General background text Pharmacogenetics - CYP1A2

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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**). The **promoter** is a section that precedes the gene, which is primarily responsible for regulating the activity (expression) of the gene. Variations in exons usually result in variations in the protein product. Variations in promoters or introns – the non-coding regions of the gene – generally do not result in variations in the protein product. However, promoters and introns - and associated variations in these regions - can influence the level of production of the protein.

Changes in (the production of) the target protein and clinical consequences
The cytochrome P450 enzymes, which include the iso-enzyme CYP1A2, are involved in the metabolism of many medicines. CYP1A2 metabolises approximately 8-10% of the medicines that are metabolised by cytochrome P450 enzymes. CYP1A2 is responsible for a wide range of metabolising reactions, such as hydroxylation, N-demethylation and O-deethylation [1]. Variations in the activity of CYP1A2 can result in an increase or decrease of the metabolisation of medicines. The causes of variations in CYP1A2 activity are largely non-genetic. CYP1A2 is induced by smoking, cruciferous vegetables, grilled meat and medicines such as omeprazole and carbamazepine. CYP1A2 is inhibited by medicines such as fluvoxamine and ciprofloxacin [1]. In addition to this, variations in the gene that encodes for CYP1A2 can result in reduced or elevated enzyme activity.

Genotyping and translation from genotype to phenotype/genotype group
The process of genotyping is used to determine the genotype. It indicates which alleles of the gene for CYP1A2 are present in the tested individual. Each allele has a name that consists of a star (*) and a number, an example of a possible CYP1A2 genotype is CYP1A2*1F/*1C. As the CYP1A2 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.

Gene variations in CYP1A2 mainly involve variations in introns and the promoter [2].
The most common gene variation is *1F. This allele contains a single variation, which is located in intron 1, an intron located in the coding part of the gene. Two studies found that for this allele there is an increased inducibility of caffeine metabolism by smoking [3,4]. One of the studies found that this allele predicts 18% of the variation in caffeine metabolism in smokers. Caffeine is primarily metabolised by CYP1A2 (approx. 95%). No effect of *1F on induction by smoking was found for clozapine and olanzapine, which are also metabolised by other enzymes. The *1F allele is more common in the Netherlands than the wild-type allele *1A. The frequency of the genotype *1F/*1F is four times higher than the genotype *1A/*1A. Therefore, recommendations will only be given for genotypes other than *1F/*1F.
Of the alleles with reduced activity, *1C is the most common. This allele has a variation in the promoter region. The other alleles with reduced or absent activity occur so rarely that they are usually not detected in studies. For this reason, the pharmacogenetic guideline is drafted separately for *1C. Few to no data can be found for the

other alleles with reduced or absent activity and the pharmacogenetic guideline is based on the pharmacogenetic guideline for *1C.
No change in enzyme activity was observed for a number of alleles (*1B, *1D, *1E). These alleles are viewed as wild-type (*1A).
A number of alleles (*1J, *1K, *1L, *1V and *1W) have other variations in addition to the variation that occurs in *1F. These alleles lack the increased inducibility of caffeine metabolism that is found for *1F, with data even demonstrating that *1K results in a reduced CYP1A2 activity.
Genotyping usually screens for the presence of the most common allele variations. As a result, the reported genotype may differ from the actual genotype (also refer to the document 'Uncertainties in genotyping results' on the KNMP site).

The table below provides an overview of the alleles and the resulting enzyme activity. The table also lists for each of the allele groups to which genotypes and genotype groups that monitoring is performed for they can belong. This last column can be used to determine which genotype group a patient should be linked to, if the patient has a genotype that does not have a separate pharmacogenetic guideline.

Table 1. CYP1A2 alleles and enzyme activity [2,3]

enzyme activity	allele number	genotypes and genotype groups
fully functional	*1A *1B *1D *1E *1J *1L *1V *1W	- normal metaboliser (two fully functional alleles) - *1A/*1F (also includes *1B/*1F, *1D/*1F, *1E/*1F, *1F/*1J, *1F/*1L, *1F/*1V and *1F/*1W alleles) - *1C heterozygous (a fully functional allele and *1C) - IM (a fully functional allele and an allele from the bottom row of the table)
increased inducibility	*1F	- *1F/*1F (the most common genotype) - *1A/*1F (also includes *1B/*1F, *1D/*1F, *1E/*1F, *1F/*1J, *1F/*1L, *1F/*1V and *1F/*1W alleles) - *1C heterozygous (*1F/*1C) - IM (*1F and an allele from the bottom row of the table)
reduced functionality	*1C	- *1C/*1C - *1C heterozygous (*1C and an allele with full functionality or increased inducibility) - PM (*1C with another reduced or non-functional allele)
reduced or non-functional	*1K *3 *4 *6 *7	- PM (two reduced or non-functional alleles, of which at least one is not *1C) - IM (one of these alleles and an allele with full functionality or increased inducibility)

Table 2. Overview of the notations used for the most important CYP1A2 alleles [2]

allele number	nucleotide change	rs number
*1C	-3860G>A as only variation	rs2069514
*1F	-163C>A as only variation	rs762551

Note 1: The 7 alleles with the -3860G>A polymorphism that is characteristic for *1C, which were found in two Dutch studies, were all *1L (normal activity) instead of *1C (reduced activity) [7,8]. *1L contains both the -3860G>A polymorphism that is characteristic for *1C and the -163C>A polymorphism that is characteristic for *1F.

