PHARMACOGENOMICS IN NEUROLOGY

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Abstract

Precision medicine is an emerging medical approach which aims to individualize therapies in patients with complex, multifactorial disease in order to increase drug effectiveness and prevent adverse drug reactions. Among high-throughput -'omic technologies (genomics, proteomics, metabolomics), pharmacogenomics investigates the application of genomics to personalize drug selection, according to the patient's genetic traits. Genetic variations influence the pharmacokinetic and pharmacodynamic profile of many therapies in different fields in neurology, such as immune-mediated disease, neurodegenerative disease and ischemic stroke. Until now, available clinically useful pharmacogenomic biomarker does not exist to distinguish between responders and non-responders regarding MS treatments. In patients with stroke who receive clopidogrel, CYP2C19 testing in clinical practice has not been established yet. In Parkinson's disease, MTHFR gene mutations may be correlated with higher incidence of hyperhomocysteinemia due to L-dopa treatment. Finally, apolipoprotein E (APOE) gene has been linked with Alzheimer's disease pathogenesis and is regarded as a reference gene in several pharmacogenetic studies. In the era of precision medicine, educating clinicians on pharmacogenomics may assist with the implementation of genetic information in the clinical practice, thus enhancing genetically-guided treatment decisions.

Key words: precision medicine; omic technologies; pharmacogenomics; genetic variations; CYP2C19 testing; apolipoprotein E

Introduction

Precision medicine is an emerging medical approach according to which the patients' genetic profile, lifestyle and environment are taken into consideration, in order to provide personalized treatment [1]. The potential of precision medicine is seemingly unlimited as scientists from multiple fields use high-throughput 'omic technologies to improve patient outcomes. -'Omic technologies (genomics, proteomics, metabolomics etc.) generate a large quantity of data, thus offering a molecular fingerprinting of a patient, aiming to assist with and/or guide clinical decisions [2]. One of the main developing applications of this novel approach is pharmacogenomics.

Response to a drug may be variable among patients, related both to pharmacokinetic (phases of absorption, distribution, metabolism) or pharmacodynamic (drug's mode of action) factors, and this variability may also depend on environmental and genetic factors [3]. Pharmacogenomics investigates the application of genomics into personalized drug selection, aiming to increase drug effectiveness and prevent adverse drug reactions [4]. In this respect, pharmacogenomic analysis may adjust drug selection according to the patient's genetic traits [5]. Pharmacogenomics have been developed within a short time over the last 50 years, upon progress in human genome sequencing, as it was first assumed that genetics might affect drug response phenotypes [6]. It became clear that deviation in drug response could be partly explained by the effects of genetic inheritance. Over the last twenty years, the Human Genome Project was brought to completion allowing for a robust evolution in pharmacogenomics, especially facilitated through the development of techniques such as Next Generation Sequencing (NGS) and genome-wide association studies (GWAS) [4]. Up to now, international scientific associations have developed and approved guidelines concerning several drug-gene interactions that are accessible at no cost as an on-line source (www.pharmgkb.org) [7].

Pharmacogenomics in Neurology

Substantial therapeutic progress has been achieved in various fields in neurology, such as neuroimmunological disease, neurodegenerative disease, ischemic stroke and epilepsy which can, however, be linked with potentially severe adverse events and high financial cost. Pharmacogenomics thus addresses an increasing need to individualize therapeutic choices and to maximize the benefits against risks [3].

Pharmacogenomics in Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS). It is classified in three types, the relapsing remitting form (RRMS) (80-85% of patients) which may evolve into secondary progressive form (SPMS) and the primary progressive MS (PPMS) (10-15% of patients) [8]. According to current evidence, 30-50% of patients are non-responders to first-line therapies and inter-individual genetic variability may, at least in part, contribute to this heterogeneity [9]. Until now, available clinically useful pharmacogenomic biomarker does not exist in order to timely distinguish between responders and non-responders regarding MS treatments [8].

Interferon-beta (IFNb) is a widely prescribed immunomodulatory treatment for MS. IFNb binds to specific receptors on the surface of the immune system cells inhibiting the synthesis of inflammatory cytokines and increase the production of anti-inflammatory ones [10]. Several gene studies investigated the association of genetic variants with response to IFNb, yielding inconclusive results [11-14]. A few recent whole-genome association studies (GWAS) investigated the association between IFNb treatment response and genetic variability with inconsistent findings, without verifying previously conducted candidate-gene studies [11, 12, 13, 14] reviewed in (8). Regarding the development of neutralizing antibodies (NAbs) against IFNb, their use as an early pharmacogenetic biomarker is limited and it seems to account for resistance towards IFNb treatment in a minority of patients [15].

