PHARMACOGENETICS AND ITS APPLICATIONS IN PERSONALISED MEDICINE: A SYSTEMATIC REVIEW

L. AMARO[1], J. CORDERO[1], A. MARTÍNEZ-ESCUDERO[1], A. AGUADO[1], M.Á. CALLEJA[1]
[1]HOSPITAL UNIVERSITARIO VIRGEN MACARENA, HOSPITAL PHARMACY, SEVILLA, SPAIN
laura.amaro.sspa@juntadeandalucia.es

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Background and importance

- Pharmacogenetics evaluates how genetic variations influence drug responses.
- Stronger clinical evidence supports its integration.

NEXT ⇨ Preventive pharmacogenetic panels

Further research on biomarkers

Aim and objectives

To examine recent evidence on genotype-drug response relationship.

Material and methods

MeSH terms: “pharmacogenetics”, “precision medicine”, “individualized dosing”, “clinical practice”.

2013-2023

N = 136

Results

49 articles included

Genotype-response association found

Opioids	Efavirenz
GLP-1 agonists	Clopidogrel
Tacrolimus	Lamotrigine
Oral anticoagulants	Anti-TNFα
Antineoplastics	Voriconazole
SSRIs	Statins
Antipsychotics	

No association found

Metformin	Bisoprolol
Quetiapine	Anti-VEGF
Irinotecan	

Table 1. Characteristics of studies

Study	Drug prescribed	Genotype(s) used	Primary outcome result	Study	Drug prescribed	Genotype (s) used	Primary outcome result
Abdelhady *et al.*	Efavirenz	CYP2B6*6*6	↑QTcF interval in *6/*6 carriers. CYP2B6*6*6 ↑EFV exposure.	Lee *et al.* (2018)	Clopidogrel	CYP2C19	Risk for adverse CV events was ↑ in LOF carriers.
Casajus *et al.*	Azathioprine	TPMT NUDT15	NUDT15 PMs/IMs ↑ risk of leukopenia.	Lee *et al.* (2021)	Clopidogrel	CYP2C19	PMs/IMs without *17 ↑risk of major atherothrombotic events.
Castaño-Amores *et al.*	Bisoprolol	ADRB1	ADRB1 Arg389Gly affect response to bisoprolol. Not confirmed with meta-analysis.	Limviphuvadh *et al.*	Gemcitabine	ABCG2 SLC29A3	ABCG2 Q141K CA/AA ↑ PFS and toxicity vs. CC. SLC29A3 S158F CT/TT ↑ OS vs. CC.
Cavallari *et al.* (2018)	Clopidogrel	CYP2C19	↑risk for adverse CV events in CYP2C19 IMs/PMs.	Linares *et al.*	Oxycodone	CYP2D6	Oxycodone concentrations: PM > EM > UM.
Cavallari *et al.* (2022)	Opioids	CYP2D6	CYP2D6 PMs/IMs may attain no relief from some opioids.	Lu *et al.*	Antipsychotics	CYP2D6	UMs and PMs are at increased risk for tardive dyskinesia.
Danese *et al.*	Coumarins	CYP4F2*3	CYP4F2 T allele variation needed ↑coumarin doses	Maagdenberg *et al.*	Acenocouma	VKORC1 CYP2C9 CYP4F2	VKORC1, CYP2C9*2/CYP2C9*3 and CYP3A4*22 ↓ stable dose.
Dapía *et al.*	Voriconazole	CYP2C19 POR CYP2C9	Contribution to interindividual variability of voriconazole AUC: CYP2C19>POR>CYP2C9.	Miroshnichenko *et al.*	Olanzapine	CYP2D6 CYP1A2	Differences were found in olanzapine concentrations in CYP2D6 PMs (G/A) and EMs (G/G).
Davis *et al.*	Cannabidiol	AOX1 SLC15A1	↑ response: AOX1 rs6729738 CC. ↓ response: SLC15A1 rs1339067 TT	Neary *et al.* (2017)	Efavirenz	CYP2B6	CYP2B6 516G>T TT ↑ EFV concentration than GG.
Dawed *et al.*	GLP-1 agonist	ARRB1 GLPR1	GLP1R Gly168Ser and ARRB1 Thr370Met ↓ HbA1c after treatment with GLP-1 agonist.	Neary *et al.* (2019)	Efavirenz	CYP2B6	Efavirenz concentration ↑ in CYP2B6 983 T>C CT vs. TT.
Degorter *et al.*	Statins	SLCO1B1 ABCG2	Rosuvastatin concentration ↑ in SLCO1B1 c.521C and ABCG2 c.421A. Atorvastatin concentrations ↑ with SLCO1B1 c.521C, ↓ with SLCO1B1 c.388G.	Ovejero-Benito *et al.* (2017)	Etanercept	HLA-B MAP3K1 PTTG1	PTTG1 rs2431697 C, HLA-B/MICA rs13437088 T ↑non-responders. MAP3K1 rs96844 C ↑ responders.