Note 2: In Caucasians, the determination of -163C>A alone is a good predictor for the *1F genotype. -163C>A occurs primarily in the *1F allele in Caucasians. However, in Koreans, -163C>A occurs primarily in the *1L and *1V alleles and determination of -163C>A only is not sufficient for identification of *1F.

Note 3: The definition and nomenclature of *1F vary in the literature. Sometimes, -164 is used instead of -163. Sometimes the definition is the opposite (-163A>C instead of -163C>A). We have followed the nomenclature and definition of the CYP450 Nomenclature Committee (www.pharmvar.org/gene/CYP1A2).

Note 4: As *1F is a variation in an intron, the name of this variant according to the HGVS nomenclature is not 163C>A, but -9-154C>A. The notation used for *1C also does not correspond to the HGVS nomenclature. This is not the notation for cDNA, but for genomic DNA. As the first intron, located in the start codon, has been removed from the cDNA, the distance from the altered nucleotide to the start codon in the cDNA is shorter than in the genomic DNA. However, in the HGVS nomenclature, changes in genomic DNA are never referenced to the start codon, but always in terms of the start of the DNA fragment and therefore do not provide insight into the position of the nucleotide change with regard to the coding section of the gene. There is no cDNA notation available for *1C due to the large distance of the nucleotide change from the start of transcription.

Phenotyping
The process of phenotyping is used to determine the phenotype, which means: measuring or estimating the activity of the CYP1A2 enzyme. As the causes of variations in CYP1A2 activity are largely non-genetic, phenotyping of CYP1A2 does not provide any information about the presence or absence of variant alleles.

Ethnic variation in prevalence of phenotypes and gene variant frequency
The frequency of occurrence of the -163C>A gene variant that is characteristic for the *1F allele varies little between ethnic groups. The *1F allele is the most common gene variant in all population groups and is therefore more common than the wildtype (no *1F).
The frequency of the -3860G>A gene variant that is characteristic for the *1C allele does vary between population groups (from 1.3% in Europe to 27% in East Asians, African or African-American individuals and individuals with Latin-American or mixed American ethnicity). These large differences in *1C gene variant frequency may contribute to the differences in CYP1A2 activities found between various ethnic groups.

Table 3. Ethnic variation in prevalence of genotypes and genotype groups and gene variant frequency [1, 6-8]

		prevalence of genotype/genotype group (%)			gene variant frequency (%)	
population group	Country/region	*1F/*1F	*1A/*1F	NM	*1F[b,c]	*1C[d]
Caucasian						
	The Netherlands	43	45	12	65	2.3
	Norway				69	
	Finland				69	5
	Europe without Finland				71	1.3
Asian	Turkey					4
	Japan					21-25
	East Asia				66	27
	South Asia				58	9
African						7
	African/African-American				61	27
Latin-American/ American, mixed ethnicity					70	27
Ashkenazi Jewish					68	3

[a] Calculated based on the gene variant frequency of *1F, thus assuming that all *1F gene variants occur in a *1F allele. This appears to be mostly the case for the Dutch situation. The 2.3% alleles with the *1C gene variant also have a *1F gene variant (*1L alleles) (see note d). However, this would correspond to just 3.5% of the *1F gene variants.
[b] In Koreans, the *1F gene variant occurs primarily in the *1L and *1V alleles and therefore the *1F gene variant frequency is much higher than the frequency for the *1F allele. This may also play a role for the other non-Caucasians. For Caucasians, the frequencies fo the *1F gene variant and the *1F allele do appear to correspond.
[c] Zhou 2010 lists a frequency < 50% for the *1F gene variant in Germany. However, the study on which this is based (Sachse 1999) found a frequency > 50%. It appears that Zhou 2010 lists the frequency of *1A here instead of *1F. For this reason, the data from Zhou 2010 about the *1F gene variant frequencies have not been included in the table above.
[d] In the Dutch studies, the *1C gene variant was present in the *1L allele instead of the *1C allele. This is not known for the other studies.

Literature

1. Zhou SF et al. Structure, function, regulation and polymorphism and the clinical significance of human cytochrome P450 1A2. Drug Metab Rev 2010;42:268-354. PubMed PMID: 19961320.
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8. Kootstra-Ros JE et al. The cytochrome P450 CYP1A2 genetic polymorphisms *1F and *1D do not affect clozapine clearance in a group of schizophrenic patients. Ann Clin Biochem 2005;42:216-9. PubMed PMID: 15949157.
9. genome aggregation database (gnomAD) v3.1.1, https://gnomad.broadinstitute.org.