General background text Pharmacogenetics – Human Leukocyte Antigen (HLA)

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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 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.** There can be a number of different polymorphisms for a certain allele.

HLA proteins

Human Leukocyte Antigen (HLA) is the name for proteins of the human Major Histocompatibility Complex (MHC). These proteins are divided into 2 classes: class I and class II, each with their own function.

MHC class I proteins are on the surface of almost all body cells. They bind peptides in the cell and present them on the surface of the cells allowing immune cells to 'see' whether the cell produces proteins that do not belong in the cell (e.g. after a viral infection). Any cells presenting abnormal peptides are killed.

MHC class II proteins are only expressed on the surface of specialised immune cells. They bind peptides from proteins that have been internalised by cells from the outside. They present these peptides on the surface allowing immune cells to 'see' whether any non-self proteins are present in the body. Any cells presenting non-self peptides cause activation of the immune system.

Class I and class II proteins are each encoded by 3 different polymorphic genes (HLA-A, HLA-B, HLA-C and HLA-DP, HLA-DQ and HLA-DR respectively). The number of different alleles per polymorphic gene is very high, so that the chances of two people with the same combination of HLA alleles meeting is very low (with the exception of identical twins).

HLA polymorphisms and clinical consequences

The polymorphic HLA proteins differ in peptides they can bind and therefore determine the nature of the peptides the body can mount an immune response to. Pathogens consist of multiple proteins, each of which are broken down to a multitude of peptides. People with different polymorphic variations in HLA can therefore all mount immune responses to pathogens and other non-self proteins, but the intensity of the response may differ between individuals.

HLA polymorphisms may therefore play an important role in the development of immune responses or antibodies to protein medicines or to medicines that lead to modification of proteins in the body (e.g. by medicines or metabolites binding to proteins).

As the immune system responds more strongly to pathogens/proteins it has encountered before, it is an important property of immune-mediated hypersensitivity that the hypersensitivity reaction becomes more severe with longer usage or rechallenge with the medicine.

Genotyping
The process of genotyping is used to determine the genotype. It indicates which alleles of the various HLA genes are present in the tested individual. Each allele has a name that consists of the name of the gene, followed by a star (*) and a number, an example of a possible HLA allele is HLA-B*5701.

As the activity of HLA alleles is highly specific, only one allele of the 6 polymorphic genes generally has a distinct effect on protein-based and other medicines. In the event of HLA drug interactions, only one set of alleles of a polymorphic gene therefore generally needs to be determined.

As HLA alleles are determined as part of tissue typing to establish whether donors and recipients are transplant compatible, typing of polymorphic HLA alleles is a standard procedure in many laboratories of immunology and clinical chemistry. However, this generally uses phenotyping rather than the more expensive genotyping. The standard genotyping method is DNA sequence-based typing.
There are cheaper methods available for specific alleles, such as PCR with sequence-specific primers for the identification of HLA-B*5701. HLA-DRB typing is also possible using an HLA chip.

*Genotyping of HLA-B*1502 based on DNA variations located beyond the gene is not sufficiently reliable.*
Sometimes HLA-B*1502 is genotyped using variations in DNA located close to the HLA-B gene (rs2844682 in the MUC21 gene and rs3909184). However, this genotyping method appears to be unreliable (Zhu GD et al. Genotypes at rs2844682 and rs3909184 have no clinical value in identifying HLA-B*15:02 carriers. Eur J Clin Pharmacol 2015;71:1021-3). Therefore, the Dutch Pharmacogenetics Working Group is of the opinion that – due to the unreliability of this genotyping method – genotyping results obtained via this method should not be used. It is better to consider these patients as not having been genotyped for HLA-B*1502.

Phenotyping
The process of phenotyping is used to determine the phenotype, which means: establishing which HLA proteins are present. This can be done using standard serology tests, involving staining cells using antibodies against various HLA proteins. Another option is functional testing (complement-dependent cytotoxicity tests for identification of class I proteins). A disadvantage of these tests is that they cannot distinguish between subtypes of polymorphic HLA proteins, meaning that they can be used to determine whether a person has HLA-B57, but not whether this person has HLA-B*5701, HLA-B*5702 or any of the other subtypes.

Ethnic variation in prevalence of phenotypes and allele frequency
The frequency of occurrence of the various HLA alleles varies significantly between ethnic groups.
The allele frequencies of six pharmacogenetic implicated HLA alleles identified in various populations are given in table 1.

Table 1. Ethnic variation in allele frequency (% of people with this allele)

Population group	**Area/country**	**HLA-B*5701**	**HLA-A*3101**	**HLA-B*1502**	**HLA-B*1511**	**HLA-B*5801**
White		0-11.2	3.0-13.4	0-1.2	0-0.38	0-9.0
	The Netherlands	6.7	3.0-6.6	0	0	1.2
	Northern Europe	1.4-11.2	3.0-6.6	0-0.04	0-0.02	0-1.8
	Southern Europe		3.6-5.0	0-1.2	0	0-9.0
Asian	USA	2.0-4.2				
	China	0-6.5	0.8 -12.6	0-59	0-24	4.6-31
	Taiwan	0.2-1.4	5.6	8.4-12	1.8	19
	Japan	0	16.8	0.06-0.2	0.8-1.8	0.8-1.2
	Thailand	3.6-6.1	2.6	17	2.0	12-17
	Malaysia	0.5-6.9	0.8-2.6	0.04-31	0.22-0.52	12-26
	India	5.7-15.7		0-12		12-18
	South Korea	0.4%	11.2	0.4-4.4	3.3-4.0	12-13
	Vietnam	5.7%		26		13
	Myanmar		4.6	18-34		
	Indonesia	2.5%		21-31		8.4-16
	Philippines			39	0	
	Middle East	0.5-4.4		0-1.2	0	2.8-14
African	Sub Saharan	0–6.1	0.8-1.8	0	0	1.4-28
	Northern Africa	0-5.9	3.0	0	0	2.4-8.0

	Burkina Faso, Guinea-Bissau, Cameroon, Kenya, Uganda, Senegal, Zouth Africa					10-16
	Cape Verde, Ghana, Sao Tomé and Principe, Sudan, Zimbabwe					7.2-9.0
	Ivory Coast, Mali, Tunisia					4.4-6.4
	Zambia					0
African-American		1.0-4.7	2.0	0-0.4	0	7.6
Hispanics		1.6-3.8				1.4-1.45
Indians		1.0-4.2				
South American		1.4-4.0	5.6-44	0-1.6	0-1.0	1.0-5.5

Literature

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