Dias *et al.*	Irinotecan	UGT1A1*28	Difference in OS, PFS between UGT1A1*28 genotypes was not statistically significant.	Ovejero-Benito *et al.* (2018)	Infliximab Adalimumab	IVL IL-12B NFKBIA	IVL rs6661932 T and NF-κB G ↑ no response. IL-12B rs2546890 A ↑ response.
Díaz-Villamarin *et al.*	Anti-VEGF	ARMS2 A69S	No statistically significant association between efficacy and ARMS2 A69S.	Packiasabapathy *et al.*	Methadone	CYP2B6	CYP2B6 PMs ↓metabolism vs. NMs. rs4803419 TT ↓ pain scores vs. CC.
Dujic *et al.*	Metformin	SLC22A1 SLC47A1	None of the variants were significantly associated with response.	Peña *et al.*	Imatinib	CYP2B6 CYP3A4	CYP2B6 G516T ↓ imatinib concentration and t1/2. ↓adverse effects in CYP3A4 *22/*22,*1/*20 and *1/*22 vs. *1/*1.
Ebid *et al.*	Tacrolimus	CYP3A4 CYP3A5	Tacrolimus levels ↑ in CYP3A4*22 and CYP3A5*3 than in CYP3A4*1 and CYP3A5*1.	Postmus *et al.*	Pravastatin	ODZ4 DNAJC5B	Not significant associations between SNPs and CV event reduction by pravastatin.
El Rouby *et al.*	Warfarin	VKORC1 CYP2C9	CYP2C9 rs4086116 T ↓ weekly warfarin dose vs. CC.	Russman *et al.*	Clopidogrel	CYP2C19	CYP2C19 IMs/PMs associated with ↓ risk of thrombotic events.
Gassó *et al.*	Fluoxetine	TPH2	rs11179002, rs60032326 and rs34517220, associated with ↑ clinical improvement.	Saiz-Rodriguez *et al.*	Clopidogrel	CYP2C19 ABCB1	CYP2C19 IM-PMs ↑ aggregation value. ABCB1 C3435T, C1236T and G2677T/A variants had ↓.
Gulilat *et al.*	Apixaban	ABCG2	ABCG2 c.421C > A predictor of ↑ apixaban concentration.	Shilbayeh *et al.*	Quetiapine	CYP3A5 ABCB1	CYP3A5 *1/*1 ↑ clearance vs. *1/*3 y *3/*3.
Guo *et al.*	Warfarin	CYP2C9 VKORC1	CYP4F2*3 associated with ↑warfarin dose requirements.	Soo *et al.*	Capecitabine	TSER	TSER (TYMS enhancer region) 3R/3R ↑ tolerance to capecitabine.
Haas *et al.* (2020)	Efavirenz	CYP2B6	CYP2B6 PMs associated with ↑ plasma efavirenz.	Talamonti *et al.*	Ustekinumab	HLA-C*6	HLA-C*06 associated with ↑ and faster response.
Haas *et al.* (2021)	Rifapentine Efavirenz	NAT2 CYP2B6	NAT2 PMs ↑rifapentine concentrations. CYP2B6 PMs ↑efavirenz concentration.	Tejpar *et al.*	Irinotecan	UGT1A1	UGT1A*28 7/7 ↑ grade III-IV irinotecan-induced neutropenia.
Ham *et al.*	Benzodiazepi	CYP2C9*2/*3	CYP2C9 *2 or *3 ↑fall risk and non-carriers did not.	Theken *et al.*	NSAIDs	CYP2C9	CYP2C9 IMs/PMs ↑ NSAID exposure and risk of adverse effects.
Kato *et al.*	Fluvoxamine	5-HTTLPR FGF2	5-HTTLPR LA/S’ and FGF2 rs1449683C/T associated with HAM-D change.	Thomas *et al.*	Metoprolol	CYP2D6	CYP2D6 AS=1 ↑Cl vs. AS 0. ↑HR reduction with AS 1 vs. AS 2–2.25.
Kim *et al.*	Sunitinib	ABCG2	ABCG2 421 AA associated with toxicity (thrombocytopenia, neutropenia, and HFS).	Wang *et al.*	Azathioprine	TPMT NUDT15	IMs of TPMT have increased risk of azathioprine-induced leukopenia compared with NMs.
Klarica *et al.*	Lamotrigine	ABCG2 421C>A	ABCG2 421C>A ↓ troughs of lamotrigine vs. wild-type.	Xia *et al.*	Warfarin	CYP2C9*3 VKORC1	VKORC1-1639G > A affect the most the initial dose of warfarin. The required stable dose ↑ in GG.
Zhao *et al.*	Tacrolimus	CYP3A5	Tacrolimus Cl ↑ in CYP3A5*1 vs.				

Conclusion and relevance

- In this review a strong genetic variability-drug responses correlation was found.
- For certain drugs the influence of genotype on their response remains unclear.
- More studies with larger sample sizes, greater ethnic diversity, etc. are needed.

Pharmacogenetics shows immense potential in personalized medicine, but further research is required.