ID: 000000000

ONCOGEN

Genetics for people

Pharmacogenetics

ONCOLOGY

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PHARMACOLOGICAL COMPATIBILITY

Below, the genetic compatibility for each of the drugs analysed in the text is shown.

In the table, pharmacological compatibility is represented by a circle with three possible colours:

green: the patient presents no problematic genetic variant for this drug.

yellow: the patient presents at least one problematic genetic variant with an evidence level 2.

red: the patient presents at least one problematic genetic variant with an evidence level 1.

✓	1. Azathioprine	✗	13. Irinotecan
✓	2. Capecitabine	✓	14. Mercaptopurine
!	3. Carboplatin	!	15. Methotrexate
✓	4. Cetuximab	!	16. Ondansentron
!	5. Cyclophosphamide	!	17. Oxaliplatin
!	6. Cisplatin	!	18. Paclitaxel
✓	7. Doxorubicin = Adriamycin	✓	19. Panitumumab
✗	8. Erlotinib	✓	20. Rituximab
!	9. Etoposide	!	21. Tamoxifen
✓	10. Fentanyl, Metadone, Morphine, Opioids, Oxycodone, Tramadol	✓	22. Tegafur
		✓	23. Thioguanine
!	11. Fluorouracil	✓	24. Trastuzumab
✗	12. Gefitinib	✓	25. Vincristine

All of the results are based on the PharmaGKB evidence level classification, except for the SNPs rs887828 for the drug Irinotecan and rs1168555232 for the drug Thioguanine, whose recommendations come from the European Medicines Agency (EMA), the US Food and Drug Administrationl (FDA), the Pharmaceuticals and Medical Devices Agency from Japan (PMDA) and the Health Canada (HCSC).

The Pharmacogenetics Knowledgebase (PharmGKB) is the biggest public access online database, formed by a consortium of pharmacogenomics and pharmacogenetics experts who are responsible for the collection, selection, incorporation and dissemination of all the knowledge related to the impact of the human genetic variation in response to the drugs.

PharmGKB is finances by the National Institutes of Health (NIH) and the National Institute of General Medical Sciences (NIGMS) in the United States, it is also a member of the Pharmacogenomics Research Network (PGRN) of the NIH.

PharmaGKB was founded by Stanford University in the year 2000.

PHARMACOGENETIC RESULTS AND RECOMMENDATION

In the following table all the drugs included in the test, the variables with only one nucleotide (SNP) of each gene that interact with the drugs, the possible genotypes for each SNP (normal and at risk) and, the patients genotype for each SNP are shown.

Also included is the column 'Level of evidence' that indicates the level of evidence for drug combination - genetic variable, (1A, 1B, 2A, 2B) coming from the Pharmacogenomics Knowledge Base PharmGKB, the drug regulatory agencies (FDA, EMA) and the international pharmacogenetics consortiums (CPIC, DPWG mainly), as well as the parameter that is affected: [**E**] Efficiency, [**D**] Dosage, [**T**] Toxicity, [**ADR**] Adverse Reactions, [ME] Metabolism and [**PK**] Pharmacokinetics.

Finally, the specific recommendations elaborated from those present on the PharmGKB database, in those SNPs that present an affectation, are included. As additional information, the maximum relevance level for the SNP or gene is included, that is included in the Drug Leaflet (DL) according to the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the two main drug regulatory agencies in the USA and Europe respectively.

Finally, the column Other Information ('Info') reflects if there are any indications for this drug. Considering the categories: "Mandatory or recommended genetic test" (**T**), "Manageable pharmacogenetic test" (**A**) and "Informative pharmacogenetic test" (**I**).

If the patient presents a variant associated with a yellow or red risk, a change or revision of the treatment at the discretion of the clinician is recommended.

