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. 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.
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]

enzyme activity	allele number	genotypes and genotype groups
fully functional	*1A *1B *1D *1E	- extensive metaboliser (two fully functional alleles) - *1A/*1F (also includes *1B/*1F, *1D/*1F and *1E/*1F 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 and *1E/*1F 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) - IM (one of these alleles and another allele with the exception of *1C)

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

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

Note 1: 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 2: The definition and nomenclature of *1F varies 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.cypalleles.ki.se).

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 allele frequency
The frequency of occurrence of the various CYP1A2 alleles and the different phenotypes varies between ethnic groups.
In the Netherlands and Scandinavia, the *1F allele is the most common allele. In, for example, Great Britain, Germany and China, the wild-type allele *1A is most common.
The frequencies found for the *1C allele vary from 1% in the Netherlands to 21-25% in Japan.
These large differences in allele frequencies 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 allele frequency [1,5,6]

		prevalence of genotype/genotype group (%)			allele frequency (%)	
ethnicity	country	*1F/*1F	*1A/*1F	EM	*1F[#]	*1C

Caucasian						
	The Netherlands	45	44	11	67	1
	Scandinavia				57-67	
	Great Britain				34	
	Germany				32	
Asian	Turkey				24	4
	Korea				8	
	China				32-34	
	Japan				37-67	21-25
African					32-51	7

[#] Many of the Asian and African studies did not perform genotyping for alleles that had another variation in addition to *1F and therefore are not *1F. Therefore, one cannot rule out that the frequencies of *1F that were found are higher than is actually the case. The determinations in Koreans included genotyping for *1K, *1L, *1V and *1W.

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.
2. http://www.cypalleles.ki.se/cyp1a2.htm
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