Glatiramer acetate (GA) is the first non-interferon approved treatment for RRMS. It acts on innate and acquired immune system and it has been linked with a shift in the T-effector phenotype from pro-inflammatory (T-helper 1 and 17 cells) to anti-inflammatory (regulatory T cells and T-helper 2 cells) [8]. Human-leucocyte antigen (HLA) class I/II polymorphisms are positively associated with response to treatment with GA, more specifically, the HLA DRB1 * 1501 [16, 17]. Two single nucleotide polymorphisms (SNPs), rs71878 in the T-cell receptor beta (TCRB) gene and rs2275235 in the cathepsin S (CTSS) gene were significant associated with GA treatment in one study [18]. Moreover, one GWAS study on GA treatment response demonstrated significant associations between GA treatment response and the ensuing genes: ZAK (rs139890339), UVRAG (rs80191572), MBP (rs1789084) and HLA-DQB2 (rs28724893), [18, 19].

Mitoxantrone, a cytotoxic agent that inhibits DNA repair, acts on macrophages B cells and T cells, and suppresses their proliferation as well as pro-inflammatory cytokine production [20]. Two pharmacogenomics studies provided conflicting results [21, 22].

Natalizumab, a humanized monoclonal antibody, prevents the entry of lymphocytes into the CNS [20]. To our knowledge, one pharmacogenetic study that has been conducted reported that the wild-type genotype or heterozygous presence of a polymorphism for NQO1 or GSTP1 gene is possibly related to beneficial clinical outcomes upon treatment with natalizumab [23].

Siponimod, a particular sphingosine-1-phosphate (S1P) receptor (S1P1 and S1P5) inhibitor blocks the egress of lymphocytes from lymphoid system cells and thus it mitigates the entry of T-lymphocytes into the CNS. Siponimod has been studied in phase II and phase III trials in RRMS and SPMS, respectively. Siponimod's metabolism is susceptible to variability in cytochrome P450 (CYP) activity among individuals, involving mainly the CYP2C9 and CYP3A4 enzymes. Hence, genetic testing is required before treatment [24].

Several other disease-modifying treatments for MS, such as dimethyl fumarate, teriflunomide or fingolimod do not exhibit known variable pharmacogenomic associations to clinical outcome [8].

Pharmacogenomics and Stroke

Genetic variations influence the pharmacokinetic and pharmacodynamics profile of several therapies for primary and secondary stroke prevention [25].

Aspirin is considered to be the most commonly prescribed antiplatelet therapy for stroke prevention (primary and secondary). Aspirin irreversibly inhibits COX (cyclooxygenase)-1 and thromboxane A2 production. Aspirin resistance has been associated with several genetic variants, most well studied being the PlA1/A2 of the GPIIIa (glycoprotein IIIa) gene and the COX-I polymorphisms [26-28]. However, the results are inconsistent and more extensive randomized controlled trials (RCTs) are required in order to reach safe conclusions.

Clopidogrel is an antiplatelet agent able to diminish the risk of recurrent ischemic stroke. For its antiplatelet action, it requires conversion to an active metabolite by cytochrome P-450 (CYP) enzymes. The majority of genetic studies have focused on the hepatic CYP2C19 enzyme. A reduced-function mutation in at least one allele of this enzyme (CYP2C19 * 2 or CYP2C19 * 3) is related to 33% reduction of plasma concentration of the active metabolite compared to the wild type genotype [29] and an increased risk of vascular events [30]. In contrast, gain-of-function allele (CYP2C19 * 17) is related to higher levels of active metabolite of clopidogrel and equivalent risk of bleeding [31]. However, in a meta-analysis including 4 placebo-controlled RCTs, the loss-of-function mutation did not affect the risk of vascular events or bleeding [32]. Due to the uncer-

tainty in the advantages of treating patients in the context of their CYP2C19 carrier status and taking into consideration that other therapeutic agents, such as ticagrelor and prasugrel may be considered apart from clopidogrel, CYP2C19 testing in clinical practice has not been established [33]. Up to date, no RCTs have estimated the efficacy of CYP2C19 testing in patients with ischemic stroke. More large-scale, well-designed trials are needed [34].

