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.

Altered metabolic capacity and clinical consequences

The cytochrome P450 enzymes, which include the iso-enzyme CYP3A5, are involved in the metabolism of many medicines. CYP3A5 and the related enzyme CYP3A4 are involved in the metabolism of 50-60% of all medicines [1-2].

Variations in the gene that encodes for the CYP3A5 iso-enzyme can result in the enzyme activity being reduced or completely absent.

The population can be divided into three phenotypes, based on the metabolic capacity of CYP3A5 that is present:

- CYP3A5 non-expressor, no metabolic capacity;
- heterozygous CYP3A5 expressor, reduced metabolic capacity;
- homozygous CYP3A5 expressor, "normal" metabolic capacity;

In contrast to most of the other polymorphic enzymes, the phenotype with "normal" metabolic activity does not occur for CYP3A5, but the phenotype without metabolic capacity is the most common in the Caucasian and Asian populations (also refer to the section on ethnic variation).

The difference in metabolic capacity can have therapeutic consequences if the plasma concentration is related to the effect or the occurrence of side effects. It may be necessary to change the standard dose or to opt for a different medicine.

As the genotype only determines part of the metabolic capacity, the guidelines for dose adjustment based on the genotype are no more than a tool that can be used to achieve the desired plasma concentration. In order to optimise the dose, therapeutic drug monitoring (TDM) can be useful for substances that usually have a therapeutic guideline and where plasma concentration is related to effect or side effects.

Genotyping

The process of genotyping is used to determine the genotype. It indicates which alleles of the gene for CYP3A5 are present in the tested individual. Each allele has a name that consists of a star (*) and a number, an example of a possible CYP3A5 genotype is CYP3A5*1/*3.

More than 10 different allele variations have been identified/described in the literature for CYP3A5. The most important variations are listed in Table 1, including their functionality. Genotyping usually screens for only the most common variant alleles. This is the *3 allele for CYP3A5. As a result, the reported genotype can differ from the actual genotype.

It has been observed for CYP3A5 that two genes can occur on one chromosome. This means that a part of the population has more than 2 CYP3A5 alleles. For example, in the Dutch population, 90% of individuals with a *2 allele also have two *3 alleles (also refer to Table 2).

Table 1. CYP3A5 alleles and metabolic capacity [2]

allele number	metabolic capacity

*1	normal
*2	reduced
*3	absent
*4	reduced
*5	reduced
*6	absent
*7	absent

Ethnic variation in prevalence of genotypes and allele frequency

In the Caucasian and Asian race and in Zimbabwe, *3 is the most common allele and the majority of the population has the *3/*3 genotype. This allele and genotype have a much lower prevalence in African-Americans.

In addition to *3, the *2 allele also occurs at a low frequency in Caucasian populations, whilst *6 and *7 occur primarily in Africans and African-Americans.

Table 2. Ethnic variation in prevalence of genotypes and allele frequency [1-3]

	prevalence of genotype (%)					allele frequency (%)						
	*1/*1	*1/*3	*2/*3	*2/*3/*3	*3/*3	*1	*2	*3	*4	*5	*6	*7
Caucasian					50-85		0.7-2	70-93		0	0	0
Dutch [1]	0.2	16.4	0.2	1.8	81.4	8	1	91.7	0	0	0.1	0
Asian					50-55			70-75		0.9	0	0
African (Zimbabwean)					60		0	78		0	22	10
African-American					7-25		0	27-50			13	10

Literature

1. van Schaik RHN et al. CYP3A5 variant alleles in Dutch Caucasians. Clin Chem 2002; 48:1668–1671.
2. Xie HG et al. Genetic variability in CYP3A5 and its possible consequences. Pharmacogenomics 2004;5:243-72.
3. Roy JN et al. CYP3A5 genetic polymorphisms in different ethnic populations. Drug Metab Dispos 2005; 33:884–887.