CYP2C9 CYTOCHROME P450 VARIANTS *2 and *3

For in vitro diagnostic use

CE IVD

ORDERING INFORMATIONS

REF: FGC-005-25
RDM Code: 1973964/R
CND Code: W0106030101
Tests: 25
Reactions: 31 x 2
Manufacturer: BioMol Laboratories s.r.l.

CONTENTS OF THE KIT

The kit consists of: reagents for Real-Time PCR amplification
**the reagents for the extraction of genomic DNA are not supplied in the kit.*

PRODUCT CHARACTERISTICS

Device belonging to the family of in vitro medical devices **REAL-TIME QUALITATIVE PCR-PHARMACOGENETICS TEST**. Determination of the genetic variants rs1799853 (*2) and rs1057910 (*3) of the CYP2C9 gene by amplification with oligonucleotides and specific probes (allele-specific genotyping) and subsequent detection with qPCR-Real-time. Kit optimized for Real-Time PCR instrumentation Biorad CFX96 Dx, Biorad Opus Dx and Agilent AriaDx.

SCIENTIFIC BACKGROUND

Cytochromes P450s are a family of enzymes responsible for approximately 75% of all drug metabolism reactions. There are multiple isoforms of cytochrome P450 but most reactions are metabolised by CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The CYP2C9 gene has been mapped to chromosome 10q24.2 and is highly variable; nucleotide sequencing has already identified nearly 60 alleles. Three alleles, namely CYP2C9 *1 (the wild-type allele, as it is the most common in the population), CYP2C9 *2 and CYP2C9 *3 (both with reduced enzyme activity) are often identified in studies in the Caucasian population.

The CYP2C9 * 2 variant (rs1799853) has a C>T transition at position 430 of exon 3 coding for arginine, resulting in a substitution at position 144 (Arg144Cys) of the CYP2C9 protein, while the analysis of the CYP2C9 *3 variant (rs1057910) demonstrated an A>C transversion at position 1075 in exon 7 causing an isoleucine to leucine substitution at position 359 (Ile359Leu).

*§ The Cytochrome P450 Slow Metabolizers CYP2C9*2 and CYP2C9*3 Directly Regulate Tumorigenesis via Reduced Epoxyeicosatrienoic Acid Production. Cancer Res. 2018 Sep 1; 78 (17):4865-4877.*
§ Applications of CYP450 testing in the clinical setting. Mol Diagn Ther. 2013 Jun; 17(3):165-84.
§ CYP2C9 polymorphisms in epilepsy: influence on phenytoin treatment. Pharmgenomics Pers Med. 2018 Mar 29;11: 51-58.
*§ Polymorphisms of CYP2C9*2, CYP2C9*3 and VKORC1 genes related to time in therapeutic range in patients with atrial fibrillation using warfarin. Appl Clin Genet. 2019 Aug 2;12:1 51-159.*

CLINICAL SIGNIFICANCE

The cytochrome P450 superfamily is mainly expressed in the liver, small intestine and kidney. CYP P450 enzymes catalyze several types of oxidation and some reduction reactions.

Genetic polymorphisms in CYP genes are the major cause of inter-individual variation in drug metabolism. They cause variations in drug response ranging from adverse effects to lack of efficacy. In addition, CYP polymorphisms have been reported to confer susceptibility or reduced risk/protection from disease. CYP2C9 plays an important role in the phase I metabolism of xenobiotics and some endogenous compounds, for example, nonsteroidal anti-inflammatories, oral anticoagulants and oral hypoglycaemics. Individuals with low CYP2C9 catalytic activity (poor and/or intermediate metabolisers) develop adverse drug reactions particularly with substrates with a narrow therapeutic index, e.g. S-warfarin, phenytoin, glipizide and tolbutamide. The combination of genotypes (www.pharmgkb.org) allows to define the patient as "Normal Metabolizer" (Homozygous CYP2C9*1), "Intermediate Metabolizer" (Heterozygous CYP2C9*2 and *3) and "Poor Metabolizer" (Homozygous or Double CYP2C9 heterozygous *2 and *3).

Recently, the importance of CYP2C9 in the metabolism of Siponimod, an orally available immunomodulatory drug used to treat relapsing forms of multiple sclerosis, has been demonstrated. Indeed, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) indicate that molecular characterization is necessary before starting treatment (CYP2C9 *3/*3 patients should not be subjected to pharmacological treatment).

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ISO 9001:2015
ISO 13485:2016

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DESCRIPTION	LABEL	VOLUME	STORAGE
		FGC-005-25	
Mix oligonucleotides and probes	Mix 10X CYP2C9 *2	1 x 85 µl	-20°C
Mix oligonucleotides and probes	Mix 10X CYP2C9 *3	1 x 85 µl	-20°C
Mix buffer and Taq-polymerase enzyme	Mix Real-Time PCR 2X	1 x 850 µl	-20°C
Deionized H_20	Deionized H_20	2 x 1 ml	-20°C
Genomic DNA or recombinant DNA	Control +1 Homozygous **CC CYP2C9*2** Homozygous **AA CYP2C9*3**	1 x 45 µl	-20°C
Genomic DNA or recombinant DNA	Control +2 Heterozygous **CT CYP2C9*2** Heterozygous **AC CYP2C9*3**	1 x 45 µl	-20°C

TECHNICAL CHARACTERISTICS

COD. FGC-005-25

STABILITY	18 months
REAGENTS STATUS	Ready to use
BIOLOGICAL MATRIX	Genomic DNA extracted from whole blood, tissue, cells
POSITIVE CONTROL	Recombinant DNA for at least 3 analytical sessions
TECHNOLOGY	Real-time PCR; oligonucleotides and specific probes; 2 FAM/HEX fluorescence channels
VALIDATED INSTRUMENTS	Biorad CFX96 Dx, Biorad Opus Dx e Agilent AriaDx
RUNNING TIME	85 min
THERMAL CYCLING PROFILE	1 cycle at 95 °C (10 min); 45 cycles at 95 °C (15 sec) + 60 °C (60 sec)
ANALYTICAL SPECIFICITY	Absence of non-specific pairings of oligonucleotides and probes; absence of cross-reactivity
ANALYTICAL SENSITIVITY : LIMIT OF DETECTION (LOD)	≥ 0,016 ng of DNA
ANALYTICAL SENSITIVITY : LIMIT OF BLANK (LOB)	0% NCN
REPRODUCIBILITY	99,9%
DIAGNOSTIC SPECIFICITY / DIAGNOSTIC SENSITIVITY	100%/98%

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