Statins are of great importance for the prevention and treatment of atherosclerotic cardiovascular disease. They act through inhibition of HMG-CoA reductase. However, some patients do not respond favorably and a number of them present with side-effects, most commonly statin-associated muscle disorder [35]. Of the plethora of candidate gene studies and GWASs, the SLCO1B1 521C genetic variant is, at present, the only clinically applicable pharmacogenetic test concerning toxicity from statins. The SLCO1B1 gene expresses a transport protein found in liver cells and this polymorphism seems to associate with myopathy following the use of simvastatin [36]. Furthermore, taking into consideration that lovastatin, atorvastatin, and simvastatin are metabolized mainly by cytochrome P450 3A enzymes, the US Food and Drug Administration (FDA) warns medical doctors about the risk of simvastatin muscle toxicity linked with concurrent use of CYP3A-inhibiting agents, such as clarithromycin, fluoxetine and omeprazole. Nevertheless, studies investigating the possible relation between CYP3A polymorphisms and the risk of statin side effects present inconsistent results. Therefore, routine CYP3A testing is not recommended at present [36].

Regarding the use of *anticoagulants* in patients with atrial fibrillation, numerous studies have focused on the pharmacogenetics of vitamin K antagonists (VKAs), particularly warfarin.

Warfarin is mainly metabolized in liver by the microsomal enzyme CYP2C9 and inhibits vitamin K metabolism targeting the vitamin K epoxide reductase complex subunit 1 (VKORC1) enzyme [37]. Additionally, the CYP4F2 gene encodes a vitamin K oxidase [38]. VKORC1, CYP2C9 and CYP4F2 polymorphisms are the genetic variants that have been studied the most [34]. Carriers of rare mutations in the protein-coding region of the VKORC1 gene [VKORC1:c.76G > A (Ala26 → Thr), VKORC1:c.76G > A (Ala26 → Thr), VKORC1: c.84C > T (Val29 → Leu), VKORC1: c. 85G > T (Val29 → Leu), VKORC1: c.107A > G (Asp36 → Gly), VKORC1: c.155C > G (Ser52 → Trp), VKORC1: c.167C>T (Ser56 → Phe), VKORC1: c.176G > T (Trp59 → Leu), VKORC1: c.177G > T (Trp59 → Cys), VKORC1: c.196G>A(Val66 → Met), VKORC1: c.197T > G (Val66 → Gly), VKORC1: c.212G > C (Gly71 → Ala), VKORC1: c.230A > G (Asn77 → Ser), VKORC1: c.229A > T (Asn77 → Tyr), VKORC1: c.368T > A (Ile123 → Asn), VKORC1: c.415T > C(Tyr139 → His)], are associated with oral anticoagulant resistance and higher dosage requirement, exhibiting a greater risk of unfavorable ischemic events" [39, 40]. Instead, carriers of the more common rs9923231 (VKORC1) variant require a lower dose of oral anticoagulant (39). A loss-of-function CYP2C9 mutation has been linked with reduction in warfarin metabolism and puts carriers at increased risk for bleeding [41]. CYP4F2 variant carriers require an increased warfarin dose [38]. Based on the results of recent trials, it is still not certain whether the integration of pharmacogenetic testing in those receiving warfarin is clinically effective and improves patient management [34].

Regarding non-vitamin K antagonist oral anticoagulants (NOACs) so far, a single GWAS has been conducted to examine the influence of genetics on dabigatran pharmacokinetic. It was based on participants from the RE-LY trial (dabigatran versus warfarin) [42] and revealed three single nucleotide polymorphisms (SNPs) (2 in the CES1 gene and 1 in the ABCB1 gene) that are associated with the fluctuation in plasma levels of dabigatran [43]. To our knowledge, no GWASs have been conducted to examine the impact of genetic variability on treatment with other NOACs such as rivaroxaban, apixaban and edoxaban. Large-scale studies are lacking; therefore, recommendations cannot be made for NOACs yet [44].

Pharmacogenomics in neurodegenerative disorders

More than 50 different neurodegenerative disorders (NDDs) can affect humans worldwide. Alzheimer's disease (AD) and Parkinson's disease (PD) are among the most common and account for high cost for the society [45].