Risk	**Drug**						
Gene	SNP	Possible genotypes		Result	Observation	Level of evidence	Info.
		Normal	Risk				
✓	**1. Azathioprine**						
NUDT15	rs116855232	CC	CT, TT	CC ✓	-	1A: D,T	Yes/T
TPMT	rs1800462	CC	CG, GG	CC ✓	-	1A: D,T	Yes/I
	rs1800584	CC	CT, TT	CC ✓	-	1A: D,T	Yes/I
	rs1800460	CC	CT, TT	CC ✓	-	1A: D,T	Yes/I
	rs1142345	TT	TC, CC	TT ✓	-	1A: D,T	Yes/I
✓	**2. Capecitabine**						
UMPS	rs1801019	GG, GC	CC	GG ✓	-	2B: T	Yes/A
DPYD	rs3918290	CC	CT, TT	CC ✓	-	1A: Pk,T	Yes/A
	rs55886062	AA	AC, CC	AA ✓	-	1A: T	Yes/A
	rs67376798	TT	TA, AA	TT ✓	-	1A: Pk,T	Yes/A
	rs75017182	GG	GC, CC	GG ✓	-	1A: T,ADR	Yes/A

Risk	Drug						
Gene	SNP	Possible genotypes		Result	Observation	Level of evidence	Info.
		Normal	Risk				
	3. Carboplatin						
ERCC1	rs11615	GG	AG, AA	AG	Moderate risk of inefficiency and toxicity	2B: E,T	-/T
	rs3212986	AA	CA, CC	CA	Moderate risk of toxicity	2B: T	-/I
GSTP1	rs1695	GG	AG, AA	AA	Moderate risk of toxicity	2A: T	-/I
MTHFR	rs1801133	AA	GA, GG	GA	Moderate risk of inefficiency	2A: E	-/I
XRCC1	rs25487	CC	CT, TT	TC	Moderate risk of inefficiency	2B: E	-/I
NQO1	rs1800566	GG	GA, AA	GG	-	2A: E	-/I
	4. Cetuximab						
KRAS	rs112445441	AC,CC,CT	AA,TT,GG,GT	CC	-	2B: D	-/T
	5. Cyclophosphamide						
SOD2	rs4880	AA	AG, GG	AG	Moderate risk of inefficiency	2B: E	-/I
GSTP1	rs1695	AA, AG	GG	AA	-	2A: E, T	-/I
TP53	rs1042522	CC	GC, GG	GC	Moderate risk of inefficiency and toxicity	2B: E,T	-/I
	6. Cisplatin						
ERCC1	rs11615	GG	AG,AA	AG	Moderate risk of inefficiency and toxicity	2B: E,T	Yes/I
	rs3212986	AA	CA, CC	CA	Moderate risk of toxicity	2B: T	Yes/I
GSTP1	rs1695	GG	AG, AA	AA	Moderate risk of toxicity	2A: T	Yes/I
XPC	rs2228001	TT	GT, GG	TT	-	1B: T	Yes/I
XRCC1	rs25487	CC	CT, TT	TC	Moderate risk of inefficiency	2B: E	Yes/I
NQO1	rs1800566	GG	GA, AA	GG	-	2A: E	Yes/I
TP53	rs1042522	CC	GC, GG	GC	Moderate risk of inefficiency and toxicity	2B: E,T	Yes/I
	7. Doxorubicin=Adriamycin						
NQO1	rs1800566	GG	GA, AA	GG	-	2A: E	Yes/I

