GENETIC VARIANTS OF THE ENZYME DIHYDROPYRIMIDINE DEHYDROGENASE (DPYD) (DPYD *2A, *13, Asp949Val, 1236 G>A, HapB3 and 2194 G>A, *6)

For in vitro diagnostic use

CE IVD

ORDERING INFORMATIONS

REF: FGC-010-25 RDM Code: 2256421/R
Tests: 25 Reactions: 31 x 5
REF: FGC-010-50 RDM Code: 2256529/R
Tests: 50 Reactions: 62 x 5
CND Code: W0106010499
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. Detection of genetic variant *2A (rs3918290, 1905 +1G>A, IVS14 +1 G>A), *13 (rs55886062, 1679 T>G), Asp949Val, (rs67376798, 2846 A>T), 1236 G>A (rs 56038477, HapB3) and DPYD *6 (2194 G>A, rs 1801160 G2677T; G>T / G2677A; G>A) of the gene DPYD 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, Agilent AriaDx, Hyris bCUBE and Hyris bCUBE3 with Hyris bAPP.

SCIENTIFIC BACKGROUND

The treatment of neoplastic pathologies has become increasingly personalized in relation to the large inter-individual differences that exist in the effect of therapy and its toxicity. Polymorphisms in genes encoding proteins responsible for drug metabolism can significantly influence the absorption, metabolism and elimination of anticancer drugs. As a result, different pharmacokinetics can significantly influence the efficacy and toxicity of drugs.
Pharmacogenetic screening and/or drug-specific phenotyping of cancer patients eligible for treatment with chemotherapy drugs can identify patients likely to be reactive or resistant to the proposed drugs. Likewise, identifying patients with an increased risk of developing toxicity allows for dose adaptation or the application of other targeted therapies.

CLINICAL SIGNIFICANCE

The main chemotherapeutic agents used in many types of cancer are fluoropyrimidines, namely 5-fluorouracil (5-FU), capecitabine and various derivatives. Treatment with these agents is not well tolerated in a subgroup of patients as moderate to severe (fatal) toxicity occurs in 20% to 40% of cases, manifested by nausea and vomiting, diarrhea, mucositis/stomatitis, myelosuppression and syndrome hand-foot.
The main degradation pathway of fluoropyrimidines is the enzyme dihydropyrimidine dehydrogenase (DPYD). The reduced functionality of this enzyme causes increased exposure to active metabolites, which can lead to varying degrees of toxicity. The DPYD gene is on chromosome 1p22 and has 23 exons. More than 100 variants have been reported. Among these, three have been associated with toxicity and decreased activity of the enzyme: DPYD *2A (c.1905 + 1G>A; rs3918290), DPYD *13 (c .1679 T>G p. [Ile560Ser], rs55886062) and c .2846A> T p.(Asp949Val), rs67376798.
As reported in the 2018 CPIC (Clinical Pharmacogenetics Implementation Consortium (CPIC®) guidelines and in the 2019 AIOM (Italian Association of Medical Oncology), SIF (Italian Society of Pharmacology) and EMA (European Medicines Agengy) recommendations, the DPYP pharmacogenetic analysis it is recommended to optimize the therapeutic dose and possibly define a reduction in the drug dose (25-50%) for Intermediate Metabolizers patients and the evaluation of an alternative therapy for Poor Metabolizers.

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§ ESMO Open. 2023 Apr;8(2):101197. doi: 10.1016/j.esmoop.2023.101197. Epub 2023 Mar 28.PMID: 36989883
§ Cancers (Basel). 2022 Jun 30;14(13):3207. doi: 10.3390/cancers14133207. Testing for Dihydropyrimidine Dehydrogenase Deficiency to Individualize 5-Fluorouracil Therapy.
§ Oncologist. 2021 Apr;26(4):e597-e602. doi: 10.1002/onco.13626. Epub 2020 Dec 23. Implementing DPYD*2A Genotyping in Clinical Practice: The Quebec, Canada, Experience
§ EMA recommendations on DPD testing prior to treatment with fluorouracil, capecitabine, tegafur and flucytosine. 30 April 2020
§ Br J Cancer. 2019 Apr; 120(8):834-839. doi: 10.1038/s41416-019-0423-8. Epub 2019 Mar 12. The Clinical Relevance of Multiple DPYD Polymorphisms on Patients Candidate for Fluoropyrimidine Based-Chemotherapy. An Italian Case-Control Study
§ Curr Ther Res Clin Exp. 2018 Oct 31; 90:1-7. doi: 10.1016/j.curtheres.2018.10.001. eCollection 2019. Evolution of Dihydropyrimidine Dehydrogenase Diagnostic Testing in a Single Center during an 8-Year Period of Time.
§ Int J Cancer. 2015 Dec 15; 137(12):2971-80. doi: 10.1002/ijc.29654. Epub 2015 Jul 14. Clinical validity of a DPYD-based pharmacogenetic test to predict severe toxicity to fluoropyrimidines.

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EN ISO 9001 CERTIFICATE
EN ISO 13485 CERTIFICATE

BioMol LABORATORIES

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DESCRIPTION	LABEL	VOLUME		STORAGE
		FGC-010-25	FGC-010-50	-20°C
Mix oligonucleotides and probes	Mix 10X DPYD *2A	1 x 85 µl	1 x 170 µl	-20°C
Mix oligonucleotides and probes	Mix 10X DPYD *13	1 x 85 µl	1 x 170 µl	-20°C
Mix oligonucleotides and probes	Mix 10X DPYD Asp949Val	1 x 85 µl	1 x 170 µl	-20°C
Mix oligonucleotides and probes	Mix 10X DPYD 1236 G>A	1 x 85 µl	1 x 170 µl	-20°C
Mix oligonucleotides and probes	Mix 10X DPYD *6	1 x 85 µl	1 x 170 µl	-20°C
Mix buffer and Taq polymerase enzyme	Mix Real-Time PCR 2X	2 x 1100 µl	4 x 1100 µl	-20°C
Deionized H_20	Deionized H_20	2 x 1 ml	2 x 1 ml	-20°C
Genomic DNA or recombinant DNA	Control +1	1 x 70 µl	2 x 70 µl	-20°C
Genomic DNA or recombinant DNA	Control +2	1 x 70 µl	2 x 70 µl	-20°C

TECHNICAL CHARACTERISTICS

COD. FGC-010-25 / COD. FGC-010-50

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, Hyris bCUBE and Hyris bCUBE3 with Hyris bAPP
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 genomic DNA
ANALYTICAL SENSITIVITY: LIMIT OF BLANK (LOB)	0% NCN
REPRODUCIBILITY	99,9%
DIAGNOSTIC SPECIFICITY / DIAGNOSTIC SENSITIVITY	100%/98%

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