General background text Pharmacogenetics – Catechol-O-methyltransferase (COMT)

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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 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.

Altered enzyme activity and clinical consequences
COMT is involved in the catabolism of catecholamines, such as dopamine and noradrenaline in nerve cell synapses. It inactivates catecholamines by methylation. COMT is especially important for the dopamine level in the prefrontal cortex, as this area contains only few dopamine transporters that remove dopamine from the synaptic cleft. Because high levels of dopamine in the prefrontal cortex act as a negative feedback signal to dopamine in other parts of the brain, COMT probably also has an indirect effect on dopamine levels elsewhere in the brain.
The *COMT* gene has two transcription start sites and therefore encodes two proteins: a long membrane-bound variant and a soluble variant in the cytoplasm which is 50 amino acids shorter. Amino acid numbering usually follows the numbering of the long, membrane-bound variant. The corresponding number for the short variant is 50 smaller.

The COMT polymorphism that leads to replacement of valine by methionine in position 158 (Val158Met) results in an enzyme with 2-4x lower activity. This raises the dopamine concentration mainly in the prefrontal cortex. This change is associated with improvements in functions such as attention, organisation and planning and may also have an effect on impulsiveness. This may influence subcortical dopaminergic neurotransmission due to prefrontal dopaminergic negative control over this neurotransmission.

Genotyping
The process of genotyping is used to determine the genotype. It indicates which alleles of the gene for COMT are present in the tested individual. COMT alleles have a name that consists of the changed amino acid (Met for the variant allele or Val for the wild-type allele) sometimes preceded by the codon number in the long enzyme variant (158Val or 158Met for the polymorphism Val158Met).

In addition to being referred to by their amino acid change, polymorphisms and alleles can also be referred to by the nucleotide change or by rs number. As all three systems appear in the literature, table 1 shows the nomenclature according to all three of these systems.

Table 1. Overview of the most important COMT polymorphism

Nucleotide polymorphism	rs number	Protein polymorphism
472G>A	rs 4680	Val158Met

Ethnic variation in prevalence of genotypes and allele frequency

Data on the prevalence of the genotypes and ethnic variation in allele frequency of the most important COMT polymorphism Val158Met are given below.

The incidence of both alleles is about equal in the Caucasian population. In the Netherlands, 30% are homozygous for the Met allele and 50% are heterozygous. Homozygotes for the Val allele make up the smallest population at 20%.

The frequency of the Met allele in Asians, Africans and South Americans is clearly lower than in Dutch people and other Europeans.

Allele frequencies and genotypes in the various populations are given in table 2.

Table 2. Ethnic variation in prevalence of genotypes and allele frequency

		Prevalence of genotype (%)			**Allele frequency (%)**
Ethnicity	**Country**	**Val/Val**	**Val/Met**	**Met/Met**	**Met**
Caucasian		18-31	42-51	19-36	43-58
	The Netherlands	20	50	30	55
Asian		39-67	30-51	3-13	18-36
African					7-38
South American					1-34

Literature

- Napolitano A et al. The role of monoamine oxidase and catechol O-methyltransferase in dopaminergic neurotransmission. J Neural Transm 1995;45:S35-45.
- Lachman HM et al. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 1996;6:243-50.
- Lotta T et al. Kinetics of human soluble and membrane-bound catechol-O-methyltransferase: a revised mechanism and description of the thermolabile variant of the enzyme. Biochemistry 1995;34:4202-10.
- Palmatier MA et al. Global variation in the frequencies of functionally different catechol-O-methyltransferase alleles. Biol Psychiatry 1999;46:557-67.
- Huppertz C et al. The dopaminergic reward system and leisure time exercise behavior: a candidate allele study. Biomed Res Int 2014;2014:591717.