Risk	Drug						
Gene	SNP	Possible genotypes		Result	Observation	Level of evidence	Info.
		Normal	Risk				
✕	**8. Erlotinib**						
EGFR	rs121434568	GG, TG	TT	TT ✕	High risk of inefficiency in patients with activating somatic mutation	1B: E	-/T
✕	**9. Etoposide**						
DYNC2H11	rs716274	AA	AG, GG	AG ✕	Moderate risk of toxicity	2B: T	-/I
✓	**10. Fentanyl, Metadone, Morphine,Opioids, Oxycodone, Tramadol**						
ABCB1	rs1045642	AA, AG	GG	AG ✓	-	2B: D,E	-
✕	**11. Fluorouracil**						
TP53	rs1042522	CC	GC, GG	GC ✕	Moderate risk of inefficiency and toxicity.	2B: E,T	Yes/A
GSTP1	rs1695	AG, GG	AA	AA ✕	Moderate risk of inefficiency	2B: E,T	Yes/A
UMPS	rs1801019	GG, GC	CC	GG ✓	-	2B: T	Yes/A
DPYD	rs3918290	CC	CT, TT	CC ✓	-	1A: Pk,T	Yes/A
	rs55886062	AA	AC,CC	AA ✓	-	1A: T	Yes/A
	rs67376798	TT	TA, AA	TT ✓	-	1A: Pk,T	Yes/A
	rs75017182	GG	GC, CC	GG ✓	-	-	Yes/A
✕	**12. Gefitinib**						
EGFR	rs121434568	GG, TG	TT	TT ✕	High risk of inefficiency in patients with activating somatic mutation	1B: E	-/T
✕	**13. Irinotecan**						
UGT1A1	rs887829	CC	CT, TT	TT ✕	In TT genotype: Doses ≥240mg/m² are contraindicated; doses 180-230mg/m² must be reduced x0,7 in 1st Cycle. In CT genotype: Rigorous surveillance due to increased toxicity risk	-	Yes/A
	rs4148323	GG	GA, AA	GG ✓	-	2A	Yes/A
SEMA3C	rs7779029	TT	TC, CC	TT ✓	-	2B: T	Yes/A

Risk **Drug**

Gene	SNP	Possible genotypes		Result	Observation	Level of evidence	Info.
		Normal	Risk				
	14. Mercaptopurine						
NUDT15	rs116855232	CC	CT,TT	CC	-	1A: D,T	Yes/T
TPMT	rs1800462	CC	CG, GG	CC	-	1A: D,T	Yes/I
	rs1800584	CC	CT, TT	CC	-	1A: D,T	Yes/I
	rs1800460	CC	CT, TT	CC	-	1A: D,T	Yes/I
	rs1142345	TT	TC, CC	TT	-	1A: D,T	Yes/I
	15. Methotrexate						
ABCB1	rs1045642	GG	AG, AA	AG	Moderate risk of toxicity	2A: T	-/ I
SLCO1B1	rs11045879	CC	TC, TT	TC	Moderate risk of toxicity	2A: T	-/I
MTHFR	rs1801133	GG	GA, AA	GA	Consider dose reduction	2A: D,E,T	-/I
MTRR	rs1801394	AA	AG, GG	AG	Moderate risk of toxicity	2B: T	-/I
ATIC	rs4673993	CC, TC	TT	TC	-	2B: E	-/I
	16. Ondansetron						
ABCB1	rs1045642	AA	AG, GG	AG	Moderate risk of inefficiency	2A: T	Yes/ I
	17. Oxaliplatin						
ERCC1	rs11615	GG	AG,AA	AG	Moderate risk of inefficiency and toxicity	2B: E,T	-/I
	rs3212986	AA	CA, CC	CA	Moderate risk of toxicity	2B: T	-/I
GSTP1	rs1695	GG	AG, AA	AA	Moderate risk of toxicity	2A: T	-/I
XRCC1	rs25487	CC	CT, TT	TC	Moderate risk of inefficiency	2B: E	-/I
NQO1	rs1800566	GG	GA, AA	GG	-	2A: E	-/I
	18. Paclitaxel						
TP53	rs1042522	CC	GC, GG	GC	Moderate risk of inefficiency and toxicity	2B: E,T	-/I
	19. Panitumumab						
KRAS	rs112445441	AC, CC, CT	AA, TT, GG, GT	CC	-	2B: D	-/T
	20. Rituximab						
FCGR2A	rs1801274	AA	AG, GG	AA	-	2B: E	-/I

Risk	Drug						
Gene	SNP	Possible genotypes		Result	Observation	Level of evidence	Info.
		Normal	Risk				
	21. Tamoxifen						
CYP2D6	rs3892097	TT,CT,CC		CC	Moderate risk of toxicity	2A: E,T	Yes/T
	22. Tegafur						
UMPS	rs1801019	GG, GC	CC	GG	-	2B: T	-/ I
DPYD	rs3918290	CC	CT, TT	CC	-	1A: Pk,T	Yes/I
	rs55886062	AA	AC,CC	AA	-	1A: T	Yes/I
	rs67376798	TT	TA, AA	TT	-	1A: Pk,T	Yes/I
	23. Thioguanine						
NUDT15	rs116855232	CC	CT,TT	CC	-	1A: D,T	Yes/T
TPMT	rs1800462	CC	CG, GG	CC	-	1A: D,T	Yes/T
	rs1800584	CC	CT, TT	CC	-	1A: D,T	Yes/T
	rs1800460	CC	CT, TT	CC	-	1A: D,T	Yes/T
	rs1142345	TT	TC, CC	TT	-	1A: D,T	Yes/T
	24. Trastuzumab						
FCGR2A	rs1801274	AA	AG,GG	AA	-	2B: E	-/T
	25. Vincristine						
CEP72	rs924607	CC, CT	TT	CC	-	2B: T	-/I