Parkinson's disease (PD) is on top of the neurodegenerative movement disorders and the second most common neurodegenerative disease nowadays [46, 47]. PD is pathologically characterized by the intracellular aggregation of α-synuclein and the loss of dopaminergic neurons [48]. The cornerstone of pharmacologic therapy is dopamine replacement with L-dopa in combination with dopamine receptor agonists, monoamine oxidase (MAO) inhibitors or catechol-O-methyltransferase (COMT) inhibitors [49]. There is a significant degree of difference in drug response which is linked to the subtypes of the disease and the patients' genetic variability. Unfortunately, despite the advances of pharmacogenomics, there are currently no guidelines in the daily medical practice of treating PD taking into account pharmacogenomics. Moreover, a search in the pharmacogenomics knowledge-base (pharmaGKB) retrieves only

ten clinical annotations most of which are associated with low level of evidence [50].

Levodopa (L-dopa), combined with dopa decarboxylase inhibitors, augments the availability of dopamine in the CNS. The COMT enzyme is involved in levodopa metabolism. Most studies have focused on the COMT gene polymorphisms but their results are conflicting, thus limiting their potential for clinical application [50]. SNPs of the genes involved in the mTOR pathway are linked with either increased or reduced chance of treatment-induced motor symptoms, nevertheless larger cohort studies are required [50].

Hyperhomocysteinemia and impulse control disorder (ICD) are well known complications of dopaminergic treatment with *L-dopa or dopamine receptor agonists (DA).* They are associated with genetic factors. MTHFR gene mutations may increase the incidence of hyperhomocysteinemia during L-dopa treatment and this effect may be attenuated by co-treatment with COMT inhibitors [51]. For younger patients who initiate therapy with *dopamine receptor agonists (DA)*, polymorphisms in Dopamine receptor 1 (DRD1), Opioid Receptor Kappa 1 (OPRK1), Opioid Receptor Mu 1 (OPRM1) and COMT genes were linked with a high risk of ICD [52]. An DRD3 mutation was also related to increased incidence of ICD during L-dopa therapy [53].

Regarding the pharmacogenomic properties of *COMT* and *MAO inhibitors* sufficient evidence for clinical recommendations is lacking [50].

In relation to the etiology of PD, genetics play a role both in the multifactorial sporadic form of the disease, as well as in the single-gene, rare inherited forms of PD [46]. Most studied single gene mutations implicate genes encoding α-Synuclein (SNCA), Leucine-rich repeat kinase 2 (LRRK2), parkin RBR E3 ubiquitin-protein ligase (PRKN), vacuolar protein sorting-associated protein 35 (VPS35), PTEN-induced putative kinase 1 (PINK1), glucocerebrosidase (GBA) and oncogene DJ-1 [54]. Published studies investigating levodopa treatment in patients with LRRK2, SNCA and GBA genes mutations resulted in inconsistent data [50]. PRKN, PINK1 and DJ1 gene mutations were linked with a steady L-dopa response at lower dose, but also with early treatment-induced motor symptoms (dyskinesias and dystonia) [50]. In this way, the clinical phenotype of early treatment-induced motor symptoms may draw suspicion of these mutations and guide genetic testing before expected.

Alzheimer's disease (AD) is considered to be the most common neurodegenerative disease and the dominant form of dementia (>50%) [55]. Genomic defects, epigenetic changes and multiple environmental factors precipitate pathogenic cascades leading to dementia.

Three acetylcholinesterase inhibitors (AChEIs), donepezil, galantamine and rivastigmine have been approved for the treatment of AD. Memantine, an N-Methyl-D-Aspartate (NMDA) receptor antagonist, was approved by the FDA in 2003 [56] and, recently, aducanumab was approved by the US FDA [57]. Most pharmacogenomics studies on AD focus on these drugs. Furthermore, apolipoprotein E (APOE) gene polymorphisms contribute to the pathogenesis of AD and it is regarded as the reference gene in the majority of pharmacogenetic studies [55].

