General background text Pharmacogenetics –

Organic Anion Transporter 1B1 (SLCO1B1, OATP1B1, OATP-C)

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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. This means that an individual has two copies (two **alleles**) of most genes. Each allele is located on one 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 within the DNA that encodes 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.

In some cases the abbreviation of the name of the gene can differ from the name of the gene product. An example here is the organic anion transporter 1B1 where the gene is abbreviated to SLCO1B1 and the protein to either SLCO1B1 (solute carrier organic anion transporter 1B1) or OATP1B1 (organic anion transporter polypeptide 1B1) or OATP-C.

Altered transporter activity and clinical consequences

Statins inhibit production of cholesterol by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-co-enzyme A reductase. This enzyme is a liver enzyme and is one of the enzymes active in cholesterol biosynthesis.

Statins may induce myopathy: creatine kinase elevation exceeding 10 times the upper limit of normal, often accompanied by sore muscles. In severe cases, this may lead to muscle breakdown and release of myoglobin (rhabdomyolysis). The risk of myopathy increases with dose and in patients with disorders that increase statin plasma levels, such as those with kidney or liver impairment.

The organic anion transporter 1B1 plays an important role in statin transport from the portal vein to liver cells. Polymorphisms that reduce the activity of this transporter may therefore lead to reduced statin levels in the liver and increased statin plasma levels. The latter may increase the risk of myopathy [1,2].

Genotyping

The process of genotyping is used to determine the genotype. It indicates which alleles of the gene for SLCO1B1 are present in the tested individual.

Various polymorphism have been found in the SLCO1B1 gene. The only polymorphism for which an association with the risk of myopathy has been found is 521T>C. 521T>C means that nucleotide 521 of the SLCO1B1 gene is thymidine (T) in the wild-type and cytidine (C) in the variant allele. The gene polymorphism is in exon 5 and leads to a change of the amino acid valine at position 174 of the transporter protein to alanine. In Caucasian populations, incidences of the variant allele found range from 8% to 22% [1,2].

There is no clear and consistent evidence for an effect on cholesterol lowering by statins for any of the polymorphisms.

There is currently no standard notation of wild-type and variant SLCO1B1 alleles, with the exception of the standard annotation *1 for a wildtype allele. Table 1 shows an overview of the notations used and characteristics of the 3 most important polymorphisms.

The haplotypes are defined by combinations of polymorphisms, with the polymorphisms each occurring in multiple haplotypes. Only the most common haplotypes have been included.

Table 1. Overview of the most important SLCO1B1 polymorphisms

Nucleotide polymorphism	**rs number**	**Protein polymorphisms**	**Haplotypes (alleles) with the variant allele**	**Pharmacological response**
521T>C	rs4149056	174 Val>Ala	*5 *15 to *17	Association with the risk of myopathy
388 A>G	rs2306283	130 Asn>Asp	*1B *14 to *17	No consistent effect
463 C>A	rs11045819	155 Pro>Thr	*4 *14	No consistent effect
None (521T)	-	- (174 Val)	*1	Normal

Ethnic variation in prevalence of phenotypes and allele frequency

In the Caucasian population, approximately 8-22% has a 521C allele [1-3]. A large study (n=2576) performed in the Netherlands found a percentage of 15% and a small study performed in the Netherlands (n=39) found a percentage of 18%, resulting in a weighed average of 15% [3,4]. This is equivalent to a percentage of approximately 2.3% of the population with the 521CC genotype and approximately 26% with the 521TC genotype. This percentage with a 521C allele in the East Asian population is similar at 8-19%. However, the prevalence is only 1-8% in the African and African American populations.
There are also strong variations between the ethnic groups in 388A>G and 463C>A polymorphisms.
Allele frequencies per population are given in table 2.

Table 2. Ethnic variation in prevalence of allele frequency [1-4]

		Allele frequency (%)		
Ethnicity	**Country/region**	**521C**	**388G**	**463A**
Caucasian		14-22	30-51	
	Europe	8-20	30-45	13-23
	The Netherlands	15		
Asian	East Asia	8-16	59-86	0-3
	Japan	15-19	63-74	
African	Sub-Saharan Africa/African-American	1-8	72-83	2-10
	African-American	1-4	74-77	

Literature

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