General background text Pharmacogenetics - CYP2D6

Last updated: 16 November 2021

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 (also refer to the document 'Uncertainties in genotyping results' on the KNMP site).

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 *12 *13 and other CYP2D6/CYP2D7 hybrid alleles *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 Group participated – has decided to assign gene dose 0.25 to *10 instead of gene dose 0.5. The KNMP Pharmacogenetics Working Group 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 n^{23} x 0.5 – 1 n^{24} x 0.5 – 0.5	EM	1.5-2.5[a]

n' x 1 – 0 n' x 1 – 0.5 n x 1 – 1 n" x 0.5 – 1	UM	≥ 3[a,b]

n ≥ 2

n' ≥ 3

n" ≥ 4

n[23] = 2-3

n[24] = 2-4

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 Group participated – has decided to assign gene dose 0.25 to *10 instead of gene dose 0.5 [19]. 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 Group 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 [19]. 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 69%. Fully dysfunctional alleles occur at a frequency of 26%, primarily *4.

By contrast, the frequency of functional alleles is much lower in the East Asian population (30%), and the prevalence of the *10 allele with reduced functionality is high (59%), resulting in very few PMs but a lot of IMs. The frequencies in the South Asian population fall between those of the East Asian and European populations (65% fully functional alleles and 20% reduced functionality alleles, of which approx. one third *10).

In Africans, the frequency of functional alleles is around 50% and the frequency of reduced functionality alleles – primarily *17 – is around 35%. Africans distinguish themselves from the other population groups by a 4 to 9-fold higher frequency of amplification of a gene with gene dose 1.

As far as allele group frequencies are concerned, of all population groups, Americans of mixed ethnicity appear to be most similar to the European population. Also refer to Tables 3a and 3b. [11]

Table 3a. Ethnic variation in prevalence of phenotypes[a] and allele group frequency [17]

	prevalence of phenotype (%)	allele group frequency (%)

population group	PM	IM	EM	UM	gene dose 0	gene dose 0.5 or 0.25 (gene dose 0.25)	gene dose ≥ 2 (amplification of a gene with gene dose 1)
European	6.8	37.6	52.5	3.1	26.1	4.8 (0.2)	2.3
East Asian	0.7	53.3	44.8	1.2	8.5	61.7 (58.7)	2
South Asian	2.1	28.6	67.3	1.9	14.6	20.3 (6.5)	1.5
African	2.8	37.3	51.9	8.0	16.7	35.5 (3.2)	9.3
American, mixed ethnicity	3.8	31.2	63.5	1.5	19.4	5.9 (0)	1

[a] Calculated based on the allele group frequencies. This calculation assumes that gene dose ≥ 2 involves a gene duplication (gene dose 2).

Table 3b. Ethnic variation in prevalence phenotypes[a] and allele frequencies [6-15, 18]

		prevalence of phenotype (%)				allele frequency (%)							
population group	country/region/sub-group	PM	IM	EM	UM	*3	*4	*5	*6	*9	*10	*17	*41
Caucasian						1-2	20	2-7	1	1-2	1-2		8-20
	The Netherlands	5.5-6.6	37.8-40	51.4-55.7	1-2	0-1.8	18.4	5	0-0.4	1	3	0	10
	Spain				7-10								
	Finland					3.6	10		2	1.3		0.02	3
	Europe (without Finland)					1.7	20		1	2.6		0.1	9
Asian							< 1	4-6			41		
	East Asia					0	0.3		0	0	59	0	3
	South Asia					0.15	10		0.17	0.2	6.5	0.1	14
African							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	
	African/African-American					0.26	8		0.2	0.4		19	2.6
Latin-American/American, mixed ethnicity						0.5	11		0.4	1.2		0.7	4
Ashkenazi Jewish						0.4	18		0.8	0.3		1.8	18

[a] Calculated for the Netherlands based on the frequencies of the most important alleles and the frequency for UM listed in Van Schaik 2006.

Note: According to the guideline of the Association for Molecular Pathology, at least the alleles *2 to *6, *9, *10, *17, *29, *41, and the presence or absence of a gene duplication or multiplication should be determined when genotyping CYP2D6 [20].

