General background text Pharmacogenetics - CYP2C19

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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.

The **promoter** is an area preceding the gene, which is primarily responsible for regulation of the activity (expression) of the gene. Variations in the promoter do not result in variations in the protein product. However, variations in the promoter can affect the level of protein production, with a higher production resulting in more enzyme and thus increased enzyme activity.

Altered metabolic capacity and clinical consequences

The cytochrome P450 enzymes, which include the iso-enzyme CYP2C19, are involved in the metabolism of many medicines. CYP2C19 metabolises approximately 8% of these medicines.

Variations in the gene that encodes for the CYP2C19 iso-enzyme can result in reduced, elevated or absent enzyme activity.

The population can be divided into four phenotypes, based on the metabolic capacity of CYP2C19 that is present:

- poor metaboliser (PM), severely reduced or absent metabolic capacity (two alleles with absent or reduced activity);
- intermediate metaboliser (IM), reduced metabolic capacity (one allele with absent or reduced activity and one allele with normal or elevated activity);
- extensive metaboliser (EM), "normal" metabolic capacity (two alleles with normal activity or one with normal activity and one with elevated activity);
- ultra-rapid metaboliser (UM), increased metabolic capacity (two alleles with elevated activity).

The degree of activity for the various alleles is presented in Table 1.

There is also a large variation in metabolic capacity within each phenotype group.

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 a part of the metabolic capacity, the recommendations 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 CYP2C19 are present in the tested individual. Each allele has a name that consists of a star (*) and a number, an example of a possible CYP2C19 genotype is CYP2C19*1/*3.

Many variations exist for CYP2C19, approximately 20 different allele variations have been identified/described in the literature. The most important variations are listed in Table 1, 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 (also refer to the document "Uncertainties in genotyping results" on the KNMP website).

Table 1. CYP2C19 alleles and metabolic capacity [1]

allele number	metabolic capacity

	in vivo	*in vitro*
*1	normal	
*2	absent	
*3	absent	
*4	absent	
*5	absent	
*6	absent	
*7	absent	
*8	absent	
*9		reduced
*10		reduced
*17 [#]	increased	

[#] As the effect of one *17 allele is limited, the KNMP Working Group decided to include *1/*17 in the EM phenotype, *2/*17 and *3/*17 in the IM phenotype and only *17/*17 in the UM phenotype.

Ethnic variation in prevalence of genotypes and allele frequency

The frequency of occurrence of the variant alleles *2 and *3 is much higher in Asian population groups than in White and African populations. This results in a higher prevalence of poor metabolisers (PM) in Asians. The *4 allele is virtually absent in Asians and Africans [2-4, 16].

The frequency of occurrence of the variant allele *17 is much higher in White and African population groups than in East Asian populations [6-8, 16].

Table 2. Ethnic variation in prevalence of phenotypes predicted by gene activity and allele frequency [2-5,9-16]

		prevalence predicted phenotype (%)[#]				allele frequency (%)						
Population group	region or sub-group	PM	IM	EM	UM	*2	*3	*4	*5	*6	*8	*17
White		2.4	26	64-68	3.2-7.3	15	0.04	0.6	0	0	0	18-27
	The Netherlands	1.7-3.3	23-30	61-71	4.8-5.8	13-18	0.2					22-24
	Finland	2.9	28	65	3.6	17	0.01	0	0	0	0.05	19
	Europe without Finland	2.4	26	66	5.3	15	0.03	0.25	0	0.03	0.3	23
Asian		12-17	46-49	34-42	0.01-0.16	30	5-11	0.2	0.1	0-0.1	0	1-4
	East Asian	14	47	39	0.005	31	6	0.04	0.01	0.09	0	0.7
	South Asian	11	45	41	2.9	33	0.4	0.03	0.01	0	0.06	17
African		2.7-3.0	27-29	65-67	3.2	16-17	0.4	0	?	0	0	18
	African/Afro-American	4.1	32	59	4.4	20	0.04	0.04	0	0.01	0.05	21
Latin-American/ American, mixed ethnicity		1.3	20	77	1.0	11	0.02	0.3	0	0.07	0.08	10
Ashkenazi jewish		2.1	25	69	3.6	13	0	1.6	0	0	0.01	19

The prevalence of the predicted phenotypes is calculated using the detected allele frequencies.

Note: According to the guideline by the Association for Molecular Pathology, at least the alleles *2, *3 and *17 should always be determined when genotyping for CYP2C19 [17].

Literature

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