CONSIDERATIONS

Pharmacogenetics studies the influence of human genetics on the activity of a drug, its transport and metabolism. It allows specific drugs to be dedicated to groups of patients classified based on their genetics, this is known as **Personalised Medicine**.

MyPharmaOnco is a pharmacogenetic test that evaluates the pharmacological compatibility of **25** drugs with the genotype of the patient. The genetic variables included in this study are single nucleotide polymorphisms (SNP).

The main aim of the MyPharma line is to give a tool of high clinical value that it easy to use and interpret by medical personnel. For this, the SNP and drug designs included in the test have been done thinking about the clinical usefulness and validity at all times. Therefore, the test includes those SNPs with the highest clinical evidence available to date for each one of the target genes.

The results of the pharmacogenetic test should serve as a tool to take into consideration for personalised therapeutic decision-making. The drug response is affected by other factors such as treatments associated with other drugs, illnesses, toxic habits, age, sex, etc.

The final decision about the treatment for each patient must always correspond to the prescribing physician based on a complete evaluation of the patient.

TECNOLOGY

DNA Microarray technology consists of a solid surface with microscopic reactions (microreactions) or DNA chip, on which molecular probes are attached to detect the presence of target DNA molecules. Probe-target hybridization is usually detected and quantified by measuring the intensity of a given fluorescence provided by the molecular probe in samples. This type of technology allows the detection of thousands of specific DNA fragments present in a DNA sample. On the other hand, the specificity in terms of DNA sequence recognition is very high since single nucleotide exchange (single-base resolution) can be detected using short oligonucleotide probes (20-25 nucleotides). As a result, DNA Microarray technology has also evolved to be applied as a DNA sequencing technique to genotype several hundred thousand single nucleotide variants (SNVs) in target genes located throughout the genome (Whole Genome DNA Microarray).

Bead Chip Infinium Global Screening Array (GSA) is a line of DNA chips developed by Illumina for its DNA Microarray iScan platform, widely used in population genetic studies and precision medicine, providing optimized content with 100% reliable and reproducible high-quality genotyping results. The construction of the GSA Chip was carried out in collaboration with a consortium of experts, and for the selection of SNVs, information from prestigious scientific databases such as gnomAD, NHGRI-EBI-GWAS Catalog, ClinVAr, MHC-HLA-KIR and PharmGKB has been used. The GSA allows the analysis of > 600,000 SNVs that cover variants of interest (hot spots) throughout the entire genome, impacting a wide range of genetic traits with physiological and pathophysiological implications. In addition, it allows the customization by users to incorporate Ad Hoc 50,000-100,000 variants of interest.

QUALITY

The analysis laboratory uses standard and efficient procedures to protect against technical and operational problems. However, the results may be altered due to problems in the sample taking (contamination) and labelling (identification) or delayed reception of the sample in the laboratory (integrity) among other problems. This could lead to the test results being invalid. In such cases, the patient would be asked to repeat the whole process in order to do the test. As is the case with all clinical analysis tests, there is a small possibility that the laboratory could report inexact information. If the suspicion of a mistake exists regarding the detected genotype, a verification analysis can be requested.

LIMITATIONS

The results of the pharmacogenetic test should be used as another tool among a wide variety of factors to take into account for therapeutic decision-making.

The drug response is affected by other factors such as treatments associated to other drugs, illnesses, toxic habits, age, sex, etc. The decisions about treatment should be done following the criteria of the physician responsible.

Genetics for people

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