General background text Pharmacogenetics –

ATP-Binding Cassette subfamily G member 2 (ABCG2)

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Concepts in pharmacogenetics

The **genotype** is the hereditary information about a certain characteristic of an individual. This information is contained in the genes, in the DNA that consists of nucleotides. The part 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** describes the final manifestation of a certain genotype. This can involve the functionality of a protein (for example, the enzyme or the receptor), or it can relate to the manifestation of a disease. The phenotype is a result of the genotype that a person has, the degree of expression of the relevant gene and the combination with environmental factors, such as co-medication, diet and disease conditions.

DNA that encodes for a protein can exist in variations within a population. Variations can result in alleles encoding for inactive or less active proteins. The most simplified form of variations are **single-nucleotide polymorphisms (SNPs),** in which a certain part of a gene differs by only a single nucleotide. If a gene variation occurs in at least 1% of the population, then it is referred to as a genetic **polymorphism. Wild type** is the name given to the most commonly occurring active allele. A specific allele can have different polymorphisms.

Altered transporter activity and clinical consequences

The ATP binding cassette subfamily G member 2 (ABCG2) is an efflux transporter that is present in the intestines, liver, kidneys and the blood-brain barrier and it plays an important role in the excretion of uric acid by the kidneys and the gastro-intestinal tract. The protein is also known as the breast cancer resistance protein (BCRP), as it also plays an important role in the efflux of mitoxantrone, doxorubicin and daunorubicin. Gene variations that reduce the activity of this transporter reduce the excretion of uric acid and can therefore increase the risk of hyperuricaemia and gout [1].

Allopurinol is rapidly converted in the body to the active metabolite oxypurinol, which is responsible for the majority of the effect on uric acid reduction. Allopurinol and oxypurinol reduce uric acid concentrations by reducing the uric acid production. They inhibit the enzyme xanthine oxidase, which breaks down hypoxanthine and xanthine to uric acid.

The mechanism by which gene variations that reduce the ABCG2 activity change the allopurinol response is not clear. On the one hand it is likely that a stronger inhibition of the uric acid production requires a higher dose of allopurinol in patients with reduced uric acid secretion, such as carriers of such a gene variation. On the other hand, oxypurinol is also a substrate of ABCG2 and reduced excretion of oxypurinol could result in higher oxypurinol concentrations and therefore a higher effectiveness of allopurinol in carriers of such a gene variation [2]. However, the latter mechanism does not appear to occur. In carriers of such a gene variation, the plasma concentration of oxypurinol was lower instead of higher, suggesting that the variant allele increases the secretion of oxypurinol [3].

Genotyping

The process of genotyping is used to determine the genotype. The genotype indicates which alleles of the gene for ABCG2 the tested individual has.

More than 100 different allele variations have been identified/described in the literature for ABCG2 [1]. Only 2 of these allele variations occur at a frequency of more than 1% (and are therefore polymorphisms). A clinical effect (reduced effectiveness of allopurinol) has only been demonstrated for one of these two allele variations. This is the allele that results in a change in the 141st amino acid of ABCG2 from glutamine (abbreviation Gln or Q) to lysine (abbreviation Lys or K). The relevant gene variation is generally referred to as Q141K. Other annotations for the gene variation have been included in table 1. The 141K allele results in a protein with reduced expression in the cell membrane and subsequently reduced transport function. This accounts for a reduction by approximately 50%.

Table 1. Overview of the annotations used and the transporter activity for the wild type and variant ABCG2 allele [1]

Annotations for the variant[a] and the accompanying polymorphism			**Transporter activity**
amino acid change	**nucleotide change**	**rs number**	
-	-	-	normal
Q141K (= Gln141Lys)	421C>A	2231142	reduced

[a] The annotation for the variant is the number in the polymorphism annotation, followed by the latter amino acid or nucleotide. The annotation for the wild type allele (normal functionality) is the number in the polymorphism annotation, followed by the former amino acid or nucleotide.

Ethnic variation in prevalence phenotypes and allele frequency

The frequency of occurrence of the ABCG2 141K allele, as well as the different phenotypes, exhibits significant variation between population groups.

The ABCG2 141K allele is very common in people of East Asian origin, common in people of European, Latin American and South Asian origin and rare in people of African origin [1]. The prevalence in a small group of Dutch people of European origin (n = 85) was 11% [5].

ABCG2 is an efflux transporter of uric acid and there are studies that have found an association between ABCG2 Q141K and hyperuricaemia and gout [1], resulting in a higher frequency of the 141K allele in these patients and thus in patients with an indication for allopurinol. For this reason, the prevalences of the 141K allele and of the genotypes with and without this allele have also been included for two groups with gout.

Detected phenotype and allele frequencies per population group are presented in table 2.

Table 2. Ethnic variation in prevalence genotypes and allele frequency [1,4-7]

population group/origin	prevalence genotype (%)			allele frequency 141K (%)
	141KK	141QK	141QQ	
European	0.9-3	17-28	69-82	9.4-17
European (non-Finnish)	1	18	81	10
Dutch	1	20	79	11
Finnish	0.5	14	86	7.3
East Asian	8-10	41-43	47-51	29-31
Chinese	12-20	45-50	30-43	34-45
Chinese, gout	26	48	26	50
Japanese	13-17	46-48	35-41	36-41
Korean	16	48	36	40
South Asian	1	17	82	9.3-9.7
African	0.02-0.07	3-5	95-97	1.3-2.7
African-American	0.3	10	90	5
Latin-American	2-5	24-34	61-74	14-22
Ashkenazi Jewish	0.4	12	88	6.5
New Zealander, gout	8	34	58	25

Literatuur

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