Donepezil, the most frequently prescribed AChEI, is a major substrate of CYP2D6, CYP3A4, acetylcholinesterase (ACHE) and UGTs (glucuronosyltransferase family polypepetides). Carriers of the APOE-4 seem to be poor responders to donepezil, whereas APOE-3 carriers seem to respond most optimally. Moreover, CYP2D6 normal metabolizers are optimal responders to donepezil, whereas CYP2D6-poor metabolizers are also poor responders to donepezil [55]. Carriers of the coomon CYP2D6 rs1080985 variant are poor donepezil responders [58]. Donepezil is not recommended for APOE-ε4/Butyrylcholinesterase K (BCHE-K *) carriers who present with an earlier disease onset and a hastened cognitive decline [59].

Rivastigmine is an inhibitor of both acetylcholinesterase (ACHE) and butyrylcholinesterase (BCHE) [60]. APOE, amyloid beta precursor protein (APP), choline acetyltransferase (CHAT), ACHE, BCHE, cholinergic receptor nicotinic alpha 4 (neuronal) (CHRNA4), cholinergic receptor, nicotinic, beta 2 (neuronal) (CHRNB2), and microtubule associated protein tau (MAPT) variants affect rivastigmine both pharmacokinetically and pharmacodynamically. Moreover, patients carrying the BChE K-variant (rs1803274) show poor clinical response to rivastigmine [55].

Memantine is an NMDA receptor antagonist. APOE, presenilin 1 (PSEN1), and MAPT variants may have an effect on the role of memantine in AD. The co-administration of CYP2B6 substrates may decrease the metabolism of the memantine by 65% [55].

Aducanumab is a monoclonal antibody targeting the N-terminus of the amyloid beta peptide (Aß). It is administered at monthly intravenous infusions [57]. According to recommendations of an Expert Panel, aducanumab is indicated for patients diagnosed with early AD. Administration of aducanumab has been associated with an increased rate of amyloid-related imaging abnormalities (ARIA) either with brain effusion or hemorrhage. These 2 types of ARIA present more common in APOE ε 4 (APOE-4) polymorphism carriers and may be more severe in APOE-4 homozygotes [61]. However, the prescription does not strictly require APOE genotyping. Moreover, aducanumab dosing scheme and monitoring instructions do not differ between APOE ε 4 carriers and non-carriers [57]. However, an informative discussion with the patient and the care partner is recommended and APOE genotyping may be sought prior to aducanumab

initiation. In case of the presence of APOE4 polymorphism, the clinician should discuss the increased likelihood for ARIA [57].

Pharmacogenomics in epilepsy

There is significant variation in the response to antiepileptic treatment in terms of seizure control and adverse reactions in people suffering from epilepsy [62]. Genetic factors contribute a lot to this variation [63].

The advances in the field of the genetics of the epilepsies provide the base for a new era in the treatment of epilepsy according to precision medicine [64].

However, guidelines on clinical management of individual epileptic patients are lacking.

Genetic factors and response to AEDs

Most antiepileptic drugs (AEDs) are metabolised by the cytochrome P450 (CYP) family. Allelic variants of some of these enzymes encode isoforms which differ in activity leading to altered serum AED concentrations.

An example to this variability are polymorphisms in CYP2C9 and CYP2C19 genes [65]. The phenytoin metabolism at a rate of 90% is mediated by CYP2C9. Carriers of CYP2C9 alleles, which encode enzymes with lessened activity metabolize *phenytoin* more slowly and carry an increased risk of concentration-dependent neurotoxicity. CYP2C9 * 3 (rs1057910(C)) and CYP2C9 * 2 (rs1799853) polymorphisms are the best recorded [66, 67].

A GWAS of cases with cutaneous adverse reactions being on *phenytoin* found out that CYP2C9 * 3 (rs1057910) polymorphism is significantly associated with these adverse events [68]. Nevertheless, testing for CYP2C9 genetic variants is not routine practice.

Studies in Asian populations found that CYP2C19 polymorphisms are associated with the serum concentration of the active metabolite of *clobazam*, N-clobazam, with clinical effectiveness [64].

Regarding *valproate* (VPA), only 15-20% of its dose is metabolized by CYP enzymes. The main enzyme is CYP2C9 and to a lesser extent CYP2A6 and CYP2B6 [69].

Population study in Japan found that CYP2C19 genotypes are responsible for some of the adverse reactions after treatment of epileptic patients with *zonisamide* [70].

CYP3A4 is considered as the main enzyme responsible for the carbamazepine metabolism. Although CYP3A4 has very known polymorphisms these are not frequent enough to although to cause significant inter-individual variability in vivo [71].

