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. The variant *28, which results in decreased UGT1A1 activity through reduced production of the enzyme, is the most important UGT1A1 variant in Caucasian population groups.
In Asian population groups, *6, which also results in decreased UGT1A1 activity, is the most important UGT1A1 variant. The *6 variant has the nucleotide variation 211G>A, which results in a change in the 71st amino acid of the enzyme from glycine to arginine. The altered enzyme is less active.

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	$[A(TA)_8TAA]$

Genotype-phenotype translation

The population can be divided into three phenotypes, based on the metabolic capacity of UGT1A1 that is present. As variant allele *28 is most common in the Caucasian population group and this is also the allele for which the most data are known, the two phenotypes with reduced metabolic capacity are further subdivided based on whether or not *28 is the only gene variant that results in decreased metabolic capacity. In the case of the allele that results in increased metabolic capacity (*36), there are currently no data to suggest that this results in clinically relevant effects. Therefore, for the time being, this is considered an allele with normal functionality (the wildtype allele *1).

The genotype-phenotype translation is presented below (and in Table 3):

- normal metaboliser (NM, *1/*1), 'normal' metabolic capacity (two alleles with normal (or increased) enzyme activity) (*1/*1 (TA6/TA6) (normal metaboliser))
- intermediate metaboliser (IM), decreased metabolic activity (one allele with decreased enzyme activity and one allele with normal (or increased) enzyme activity), subdivided into *28 or another allele with reduced enzyme activity:
  - allele with reduced enzyme activity is *28 (*1/*28)
  - allele with reduced enzyme activity is not *28 (IM OTHER)
- poor metaboliser (PM), severely decreased metabolic capacity (two alleles with decreased enzyme activity), subdivided into *28 only or (also) another allele with decreased enzyme activity:
  - two *28 alleles (*28/*28)
  - at least one of the 2 alleles with decreased enzyme activity is not *28 (PM OTHER)

Table 3. Genotype-phenotype translation

genotype		**phenotype predicted based on genotype (pharmacogenetic contraindication)**
description	**examples**	
two alleles with normal (or increased) enzyme activity	*1/*1, *1/*36	*1/*1 (TA6/TA6) (normal metaboliser) (abbreviated: *1/*1 (TA6/TA6) (NM))
*28 and one allele with normal (or increased) enzyme activity	*1/*28, *28/*36	*1/*28 (TA6/TA7)
one allele with decreased enzyme activity other than *28 and one allele with normal (or increased) enzyme activity	*1/*6, *1/*37, *36/*37	genotype other - phenotype interm.metab (abbreviated: IM OTHER)
two *28 alleles	*28/*28	*28/*28

two alleles with decreased enzyme activity, of which at least one is not *28	*6/*6, *6/*28, *28/*37	genotype other - phenotype poor metab (abbreviated: PM OTHER)

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 4. Ethnic variation in prevalence of genotypes and frequency of alleles [3,4,5,6,7,10]

	prevalence of genotype (%)								allele frequency (%)		
Population group/region	*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	*28	*6	*37
Whites	34-38	46-55	11-13	0-2	0	0	0	0-2	33-36		0-2.8
The Netherlands (Whites)	37	54	9						36		
Europe	30-50	40-60	5-15						22-39		
Europe (without Finland)									32	0.2	0.07
Finland									42	4.6	0.05
Africa	20-60	30-50	6-18	4-12	7-8	1-2	3-8	1-14	24-42		1.2- 29
African-American	26	33-37	13-19	0-2	5	3	4-15	5-6	36-44		5.7-8.3
African/ African-American									40	0.07	5
Asia	25-75	15-60	2-20	0	0	0	0	0	14-45		0
East Asia									12	15.3	
Japan									10.4	22.2	
South Asia									41	2.0	0.2
South America	55	30	12						27		
Latin-American/ American, mixed ethnicity									31	2.4	0.4
Pacific	75-95	5-20	2						4.5-12		
Ashkenazi Jewish									38	0.5	

Literature

1. Nagar S, Blanchard RL. Pharmacogenetics of uridine diphosphoglucuronosyltransferase (UGT) 1A family members and its role in patient response to irinotecan. Drug Metab Rev 2006;38:393-409.
2. http://galien.pha.ulaval.ca/alleles/UGT1A/UGT1A1.htm geraadpleegd op 4 oktober 2006.
3. Premawardhena A, Fisher CA, Liu YT, Verma IC, de Silva S, Arambepola M, Clegg JB, Weatherall DJ. The global distribution of length polymorphisms of the promoters of the glucuronosyltransferase 1 gene (UGT1A1): hematologic and evolutionary implications. Blood Cells Mol Dis 2003;31:98-101.
4. Innocenti F, Grimsley C, Das S, Ramirez J, Cheng C, Kuttab-Boulos H, Ratain MJ, Di Rienzo A. Haplotype structure of the UDP-glucuronosyltransferase 1A1 promoter in different ethnic groups. Pharmacogenetics. 2002;12:725-33.

5. Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? Proc Natl Acad Sci U S A 1998;95:8170-4.
6. Bosch TM, Doodeman VD, Smits PH, Meijerman I, Schellens JH, Beijnen JH. Pharmacogenetic screening for polymorphisms in drug-metabolizing enzymes and drug transporters in a Dutch population. Mol Diagn Ther. 2006;10:175-85.
7. Akiyama Y et al. Genetic testing for UGT1A1*28 and *6 in Japanese patients who receive irinotecan chemotherapy. Ann Oncol 2008;19:2089-90.
8. Teh LK et al. Polymorphisms of UGT1A1*6, UGT1A1*27 & UGT1A1*28 in three major ethnic groups from Malaysia. Indian J Med Res 2012;136:249-59.
9. Sung C et al. Pharmacogenetic risk for adverse reactions to irinotecan in the major ethnic populations of Singapore: regulatory evaluation by the health sciences authority. Drug Saf 2011 1;34:1167-75.
10. genome aggregation database (gnomAD) v2.1.1 (*6) and v3.1.1 (*28 and *37), https://gnomad.broadinstitute.org.