General background text Pharmacogenetics - UGT1A1

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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.

The DNA contains the information for the production of proteins. The first step in forming proteins is reading the DNA. The **promoter** forms the starting point for this reading and is therefore the part of the gene that regulates gene expression. The **TATA box** is a part of the promoter in which the base pair sequence "TATA" occurs often. We refer to a **tandem repeat** if a number of bases are repeated in tandem (recurring pattern).

Altered metabolic capacity and clinical consequences

Uridine diphospho-glucuronosyl transferases (UGT), which include the iso-enzyme UGT1A1, are involved in the glucuronidation of many medicines and endogenous substrates. The UGT super family is divided into the UGT1 and UGT2 families. The functional proteins UGT1A1, UGT1A6, UGT1A7, UGT1A9 and UGT1A10 are known for UGT1. UGT1A1 catalyses the glucuronidation of bilirubin and it is expressed in various tissues, including the liver, intestines and stomach [1].

Variations in the gene that encodes for UGT1A1 can result in reduced, elevated or absent enzyme activity.

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.

Genotyping

The process of genotyping is used to determine the genotype. It indicates which alleles of the gene for UGT1A1 are present in the tested individual. Each allele has a name that consists of a star (*) and a number, an example of a possible UGT1A1 genotype is UGT1A1*1/*28.

Many variations exist for UGT1A1, more than 60 different allele variations have been identified/described in the literature [2]. A number of these are listed in Table 1, including their functionality. Much studied polymorphisms of UGT1A1 involve polymorphisms in the promoter region of the UGT1A1 gene. The number of "TA" tandem repeats in the TATA box of the promoter region can vary. The enzyme activity decreases with an increasing number of TA repeats. Also refer to Table 2.

When performing genotyping, one usually screens for the presence of the most common allele variations. As a result, the reported genotype can differ from the actual genotype.

Table 1. UGT1A1 alleles and metabolic capacity [2]

metabolic capacity	allele number

increased functionality	*36
fully functional	*1 (= wild-type, wt)
reduced functionality	*6 through *9 *12 *27 through *30 *32 through *35 *37
fully dysfunctional (null alleles)	*2 through *5 *10 through *11 *13 through *26 *31

Table 2. Polymorphisms in UGT1A1 promoter [2]

allele number	**number of TA repeats**	**TATA box**
*1	TA_6	$[A(TA)_6TAA]$
*28	TA_7	$[A(TA)_7TAA]$
*36	TA_5	$[A(TA)_5TAA]$
*37	TA_8	$[A(TA)_8TAA]$

Ethnic variation in prevalence genotypes

The frequency of occurrence of the various UGT1A1 alleles varies significantly between ethnic groups.
Broadly speaking, the *28/*28 (TA_7/TA_7) genotype occurs frequently in inhabitants of the Indian sub-continent (Sri Lanka 24%, India and Bangladesh 19%) and much less frequently in the rest of Asia (2-10%). The prevalence varies strongly within Europe, also refer to Table 3.
The variant allele *6 is common in Asian population groups [7-9]. The frequency of *6 is 22.2% in Japanese individuals and the frequency of *28 is 10.4% [7]. In these population groups, genotyping for *28 alone does not provide sufficient information about the genotype.

Table 3. Ethnic variation in prevalence of genotypes [3,4,5,6]

	prevalence of genotype (%)							
	*1/*1 TA_6/TA_6	*1/*28 TA_6/TA_7	*28/*28 TA_7/TA_7	*36/*1 TA_5/TA_6	*36/*28 TA_5/TA_7	*36/*37 TA_5/TA_8	*1/*37 TA_6/TA_8	*28/*37 TA_7/TA_8
The Netherlands (Caucasians)	37	54	9					
Europe	30-50	40-60	5-15					
Africa	20-60	30-50	6-18	4-12	7-8	1-2	3-8	1-14
Asia	25-75	15-60	2-20					
South America	55	30	12					
Pacific	75-95	5-20	2					
Caucasian	34-38	46-55	11-13	0-2	0	0	0	0-2
Asian	70	28	2	0	0	0	0	0
African-American	26	33-37	13-19	0-2	5	3	4-15	5-6

Literature

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