

PHARMACOGENETICS AND ITS APPLICATIONS IN PERSONALISED MEDICINE: A SYSTEMATIC REVIEW

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Background and importance

Aim and objectives

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

NEXT Preventive pharmacogenetic panels





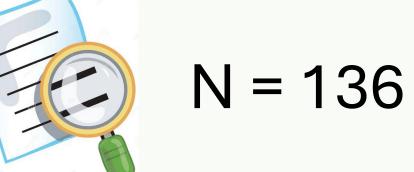
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To examine recent evidence on genotype-drug response relationship.

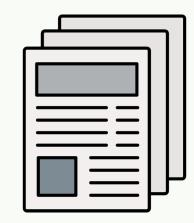
Material and methods

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

2013-2023



Results



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Table 1. Charact							
Study	Drug prescribed	Genotype(s) used	Primary outcome result	Study	Drug prescribed	Genotype (s) used	Primary outcome result
Abdelhady <i>et al</i> .	and the second se	CYP2B6*6*6	个QTcF interval in *6/*6 carriers. CYP2B6*6*6 个EFV exposure.	Lee <i>et al.</i> (2018)	The second secon	CYP2C19	Risk for adverse CV events was ↑ in LOF carriers.
Casajus <i>et al</i> .	Azathioprine	TPMT NUDT15	NUDT15 PMs/IMs 个 risk of leukopenia.	Lee <i>et al.</i> (2021)	Clopidogrel	CYP2C19	PMs/IMs without *17 个risk of major atherothrombotic events.
Castaño- Amores <i>et al</i> .	Bisoprolol	ADRB1	ADRB1 Arg389Gly affect response to bisoprolol. Not confirmed with meta- analysis.	Limviphuvadh et al.	Gemcitabine		ABCG2 Q141K CA/AA ↑ PFS and toxicity vs. CC. SLC29A3 S158F CT/TT ↑ OS vs. CC.
Cavallari <i>et al.</i> (2018)	Clopidogrel	CYP2C19	↑risk for adverse CV events in CYP2C19 IMs/PMs.	Linares <i>et al.</i>	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.	Antipsychoti cs	CYP2D6	UMs and PMs are at increased risk for tardiv dyskinesia.
Danese <i>et al</i> .	Coumarins	CYP4F2*3	CYP4F2 T allele variation needed 个coumarin doses	Maagdenberg <i>et</i> al.		VKORC1 CYP2C9 CYP4F2	VKORC1, CYP2C9*2/CYP2C9*3 and CYP3A4*22 ↓ stable dose.
Dapía <i>et al</i> .	Voriconazole	CYP2C19 POR CYP2C9	Contribution to interindividual variability of voriconazole AUC: CYP2C19>POR>CYP2C9.	Miroshnichenko <i>et al.</i>	Olanzapine	CYP2D6	Differences were found in olanzapine concentrations in CYP2D6 PMs (G/A) and EN (G/G).
Davis <i>et al.</i>	Cannabidiol	AOX1 SLC15A1	↑ response: AOX1 rs6729738 CC. ↓ response: SLC15A1 rs1339067 TT	Neary <i>et al.</i> (2017)	Efavirenz	CYP2B6	CYP2B6 516G>T TT ↑ EFV concentration that GG.
Dawed <i>et al.</i>	GLP-1 agonis	ARRB1 GLPR1	GLP1R Gly168Ser and ARRB1 Thr370Met ↓ HbA1c after treatment with GLP-1 agonist.	Neary <i>et al.</i> (2019)	Efavirenz	CYP2B6	Efavirenz concentration ↑ in CYP2B6 983 T> CT vs. TT.
Degorter <i>et al</i> .	Statins	SLCO1B1 ABCG2	Rosuvastatin concentration \uparrow in SLCO1B1 c.521C and ABCG2 c.421A. Atorvastatin concentrations \uparrow with SLCO1B1 c.521C, \downarrow with SLCO1B1 c.388G.	Ovejero-Benito <i>et al.</i> (2017)	Etanercept	HLA-B MAP3K1 PTTG1	PTTG1 rs2431697 C, HLA-B/MICA rs1343708 T 个non-responders. MAP3K1 rs96844 C 个 responders.