A study in Han people with epilepsy discovered that sodium voltage-gated channel alpha subunit 1 (SCN1A), ATP Binding Cassette Subfamily C Member 2 (ABCC2) and UDP Glucuronosyltransferase Family 2 Member B7 (UGT2B7) genetic polymorphisms are related with *oxcarbazepine* maintenance doses [72].

Human leukocyte antigen (HLA) alleles and AEDs side effects

Genetic polymorphisms, especially in certain human leukocyte antigen (HLA) alleles, have also been linked with the risk of idiosyncratic adverse reactions to AEDs.

HLA-B * 15:02 allele has been reported to be strongly associated with the Stevens-Johnson syndrome in Han Chinese people on treatment with *carbamazepine* [73].

Guidelines recommend that patients of South Asian origin be tested for HLA-B * 15:02 allele carriage before treatment with carbamazepine and carriers of this allele optimally avoid carbamazepine [74, 75].

Association has also been found between HLA-B * 15:02 allele and the risk of Stevens-Johnson syndrome in patients treated with *phenytoin* [76], *oxcarbazepine* [77] and *lamotrigine* [76].

HLA-A * 31:01 is another allele that has been linked with elevated risk of cutaneous adverse reactions, such as maculopapular exanthema or blistering, in European and Japanese patients treated with *carbamazepine* [78, 79]. However, its testing in routine practice has recently been regarded as cost-effective.

A summary of all the findings is presented in Table 1.

Conclusions

With the progress in precision medicine, Neurology has entered a new era in relation to several therapeutic approaches. Among '-omic technologies, pharmacogenomics plays an important role as it may enable drug selection considering the patient's genetic profile.

As healthcare shifts from a traditional pathway toward precision medicine, standardized pharmacogenomic education for clinicians becomes necessary. Recently, therapeutic agents have been developed in the context of pharmacogenomic biomarkers related to their safety and efficacy. In the era of precision medicine, educating clinicians on pharmacogenomics may assist with the implementation of genetic information in the clinical practice, thus enhancing genetically-guided treatment decisions.

Abbreviation List

ACHE:	Acetylcholinesterase
AD:	Alzheimer's disease
APOE:	Apolipoprotein E
APP:	Amyloid Beta Precursor Protein
ARIA:	amyloid-related imaging abnormality
BCHE:	butyrylcholinesterase
CHAT:	choline acetyltransferase

Table 1. Clinical effects associated with specific gene and genetic variants according to neurological disease and medication

Disease	Treatment	Polymorphism / Genes	Clinical effects	References
MS	*IFNβ*		candidate gene studies: inconclusive results; GWAS: inconsistent findings; NAbs against IFNb: resistance towards IFNb treatment	[11-15, 80-84]
	GA	HLA DRB1 * 1501	positively associated with GA treatment response	[16, 17]
		rs71878 in TCRB gene	significantly associated with GA treatment	[18]
		rs2275235 in CTSS gene	significantly associated with GA treatment	[18]
		UVRAG (rs80191572)	significantly associated with GA treatment	[18, 19]
		HLA-DQB2 (rs28724893)	significantly associated with GA treatment	[18, 19]
		MBP (rs1789084)	significantly associated with GA treatment	[18, 19]
		ZAK (rs139890339)	significantly associated with GA treatment	[18, 19]
	Mitoxantrone		conflicting results	[21, 22]
	Natalizumab	wild-type genotype or heterozygous presence of one polymorphism for NQO1 or GSTP1	possibly related to beneficial clinical outcomes upon treatment with natalizumab	[23]
	Siponimod	CYP2C9; CYP3A4	affect Siponimod's metabolism	[24]
Stroke	*Aspirin*	PlA1/A2 of the GPIIIa gene	associated with aspirin resistance; inconsistent results; more large-scale RCTs required	[26-28]
		COX-I polymorphisms	associated with aspirin resistance; inconsistent results; more large-scale RCTs required	[26-28]
	Clopidogrel	reduced-function mutation in CYP2C19 * 2 or CYP2C19 * 3	33% reduction of plasma exposure to the active metabolite compared to the wild type genotype and increased risk of vascular events (?); more large-scale trials needed	[29, 30, 32, 34]
		gain-of-function allele CYP2C19 * 17	increased levels of clopidogrel active metabolite and increased risk of bleeding; more large-scale trials needed	[31, 34]
	Statins	SLCO1B1 521C genetic variant	associated with myopathy following the use of simvastatin; the only clinically relevant pharmacogenetic test concerning statin toxicity	[36]
		CYP3A polymorphisms	studies on its possible effects on the risk of statin side effects: inconsistent results	[85]
	VKAs and Warfarin	VKORC1 mutation	resistance and increased risk of unfavorable ischemic events	[39, 40]
		loss-of-function CYP2C9 mutation	reduction in warfarin metabolism and increased risk of bleeding	[41]
		CYP4F2 variant	increased warfarin dose required	[38]
	NOACs	3 SNPs (2 in CES1 gene and 1 in ABCB1 gene)	associated with the variability in plasma levels of dabigatran; large-scale studies needed	[43]
PD	*L-dopa*	COMT polymorphisms	conflicting results	[86-95]
		SNPs of mTOR pathway-related genes	either increased or reduced risk for treatment-induced dyskinesias; larger cohort studies required	[96-108]
		MTHFR mutations	may increase the incidence of hyperhomocysteinemia	[51]
		DRD3 mutation	increased incidence of ICD	[53]
		LRRK2 gene mutations	inconsistent data	[109-112]

