General background text Pharmacogenetics - CYP2C9

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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 person generally has two copies (**alleles**) of a gene, one on each 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 CYP2C9, are involved in the metabolism of many medicines. CYP2C9 is involved in the metabolism of approx. 10%-20% of all medicines [1,2].

Variations in the gene that encodes for the CYP2C9 iso-enzyme can result in reduced or absent enzyme activity. The population can be divided into three phenotypes, based on the metabolic capacity of CYP2C9 that is present: As there is a clinically significant difference in the remaining metabolic capacity of the two most common alleles (*2 and *3), the two phenotypes with reduced metabolic capacity are further sub-divided based on the presence of this or other alleles (see below and table 1).

- poor metaboliser (PM), severely reduced metabolic capacity (two alleles with reduced enzyme activity), sub-divided into (first three ranked according to decreasing metabolic capacity):
  - two *2 alleles (*2/*2)
  - one *2 allele and one *3 allele (*2/*3)
  - two *3 alleles (*3/*3)
  - two alleles with reduced activity, of which at least one is not *2 or *3 (PM OTHER)
- intermediate metaboliser (PM), reduced metabolic capacity (one allele with reduced enzyme activity and one allele with normal enzyme activity), sub-divided into (first two ranked according to decreasing metabolic capacity):
  - allele with reduced enzyme activity is *2 (*1/*2)
  - allele with reduced enzyme activity is *3 (*1/*3)
  - allele with reduced enzyme activity is neither *2 nor *3 (IM OTHER)
- extensive metaboliser (EM), "normal" metabolic capacity (two alleles with normal enzyme activity) (*1/*1).

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.

Table 1. Genotype-phenotype translation

genotype		**phenotype predicted based on genotype (pharmacogenetic contraindication)**
description	**examples**	
two alleles with normal enzyme activity	*1/*1, *1/*9	*1/*1
*2 and one allele with normal enzyme activity	*1/*2	*1/*2
*3 and one allele with normal enzyme activity	*1/*3	*1/*3
one allele with decreased enzyme activity other than *2 and *3 and one allele with normal enzyme activity	*1/*8, *1/*11	genotype other - phenotype interm.metab (abbreviated: IM OTHER)
two *2 alleles	*2/*2	*2/*2
one *2 and one *3 allele	*2/*3	*2/*3

two *3 alleles	*3/*3	*3/*3
two alleles with decreased enzyme activity, of which at least one is neither *2 or *3	*2/*8, *3/*11, *8/*11	genotype other - phenotype poor metab (abbreviated: PM OTHER)

Genotyping

The process of genotyping is used to determine the genotype. It indicates which alleles of the gene for CYP2C9 are present in the tested individual. Each allele has a name that consists of a star (*) and a number, an example of a possible CYP2C9 genotype is CYP2C9*1/*3.

Many variations exist for CYP2C9, approximately 30 different allele variations have been identified/described in the literature. The most important variations are listed in Table 2, including their functionality. Genotyping usually screens for only the most common variant alleles. As a result, the reported genotype can differ from the actual genotype.

Table 2. CYP2C9 alleles and metabolic capacity [3,6,7]

allele number	metabolic capacity	
	in vivo	*in vitro*
*1	normal	
*2	reduced	
*3	reduced	
*4		reduced
*5	reduced	
*6	absent	
*7		
*8	reduced	
*9		
*10		
*11	reduced	
*12		reduced
*13	reduced	

For at least the variant alleles *2 and *3, there are large substrate-specific differences in metabolism. In the case of CYP2C9*2, the substrate affinity is not significantly altered, but the maximum conversion rate (Vmax) is approximately half that of CYP2C9*1. In the case of the variant allele CYP2C9*3, both the Michaelis-Menten constant Km and the maximum conversion rate Vmax are significantly altered in comparison to CYP2C9*1 (increased and reduced, respectively) [2,4].

Ethnic variation in prevalence of genotypes and allele frequency

The variant alleles *2 and *3 have a particularly high prevalence in the Caucasian race. There is a large variation in the frequency of occurrence between the different Caucasian populations. For *2, this varies from 8% to 19% and for *3 from 3% to 16% [1]. These alleles have a much lower prevalence in the African and Asian population groups. Other alleles (*5, *6, *8 and *11) are more common in the African population group [2].

Table 3. Ethnic variation in prevalence of genotypes and allele frequency [1,2,4,5]

	prevalence of genotype (%)						allele frequency (%)						
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	*2	*3	*4	*5	*6	*8	*11
Caucasian	65.3	20.4	11.6	0.9	1.4	0.4	11 (8-19)	7 (3-16)	0	0	0	?	0.4
Dutch [1]							14.2	9.2					
Asian	96.5	0	3.5	0	0	0	0-4	2-8	?	0	0	?	?
African	87.0	8.7	4.5	0	0	0	3-4	2	0	0-1.8	0.6-1.5	6.7	2.7

The data for allele frequency and for the prevalence of genotypes were obtained from various studies. As a result, they are not in agreement.

Literature

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