General background text Pharmacogenetics - CYP2B6

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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.

Most human genes consist of coding regions (**exons**) interspersed with non-coding regions (**introns**). Variations in exons usually result in variations in the protein product.

Altered metabolic capacity and clinical consequences

The cytochrome P450 enzymes, which include the iso-enzyme CYP2B6, are involved in the metabolism of many medicines. CYP2B6 is the primary metabolising enzyme for a number of medicines, including efavirenz. CYP2B6 is a hydroxylating enzyme.[1]

Variations in the activity of CYP2B6 can result in an increase or decrease of the metabolisation of medicines. The causes of variations in CYP2B6 activity are largely non-genetic. CYP2B6 is induced by xenobiotics, including pesticides and medicines such as efavirenz, rifampicin, phenytoin, phenobarbital, cyclophosphamide, carbamazepine, artemisinin derivatives, metamizole, ritonavir and statins. The constitutive androstane receptor and the pregnane-X receptor probably play a role in this induction. CYP2B6 is inhibited by medicines such as clopidogrel, ticlopidine and thiotepa [1]. In addition to this, variations in the gene that encodes for CYP2B6 can result in reduced or absent enzyme activity.

Based on the metabolic capacity of CYP2B6 present, the population can be divided into three phenotypes (see below and table 3):

- poor metaboliser (PM), severely reduced or absent metabolic capacity;
- intermediate metaboliser (IM), reduced metabolic capacity;
- normal metaboliser (NM), 'normal' metabolic capacity;

Poor metabolisers have two alleles leading to reduced or absent metabolic capacity (*6 and/or *18). Intermediate metabolisers have one allele leading to normal activity and one allele leading to reduced or absent metabolic capacity. Normal metabolisers have two alleles leading to normal activity.

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 CYP2B6 are present in the tested individual. Each allele has a name that consists of a star (*) and a number, an example of a possible CYP2B6 genotype is CYP2B6*1/*6. As the CYP2B6 alleles are still often described in the literature using different notations, the table at the end of this paragraph also lists the alternative notations for the most important alleles.

The most common gene variation is *6. This allele contains a single variation, which is located in exon 4. The *6 allele results in reduced or absent CYP2B6 activity.
Patients with African heritage can also have a second allele with reduced or absent activity, *18. This allele has a variation in exon 7.

Table 1. CYP2B6 alleles and enzyme activity [3]

enzyme activity	allele number
fully functional	*1 *5
reduced or non-functional	*6 (*7[a]) *18

[a]: The *7 allele contains, in addition to the same two nucleotide changes as in *6, the nucleotide change found in *5 [13]. In the German population, it has a prevalence of 3% compared to 11% for *5. When determining *6, this allele is also identified and will likely be classified as *6, which has the same lack of activity.

Note: PharmVar lists alleles *4 and *22 as alleles with increased activity [3]. However, CPIC indicates in its efavirenz guideline that there is insufficient evidence for clinical relevance of, and thus need for, surveillance for heterozygotes (rapid metabolisers) or homozygotes (ultra-rapid metabolisers) of these alleles (and thus insufficient evidence that *4 and *22 are clinically significantly different from alleles with normal activity and rapid and ultra-rapid metabolisers are clinically significantly different from normal metabolisers) [15].

Table 2. Overview of the notations used for the most important CYP2B6 alleles [1-3]

allele number	nucleotide change	amino acid change	Rs number
*6	516G>T	Gln172His	Rs3745274
*18	983T>C	Ile328Thr	Rs28399499

Note 1: Allele *6 also contains the polymorphism 785G>A, in addition to 516G>T. (the characteristic polymorphism in *4). However, in all the population groups that were studied, a strong linkage disequilibrium was found between both polymorphisms. As a result, determination of 516G>T corresponds well with determination of *6. [2]

Note 2: In some population groups (Tanzanians and Turkish individuals), 983T>C also occurs in combination with 785G>A (allele *16). As the *16 allele also results in reduced or absent activity, as the *18 allele does, it is not relevant for the determination of the predicted metabolic activity. [3]

Translation of genotype to phenotype/genotype group

In order to link a patient to the correct pharmacogenetic contra-indication, the genotyping result needs to be translated to a predicted phenotype or a genotype group. The table below provides the correct translation for various genotyping results.

Table 3. Link between genotyping result and predicted phenotype/genotype group

genotyping result	pharmacogenetic contra-indication (= predicted phenotype)
no gene variant with reduced activity (e.g. *1/*1 or *1/*5)	normal metaboliser (NM)
one reduced functional or non-functional gene variant (e.g. *1/*6 or *1/*18)	intermediate metaboliser (IM)
two reduced or non-functional gene variants (*6/*6, *6/*18 or *18/*18)	poor metaboliser (PM)

Phenotyping
The process of phenotyping is used to determine the phenotype, which means: measuring or estimating the activity of the CYP2B6 enzyme. As the causes of variations in CYP2B6 activity are largely non-genetic, phenotyping of CYP2B6 does not provide any information about the presence or absence of variant alleles.

Ethnic variation in prevalence of phenotypes and allele frequency

The frequency of occurrence of the various CYP2B6 alleles and the different phenotypes varies between ethnic groups.

The *6 allele occurs in all population groups, but the frequency can vary strongly between countries and ethnic groups. The *18 allele occurs almost exclusively in people of African heritage.

Table 4. Ethnic variation in prevalence of genotypes and genotype groups and allele frequency [1,2,4-12, 14]

		prevalence of genotype/genotype group (%)			allele frequency (%)		
ethnicity	country	NM	IM	PM	*6	*18	
White		44-85	15-45	6-12	8-34	0	
	Germany	49	42	9	30	0	
	Italy	59	36	5	23	0	
	USA				3.4		
	Finland	65	31	4	19		
	Europe without Finland	58	36	6	24	0.015	
Asian		62-81	18-33	1-4	10-21	0	
	Japan	65	31	4	19	0	
	China				19		
	Cambodia				32		
	East Asia	65	31	4	19		
	South Asia	37	48	15	39	0.016	
African		14-38	47-50	14-38	33-50	5-12	
	Ghana	23	50	27	48	4	
	Ethiopia				31		
	Tanzania				42		
	Zimbabwe				49		
	Uganda				35		
	European-African	35	48	17	37	4	
	African-American	18-58	36-49	6-34	20-50	4-8	
	African/Afro-American	31	49	19	37	7.0	
Oceania	Papua New Guinea	12-14	45-47	38-42	62-65	0	
Latin American		38-85	15-47	0.6-14	7-37	1	
Latin American/American, mixed ethnicity		47	43	10	31	0.35	
Ashkenazi Jewish		53	40	7	27	0	

#: calculated from the allele frequencies.

Literature

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