Literature

1. Metabolic Drug Interactions. Editors: Rene H Levy, Kenneth E Thummel, William F Trager, Philip D Hansten and Michel Eichelbaum. Lippincott Williams and Wilkins, Philadelphia. ISBN: 0-7817-1441-9. Hoofdstuk 8, 87-94: CYP2D6 door Ulrich M Zanger and Michel Eichelbaum.
2. Dalen P, Dahl ML, Ruiz MLB et al. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. Clin Pharmacol Ther 1998;63:444-52.

3. Kvist EE, Al-Shurbaji, Dahl MJ et al. Quantitative Pharmacogenetics of Nortriptyline. Clin Pharmacokinet 2001;40:869-77.
4. Zanger UM, Raimundo S and Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. Naunyn-Schmiedeberg's Arch Pharmacol 2004; 369: 23-37.
5. Kirchheiner J, Nickchen K, Bauer M, et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry 2004;9:442-73.
6. Tamminga WJ, Wemer J, Oosterhuis B, Weiling J, Wilffert B, de Leij LF, de Zeeuw RA, Jonkman JH. CYP2D6 and CYP2C19 activity in a large population of Dutch healthy volunteers: indications for oral contraceptive-related gender differences. Eur J Clin Pharmacol 1999;55:177-84.
7. Tamminga WJ, Wemer J, Oosterhuis B, de Zeeuw RA, de Leij LF, Jonkman JH. Related Articles, The prevalence of CYP2D6 and CYP2C19 genotypes in a population of healthy Dutch volunteers. Eur J Clin Pharmacol 2000;57:717-22.
8. Raimundo S, Fischer J, Eichelbaum M, Griese EU, Schwab M, Zanger UM. Elucidation of the genetic basis of the common 'intermediate metabolizer' phenotype for drug oxidation by CYP2D6. Pharmacogenetics 2000;10:577-81.
9. Sachse C, Brockmoller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. Am J Hum Genet 1997;60:284-295.
10. Masimirembwa C, Hasler JA. Genetic polymorphism of drug metabolising enzymes in African populations: implications for the use of neuroleptics and antidepressants. Brain Res Bull 1997;44:561–571.
11. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics 2002; 3:229-243.
12. Aklillu E, Persson I, Bertilsson L, Johansson I, Rodrigues F, Ingelman-Sundberg M. Frequent distribution of ultrarapid metabolizers of debrisoquine in an Ethiopian population carrying duplicated and multiduplicated functional CYP2D6 alleles. J Pharmacol Exp Ther 1996;278:441-6.
13. McLellan RA, Oscarson M, Seidegard J, Evans DA, Ingelman-Sundberg M. Frequent occurrence of CYP2D6 gene duplication in Saudi Arabians. Pharmacogenetics 1997;7:187-91.
14. Zanger UM, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. Naunyn Schmiedebergs Arch Pharmacol 2004;369:23-37.
15. Van Schaik RHN, Van Fessem MAC, Schenk PW, Lindemans J. CYP2D6-genotypen in de Nederlandse populatie, bepaald met de Roche AmpliChip CYP450. Ned Tijdschr Klin Chem Labgeneesk 2006;31:234-5.
16. https://www.pharmvar.org/gene/CYP2D6
17. Zhou Y, Ingelman-Sundberg M, Lauschke VM. Worldwide distribution of cytochrome P450 alleles: a meta-analysis of population-scale sequencing projects. Clin Pharmacol Ther 2017;102:688-700.
18. genome aggregation database (gnomAD) v2.1.1, https://gnomad.broadinstitute.org.
19. Caudle KE et al. Standardizing CYP2D6 genotype to phenotype translation: consensus recommendations from the Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group. Clin Transl Sci 2020;13:116-24.
20. Pratt VM et al. Recommendations for clinical CYP2D6 genotyping allele selection: a joint consensus recommendation of the Association for Molecular Pathology, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, and the European Society for Pharmacogenomics and Personalized Therapy. J Mol Diagn 2021;23:1047-64.