General background text Pharmacogenetics - CYP2D6

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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 CYP2D6, are involved in the metabolism of many medicines. CYP2D6 metabolises approximately 25% of these medicines. CYP2D6 is responsible for a wide range of metabolising reactions, such as aromatic hydroxylation, N-demethylation, O-deethylation and benzyl hydroxylation [1].

Variations in the gene that encodes for CYP2D6 can result in reduced or absent enzyme activity.

The presence of gene duplications can result in increased enzyme activity.

The population can be divided into four phenotypes, based on the metabolic capacity of CYP2D6 that is present:

- poor metaboliser (PM), severely reduced or absent metabolic capacity;
- intermediate metaboliser (IM), reduced metabolic capacity;
- extensive metaboliser (EM), "normal" metabolic capacity;
- ultra-rapid metaboliser (UM), increased metabolic capacity.

There is also a large variation in metabolic capacity within each 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 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 CYP2D6 are present in the tested individual. Each allele has a name that consists of a star (*) and a number, an example of a possible CYP2D6 genotype is CYP2D6*1/*3.

Many variations exist for CYP2D6, more than 80 different allele variations have been identified/described in the literature. A number of these variations, including their functionality, are listed in Table 1. Genotyping usually screens for only the most common variant alleles. As a result, the reported genotype can differ from the actual genotype.

Table 1. CYP2D6 alleles, metabolic capacity and gene dose (gene activity score) [1- 4, 16]

metabolic capacity	Gene dose (gene activity score)	allele number
increased functionality	≥ 2	*1 duplication (2-13x) *2 duplication (2-13x) *35 duplication
fully functional	1	*1 (= wild-type, wt) *2 *33 *35 *39
reduced functionality	0.5	*9 (also duplication) *10 (also duplication)[a] *14 *17 (also duplication) *29 (also duplication) *41 (also duplication)
fully dysfunctional (null alleles)	0	*3 through *8 (*3, *4 and *6 also duplication) *11 through *13 *15 *18 through *21 *31 *36 (also duplication) *38 *40 *42 *114

[a] As *10 has significantly reduced functionality, an international working party – in which the KNMP Pharmacogenetics Working Party participated – has decided to assign gene dose 0.25 to *10 instead of gene dose 0.5. The KNMP Pharmacogenetics Working Party has decided to implement this change gradually. The change will be implemented during an update of existing risk analyses and in new risk analyses. Once the change has been implemented in all risk analyses, the change will also be included in the general background information and in the genotype-phenotype translation table of CYP2D6.

Translation from genotype to phenotype

When an individual's genotype has been determined and one wants to know what the metabolic capacity for CYP2D6 is, then the genotype needs to be "translated" to the phenotype. A consensus has been achieved in the Netherlands for the interpretation of the genotype by the Translation Table Consensus Working Group, in which hospital pharmacists, clinical chemists, the KNMP Medicines Information Centre and a representative from Roche Diagnostics participated.

The outcome of this consensus is reflected in Table 3. This translation table is used when drafting the recommendations. In studies where the genotypes have not been translated or their translation differs from this table, then this table was used in the calculation of the dose adjustment if possible. A full table with the predicted phenotype per allele combination is available on www.knmp.nl.

Table 2. Translation Table for CYP2D6

Genotype (expressed in allele activity (gene dose))	phenotype	Gene dose (total gene activity score) of the phenotype
0 – 0	PM	0
0 – 0.5 0.5 – 0.5 0 – 1 n x 0 – 1	IM	0.5-1.0[a]
0.5 – 1 1 – 1 2 x 1 – 0 2 x 1 – 0.5	EM	1.5-2.5[a]

n^{23} x 0.5 – 1 n^{24} x 0.5 – 0.5		
n' x 1 – 0 n' x 1 – 0.5 n x 1 – 1 n" x 0.5 – 1	UM	$\geq 3^{a,b}$

$n \geq 2$

$n' \geq 3$

$n'' \geq 4$

$n^{23} = 2\text{-}3$

$n^{24} = 2\text{-}4$

allele activity/gene dose 0 = fully dysfunctional allele
allele activity/gene dose 0.5 = allele with reduced functionality
allele activity/gene dose 1 = fully functional allele