Table 1. Continuity

Disease	Treatment	Polymorphism / Genes	Clinical effects	References
PD		GBA gene mutations	inconsistent data	[113-116]
		SNCA mutations	inconsistent data	[117]
		PRKN mutations	steady L-dopa response at lower dose; early treatment-induced motor symptoms (dyskinesias and dystonia)	[118-120]
		PINK1 mutations	steady L-dopa response at lower dose; early treatment-induced motor symptoms (dyskinesias and dystonia)	[118]
		DJ1 mutations	steady L-dopa response at lower dose; early treatment-induced motor symptoms (dyskinesias and dystonia)	[121-123]
	DA	DRD1	high prediction rate of ICD	[52]
		OPRK1	high prediction rate of ICD	[52]
		OPRM1	high prediction rate of ICD	[52]
		polymorphisms in COMT genes	high prediction rate of ICD	[52]
	COMT inhibitors		insufficient evidence for clinical recommendations	[124-128]
	MAO inhibitors		insufficient evidence for clinical recommendations	[129]
AD	*Donepezil*	APOE-4	poor responders	[55]
		APOE-3	optimal responders	[55]
		CYP2D6 (rs1080985)	poor responders	[58]
		APOE-ε4/BCHE-K *	donepezil not recommended	[59]
	Rivastigmine	BChE K (rs1803274)	poor clinical response	[55]
		APOE	affect pharmacokinetics and pharmacodynamics of rivastigmine	[55]
		APP	affect pharmacokinetics and pharmacodynamics of rivastigmine	[55]
		CHAT	affect pharmacokinetics and pharmacodynamics of rivastigmine	[55]
		ACHE	affect pharmacokinetics and pharmacodynamics of rivastigmine	[55]
		BCHE	affect pharmacokinetics and pharmacodynamics of rivastigmine	[55]
		CHRNA4	affect pharmacokinetics and pharmacodynamics of rivastigmine	[55]
		CHRNB2	affect pharmacokinetics and pharmacodynamics of rivastigmine	[55]
		MAPT	affect pharmacokinetics and pharmacodynamics of rivastigmine	[55]
	Memantine	APOE	may influence the effect of memantine in AD	[55]
		PSEN1	may influence the effect of memantine in AD	[55]
		MAPT	may influence the effect of memantine in AD	[61]
	Aducanumab	APOE-4	increased rate of ARIA; more severe in homozygotes	[61]
Epilepsy	*Phenytoin*	CYP2C9 * 2 (rs1799853)	slower metabolism of phenytoin, concentration-dependent neurotoxicity	[66, 67]
		CYP2C9 * 3 (rs1057910(C))	slower metabolism of phenytoin, concentration-dependent neurotoxicity	[66, 67]
		CYP2C9 * 3 (rs1057910)	cutaneous adverse reactions	[68]
		HLA-B * 15:02 allele	risk of Stevens-Johnson syndrome	[76]