Dias et al.	Irinotecan	UGT1A1*28	Difference in OS, PFS between UGT1A1*28 genotypes was not statistically significant.	Ovejero-Benito <i>et al.</i> (2018)	Infliximab Adalimumab	IVL IL-12B NFKBIA	IVL rs6661932 T and NF-кВ G 个 no response IL-12B rs2546890 A 个 response.
Díaz-Villamarin <i>et al.</i>	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 <i>et al.</i>	Metformin	SLC22A1 SLC47A1	None of the variants were significantly associated with response.	Peña <i>et al.</i>	Imatinib	CYP2B6 CYP3A4	CYP2B6 G516T \downarrow imatinib concentration an t1/2. \downarrow adverse effects in CYP3A4 *22/*22,*1/*20 and *1/*22 vs. *1/*1.
Ebid <i>et al.</i>	Tacrolimus	CYP3A4 CYP3A5	Tacrolimus levels ↑ in CYP3A4*22 and CYP3A5*3 than in CYP3A4*1 and CYP3A5*1.	Postmus <i>et al.</i>	Pravastatin	ODZ4 DNAJC5B	Not significant associations between SNPs and CV event reduction by pravastatin.
El Rouby <i>et al</i> .	Warfarin	VKORC1 CYP2C9	CYP2C9 rs4086116 T↓ weekly warfarin dose vs. CC.	Russman <i>et al.</i>	Clopidogrel	CYP2C19	CYP2C19 IMs/PMs associated with \downarrow risk of thrombotic events.
Gassó et al.	Fluoxetine	TPH2	rs11179002, rs60032326 and rs34517220, associated with \uparrow clinical improvement.	Saiz-Rodriguez et al.	Clopidogrel	CYP2C19 ABCB1	CYP2C19 IM-PMs ↑ aggregation value. ABCB1 C3435T, C1236T and G2677T/A variants had ↓.
Gulilat <i>et al.</i>	Apixaban	ABCG2	ABCG2 c.421C > A predictor of \uparrow apixaban concentration.	Shilbayeh <i>et al.</i>	Quetiapine	CYP3A5 ABCB1	CYP3A5 *1/*1 个 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 (TYMS enhancer region) 3R/3R ↑ tolerance to capecitabine.
Haas <i>et al.</i> (2020)	Efavirenz	CYP2B6	CYP2B6 PMs associated with 个 plasma efavirenz.	Talamonti <i>et al.</i>	Ustekinuma b	HLA-C*6	HLA-C*06 associated with ↑ and faster response.
Haas <i>et al.</i> (2021)	Rifapentine Efavirenz	NAT2 CYP2B6	NAT2 PMs 个rifapentine concentrations. CYP2B6 PMs 个efavirenz concentration.	Tejpar <i>et al</i> .	Irinotecan	UGT1A1	UGT1A*28 7/7 ↑ grade III-IV irinotecan- induced neutropenia.
Ham <i>et al</i> .		CYP2C9*2/*3		Theken <i>et al.</i>	NSAIDs	CYP2C9	CYP2C9 IMs/PMs ↑ NSAID exposure and ris of adverse effects.
Kato <i>et al.</i>	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 个Cl vs. AS 0. 个HR reduction with AS 1 vs. AS 2-2.25.
Kim <i>et al.</i>	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 <i>et al.</i>	Lamotrigine	ABCG2 421C>A	ABCG2 421C>A \downarrow troughs of lamotrigine vs. wild-type.	Xia <i>et al.</i>	Warfarin	CYP2C9*3 VKORC1	VKORC1-1639G > A affect the most the initia dose of warfarin. The required stable dose 1 in GG.
Zhao et al.	Tacrolimus	CYP3A5	Tacrolimus Cl 个 in CYP3A5*1 vs.				

Genotype-response	
association found	

Opioids GLP-1 agonists Tacrolimus Oral anticoagulants Antineoplastics SSRIs Antipsychotics

tound
Efavirenz
Clopidogrel
Lamotrigine
Anti-TNFα
Voriconazole
Statins

NO	associ	ation	TOUDO
	400001		IUGIIG

Metformin	Bisoprolol
Quetiapine	Anti-VEGF
Irinotecan	

Concl	usion	and	ro	levance	
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- 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.



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