[a] As *10 has significantly reduced functionality, an international working party – in which the KNMP Pharmacogenetics Working Party participated – has decided to assign gene dose 0.25 to *10 instead of gene dose 0.5. As the international working party also decided to change the gene dose lower limits of the phenotypes in such a way that this change does not result in a different genotype-phenotype categorisation for the majority of the genotypes with *10, this change will result in a change in the gene dose limits for IM to 0.25-1.0, for EM to 1.25-2.5 and for UM to ≥ 2.75. The KNMP Pharmacogenetics Working Party has decided to implement this change gradually. The change will be implemented during an update of existing risk analyses and in new risk analyses. Once the change has been implemented in all risk analyses, the change will also be included in the general background information and in the genotype-phenotype translation table of CYP2D6.

[b] The international working party has also decided to move gene dose 2.5 from EM to UM. However, this means that for genotypes with a completely active allele, an allele with reduced activity and a duplication (e.g. *1/*41)xN) it is necessary to determine which allele is duplicated. Duplication of the fully active allele will result in a gene dose of 2.5 (i.e. UM), whilst duplication of the allele with reduced activity will result in a gene dose of 2 (i.e. EM). At the moment, in the Netherlands we do not determine/report which allele has been duplicated and therefore it is not possible to distinguish between these in the Netherlands. For this reason, it was decided to hold off on the implementation of this change until the duplicated allele is reported by the majority of the Dutch genotyping laboratories.

Phenotyping

The process of phenotyping is used to determine the phenotype, which means: measuring or estimating the activity of the CYP2D6 enzyme. The phenotype is determined by determining the metabolic capacity of the enzyme using substances that are exclusively metabolised by CYP2D6. The ratio between the mother substance and the metabolite (metabolic ratio, MR) is a measure of the phenotype. The role of phenotyping is limited due to the availability of improved techniques for genotyping. Phenotyping can be used to distinguish PM from the other phenotypes (EM+IM+UM). Genotyping also provides information to distinguish IM and UM from EM.

Substances that are commonly used to determine the phenotype include debrisoquine, dextromethorphan and sparteine. The following cut-off values are used for the metabolic ratios [1]:

debrisoquine: EM+IM+UM = MR < 12.6, PM = MR ≥ 12.6
dextromethorphan: EM+IM+UM = MR < 0.3, PM = MR ≥ 0.3
sparteine: EM+IM+UM = MR < 20, PM = MR ≥ 20

Ethnic variation in prevalence of phenotypes and allele frequency

The frequency of occurrence of the various CYP2D6 alleles and the different phenotypes varies between ethnic groups.

Generally speaking, the functional alleles occur most often in the European Caucasian race, at a frequency of 71%. Fully dysfunctional alleles occur at a frequency of 26%, primarily *4.

By contrast, the frequency of functional alleles is much lower in the Asian population, approx. 50% and the prevalence of the *10 allele with reduced functionality is high (41%), resulting in very few PMs but a lot of IMs.

In Africans and African-Americans, the frequency of functional alleles is also round 50%, both groups have a frequency of alleles with reduced functionality of 35%, primarily *17. African-Americans have a two-fold higher frequency of dysfunctional alleles than Africans (14.5% versus 6.3%). The variation in dysfunctional alleles and alleles with reduced functionality is much greater in Africans and African-Americans than in Asians. Also refer to Table 2. [11]

Table 3. Ethnic variation in prevalence of phenotypes[a] and allele frequency [6-15]

		prevalence of phenotype (%)				allele frequency (%)							
ethnicity	country	PM	IM	EM	UM	*3	*4	*5	*6	*9	*10	*17	*41
Caucasian		5-10	10-40[a]	70-80	5-10	1-2	20	2-7	1	1-2	1-2		8-20
	The Netherlands	5.4-9	10	80	1-2	0-1.8	18.4	5	0-0.4	1	3	0	10
	Spain				7-10								
Asian		1-2					< 1	4-6			41		
African		0-20					2	4				24	
	West Africa (Ghana and Gabon)						7						
	North Africa (Ethiopia)				20-30						8.6	3-9	
	African-American						7.5	6.2				22	

[a] Depends on the translation from genotype to phenotype, which is why percentages vary significantly.

Literature

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