Table 1. Continuity

Disease	Treatment	Polymorphism / Genes	Clinical effects	References
Epilepsy	*Clobazam*	CYP2C19	Asian populations, associated with the serum concentration and clinical effectiveness	[64]
	Valproate	CYP2C9	metabolism of valproate	[69]
		CYP2A6	metabolism of valproate	[69]
		CYP2B6	metabolism of valproate	[69]
	Zonisamide	CYP2C19	adverse reactions	[70]
	Carbamazepine	CYP3A4	infreqent polymorphisms, insignificant inter-individual variability *in vivo*	[71]
		HLA-B * 15:02 allele	Stevens-Johnson syndrome in Han Chinese people	[73]
		HLA-A * 31:01 allele	increased risk of cutaneous adverse reactions in European and Japanese patients	[78, 79]
	Oxcarbazepine	SCN1A	related with oxcarbazepine maintenance doses	[72]
		ABCC2	related with oxcarbazepine maintenance doses	[72]
		UGT2B7	related with oxcarbazepine maintenance doses	[72]
		HLA-B * 15:02 allele	risk of Stevens-Johnson syndrome	[77]
	Lamotrigine	HLA-B * 15:02 allele	risk of Stevens-Johnson syndrome	[76]

MS: Multiple Sclerosis; **IFNβ**: interferon-β; **GWAS**: Genome-Wide Association Study; **Nabs**: neutralizing antibodies; **GA**: glatiramer acetate; **HLA**: Human Leukocyte Antigens; **MBP**: myelin basic protein; **ZAK**: zipper containing kinase AZK; **CYP**: cytochrome; **RCTs**: randomization - controlled studies; **COX**: cyclooxygenase; **VKAs**: vitamin K antagonists; **NOACs**: novel oral anticoagulants; **SNPs**: single-nucleotide polymorphism; **mTOR**: mammalian target of rapamycin; **MTHFR:** methylenetetrahydrofolate reductase; **DRD:** Dopamine Receptor D; **ICD**: idiopathic cervical dystonia; **LRRK**: Leucine-rich repeat kinase; **GBA**: Glucosylceramidase Beta; **SNCA**: Synuclein Alpha; **PRKN**: Parkin RBR E3 Ubiquitin Protein Ligase; **PINK**: PTEN Induced Kinase; **DJ1**: Protein DJ-1; **DA:** dopamine agonist; **OPRK**: Opioid Receptor Kappa; **OPRM**: Opioid Receptor Mu; **COMT**: catechol-O-methyltransferase; **MAO**: monoamine oxidase; **AD:** Alzheimer's disease; **BCHE**: butyrylcholinesterase; **APOE**: Apolipoprotein E; **APP**: Amyloid Beta Precursor Protein; **CHAT:** choline acetyltransferase; **ACHE**: Acetylcholinesterase; **CHRNA4**: Cholinergic Receptor Nicotinic Alpha 4 Subunit; **CHRNB2**: Cholinergic Receptor Nicotinic Beta 2 Subunit; **MAPT**: Microtubule Associated Protein Tau; **PSEN**: Presenilin; **ARIA**: amyloid-related imaging abnormality

CHRNA4: Cholinergic Receptor Nicotinic Alpha 4 Subunit
CHRNB2: Cholinergic Receptor Nicotinic Beta 2 Subunit
COMT: catechol-O-methyltransferase
COX: cyclooxygenase
CYP: cytochrome
DA: dopamine agonist
DJ1: Protein DJ-1
DRD: Dopamine Receptor D
GA: glatiramer acetate
GBA: Glucosylceramidase Beta
GWAS: Genome-Wide Association Study
HLA: Human Leukocyte Antigens
ICD: idiopathic cervical dystonia
IFNβ: interferon-β
LRRK: Leucine-rich repeat kinase
MAO: monoamine oxidase
MAPT: Microtubule Associated Protein Tau
MBP: myelin basic protein
MS: Multiple Sclerosis
MTHFR: methylenetetrahydrofolate reductase
mTOR: mammalian target of rapamycin
Nabs: neutralizing antibodies
NOACs: novel oral anticoagulants
OPRK: Opioid Receptor Kappa
OPRM: Opioid Receptor Mu
PINK: PTEN Induced Kinase
PRKN: Parkin RBR E3 Ubiquitin Protein Ligase
PSEN: Presenilin
RCTs: randomization - controlled studies
SNCA: Synuclein Alpha
SNPs: single-nucleotide polymorphism
VKAs: vitamin K antagonists
ZAK: zipper containing kinase AZK

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