General background text Pharmacogenetics - CYP2B6

Last updated: 21 December 2017

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.

The population can be divided into six groups, based on the metabolic capacity of CYP2B6 that is present:
- poor metaboliser, other genotype (PM), severely reduced or absent metabolic capacity;
- intermediate metaboliser, other genotype (IM), reduced metabolic capacity;
- *5/*5, depending on the medicine: strongly reduced or normal metabolic capacity;
- *1/*5, depending on the medicine: reduced or normal metabolic capacity;
- *5/*6 or *5/*18, depending on the medicine: strongly reduced or reduced metabolic capacity;
- extensive metaboliser (EM), "normal" metabolic capacity;

Poor metabolisers have two alleles that result in reduced or absent metabolic capacity (*6 and/or *18). Intermediate metabolisers have one allele that results in normal activity and one allele that results in reduced or absent metabolic capacity. Extensive metabolisers have two alleles that result in normal activity. *5 is an allele that results in reduced metabolic activity for some medicines and not for others.

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.
The second most common gene variation in Caucasians is *5. This allele results in reduced metabolism for certain medicines, but does not affect the metabolism of other medicines, including efavirenz. This allele has a variation in exon 9.

Table 1. CYP2B6 alleles and enzyme activity [3]

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

[a]: In addition to the same two nucleotide changes as in *6, the *7 allele also contains the nucleotide change in *5 [14]. In the German population, this allele has a prevalence of 3% versus 11% for *5. This allele is also determined when determining *6 and will probably be reported as *6, which has the same lack of activity. When determining *5 only, this allele will probably be reported as *5. This is not correct for medicines for which *5 does not affect metabolism. *6 should always be determined in addition to *5 in patients. For patients who have both the nucleotide changes in *5 and in *6, it is important to determine whether these patients have genotype *5/*6 (genotype group *5/*6 or *5/*18) or genotype *1/*7 (phenotype IM, other genotype), by either cloning and sequencing a cDNA fragment that contains the position of both nucleotide changes or by determining the pharmacokinetics of a medicine whose metabolism is affected by *5.

[b]: The *5 allele results in reduced expression of CYP2B6. However, for a number of medicines, including efavirenz, this appears to be partially compensated by a higher specific activity [1,15]. One study involving 228 patients found no significant effect of the *5 allele on the pharmacokinetics of efavirenz [13].

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
*5	1459C>T	Arg487Cys	Rs3211371

Note 1: Allele *6 also contains the polymorphism 785G>A, in addition to 516G>T. 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 or genotype group)
no gene variant (*1/*1)	extensive metaboliser (EM)
one reduced functional or non-functional gene variant (*1/*6 or *1/*18)	intermediate metaboliser, other genotype (IM, other genotype)
one medicine-dependent reduced or fully functional gene variant (*1/*5)	*1/*5
two reduced or non-functional gene variants (*6/*6, *6/*18 or *18/*18)	poor metaboliser, other genotype (PM, other genotype)

two medicine-dependent reduced or fully functional gene variants (*5/*5)	*5/*5	
one reduced functionality or non-functional gene variant and one medicine-dependent reduced or fully functional gene variant (*5/*6 or *1/*7, *5/*18) (*7 has the *5 and *6 variations on the same allele)	*5/*6 or *5/*18:	*5/*6 or *5/*18
	*1/*7:	intermediate metaboliser, other genotype (IM, other genotype)

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. The *5 allele occurs in all population groups, but the frequency is highest in Caucasians.

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

ethnicity	country	prevalence of genotype/genotype group (%)			allele frequency (%)		
		EM	IM	PM	*6	*18	*5
Caucasian		44-85	15-45	6-12	8-34	0	9-12
	Germany				30	0	
	Italy				23	0	
	USA				3.4		
Asian		62-81	18-33	1-4	10-21	0	1-4
	Japan				19	0	
	China				19		
	Cambodia				32		
African		14-38	47-50	14-38	33-50	5-12	1-4
	Ghana				48	4	
	Ethiopia				31		
	Tanzania				42		
	Zimbabwe				49		
	Uganda				35		
Oceania	Papua New Guinea	12-14	45-47	38-42	62-65	0	
European-African					37	4	
African-American					20-50	4-8	1-4
Spanish-American					7-37	1	5-12

Literature
1. Zanger UM et al. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance. Front Genet 2013;4:24. PubMed PMID: 23467454.
2. Li J, Menard V et al. Worldwide variation in human drug-metabolism enzyme genes CYP2B6 and UGT2B7: implications for HIV/AIDS treatment. Pharmacogenomics 2012;13:555-70. PubMed PMID: 22462748.
3. https://www.pharmvar.org/gene/CYP2B6
4. Sarfo FS et al. Pharmacogenetic associations with plasma efavirenz concentrations and clinical correlates in a retrospective cohort of Ghanaian HIV-infected patients. J Antimicrob Chemother 2014;69:491-9. PubMed PMID: 24080498.

5. Ngaimisi E et al. Importance of ethnicity, CYP2B6 and ABCB1 genotype for efavirenz pharmacokinetics and treatment outcomes: a parallel-group prospective cohort study in two sub-Saharan Africa populations. PLoS One 2013;8:e67946. PubMed PMID: 23861838.
6. Nyakutira C et al. High prevalence of the CYP2B6 516G-->T(*6) variant and effect on the population pharmacokinetics of efavirenz in HIV/AIDS outpatients in Zimbabwe. Eur J Clin Pharmacol 2008;64: 357-65. PubMed PMID: 18057928.
7. Mukonzo JK et al. A novel polymorphism in ABCB1 gene, CYP2B6*6 and sex predict single-dose efavirenz population pharmacokinetics in Ugandans. Br J Clin Pharmacol 2009;68: 690-9. PubMed PMID: 19916993.
8. Wyen C et al. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. J Antimicrob Chemother 2011;66:2092-8. PubMed PMID: 21715435.
9. Gatanaga H et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. Clin Infect Dis 2007;45:1230-7. PubMed PMID: 17918089.
10. Cusato J et al. Efavirenz pharmacogenetics in a cohort of Italian patients. Int J Antimicrob Agents 2016;47:117-23. PubMed PMID: 26774523.
11. Meng X et al. Effect of CYP2B6 gene polymorphisms on efavirenz plasma concentrations in Chinese patients with HIV infection. PLoS One 2015;10:e0130583. PubMed PMID: 26107645.
12. Bertrand J et al. Dependence of efavirenz- and rifampicin-isoniazid-based antituberculosis treatment drug-drug interaction on CYP2B6 and NAT2 genetic polymorphisms: ANRS 12154 study in Cambodia. J Infect Dis 2014;209:399-408. PubMed PMID: 23990572.
13. Burger D et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J Clin Pharmacol 2006;61:148-54. PubMed PMID: 16433869.
14. Lang T et al. Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver. Pharmacogenetics 2001;11:399-415. PubMed PMID: 11470993.
15. Desta Z et al. Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro. Pharmacogenomics 2007;8:547-58. PubMed PMID: 17559344.