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Titre en Français : Implications cliniques en neuropharmacogénétique

Titre en anglais : Clinical implications of Neuropharmacogenetics

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Résumé

Introduction : La pharmacogénétique vise à identifier des facteurs génétiques participant à la variabilité de la réponse au traitement avec pour objectif ultime d'aboutir à une médecine personnalisée. Les facteurs génétiques peuvent modifier le métabolisme ou la cible d'une drogue sur le plan individuel, avec la particularité en Neurologie d'une relation non linéaire entre les concentrations périphériques du médicament et ses effets centraux.

Méthodes : une recherche de la littérature a été effectuée pour passer en revue les études de pharmacogénétique réalisées dans les maladies neurologiques.

Résultats : De nombreux gènes ont identifiés, associés à la réponse au traitement neurologie. Cependant, la plupart d'entre ont un effet prédictif faible au niveau individuel, suggérant des interactions multiples entre les facteurs génétiques et d'autres facteurs liés à la maladie et aux interactions médicamenteuses.

Conclusion/discussion : L'effort de recherche en pharmacogénétique dans les maladies neurologiques doit être poursuivi pour répliquer les résultats dans des populations indépendantes ou, idéalement, dans des épreuves cliniques de pharmacogénétique afin de démontrer leur pertinence pour la pratique clinique.

Mots clés : Génétique, pharmacogénétique, neurologie

Abstract

Introduction: Pharmacogenetics aims to identify the underlying genetic factors participating in the variability of drug response. Indeed, genetic variability at the DNA or RNA levels can directly or indirectly modify the pharmacokinetic or the pharmacodynamic parameters of a drug. The ultimate aim of pharmacogenetics is to move towards a personalised medicine by predicting responders and non-responders, adjusting the dose of the treatment, and identifying individuals at risk of adverse drug effects.

Methods: a literature research was performed in which we reviewed all pharmacogenetic studies in neurological disorders including neurodegenerative diseases, multiple sclerosis, stroke and epilepsy.

Results: Several pharmacogenetic studies have been performed in neurology, bringing insights into the inter-individual drug response variability and in the pathophysiology of neurological diseases. The principal implications of these studies for the management of patients in clinical practice are discussed.

Conclusion/discussion: Although several genetic factors have been identified in the modification of drug response in neurological disorders, most of them have a marginal predictive effect at the single gene level, suggesting mutagenic interactions as well as other factors related to drug interaction and disease subtypes. Most pharmacogenetic studies deserve further replication in independent populations and, ideally, in pharmacogenetic clinical trials to demonstrate their relevance in clinical practice.

Keywords: Pharmacogenetic, neurology, genetic

Introduction

The response to a drug, i.e. its efficacy or toxicity, is highly variable between individuals. This variability is related to the pharmacokinetics (absorption, distribution, metabolism and elimination) and/or the pharmacodynamics (target-level action) of the drug. These parameters may be influenced by environmental factors, such as drug interactions, or by factors related to the individual pathological or physiological conditions, including genetic variability. Pharmacogenetics aims to identify the genetic factors participating in the heterogeneity of drug response. Indeed, genetic variations at the DNA (polymorphisms, mutations, epigenetics) or at the RNA (differences in gene expression, micro-RNA) levels can directly or indirectly modify the expression or the activity of proteins involved in the mechanism of action of a drug or its metabolism. Genetic factors may also modify the disease itself, segregating patients into sub-populations with different responses to the same drug.

Pharmacogenetics is an interesting tool to better understand the pharmacology of a drug, i.e. its mechanism of action and its metabolism. Consequently, a better understanding of the interindividual variability in drug response may also bring new insights into the pathophysiology of the disease. Finally, the ultimate objective of Pharmacogenetics is to personalise the treatment to the individual by identifying responders and non-responders, adjusting the dose of the treatment, and identifying individual at risk of developing drug adverse effects. This ambitious goal is currently far from being achieved, at least in Neurology, for several reasons. Genetic effects on drug response are likely to be complex, related to multiple genes for a single drug, each variant explaining a small proportion of the variance. In addition, the relationship between plasma and brain concentrations of drugs is not linear and potentially involves proteins related to blood-brain barrier permeability in which genetics could play an important role. Finally, the identification of factors associated with the response of a drug needs reliable markers of this response which often are lacking in neurological diseases. However, the increasing number of drugs for neurological diseases combined with recent advances in molecular genetics and neuroscience have led to a growing interest in Pharmacogenetics in the field of Neurology.

Neurodegenerative diseases

Pharmacogenetic data available for neurodegenerative diseases are mostly related to Alzheimer's disease (AD) and Parkinson's disease (PD), both of which will be expanded and developed in this review. In addition, one study on Riluzol, the only FDA approved drug for the treatment of amyotrophic lateral sclerosis (ALS), failed to find any association between the Riluzol metabolic profile and polymorphisms of CYP1A1 and CYP1A2 involved in its metabolism [1].

Alzheimer's disease

Treatment for AD is currently limited to the use of cholinesterase inhibitors. The response to anticholinergic drugs is highly variable with a good response rate of only 10-20% whereas side-effects, intolerance, and non-compliance occur in more than 60% of the patients [2]. Historical studies with tacrine suggested an association between its clinical efficacy with the APOE gene [3], and its hepatotoxicity with genes coding for drug metabolism enzymes [4; 5]. Following these first observations, several pharmacogenetic analyses have been performed in randomised controlled, open-label trials as well in routine clinical cohorts. Candidate genes explored were those encoding proteins related to Alzheimer's disease pathogenesis (e.g. ApoE), cholinesterase enzymes or drug metabolism [6]. The APOE gene is the principal genetic risk factor associated with AD, with the APOE-4 allele being a risk factor, and the APOE-2 allele being protective. A large number of pharmacogenetic studies or analyses have been performed looking at the different responses of the three currently used cholinesterase inhibitors donepezil, rivastigmine, and galantamine. Controlled randomised clinical trials found no association between APOE genotypes and the clinical response to donepezil [7], galantamine [8; 9], or rivastigmine [10]. Most subsequent open-label label studies or cohorts of patients have confirmed these results [11-21], although some of them reported a better response to cholinesterase inhibitors for APOE-4 allele carriers [22; 23], but also the reverse result [24; 25]. This discrepancy is probably due to different effects of the drugs depending on treatment duration and/or of the stage of the disease [10; 22]. Overall, if the APOE gene is clearly associated with AD susceptibility and disease progression, it probably only marginally affects the response to anticholinesterase inhibitors. Interestingly, because of this disease modifying effect of the APOE gene, recent clinical trials in AD using immunotherapy have been classified according to APOE genotype [26]. Finally, recent studies have found that therapy with brain-penetrating ACEIs may slow cognitive decline in patients with AD and this effect may depend on both APOE and ACE genotypes [27; 28].

More robust results have been obtained by looking at the enzymes implicated in drug metabolism. Particularly, CYP2D6 genotype has been consistently associated with the response to donepezil which is metabolised by this cytochrome [12; 17; 21; 29-31]. Most of these studies show evidence of better responses in poor metabolisers although one study found a trend in the opposite direction [29] and no association was found in another study [15].

One study found a significant association between clinical response to different cholinesterase inhibitors and a variant in the promoter of the acetylcholinesterase (*ACHE*) gene [32]. In a retrospective analysis of a randomised double-blind trial, patients with the wild-type butyrylcholinesterase (*BCHE*) genotype

showed significantly better responses to rivastigmine than to donepezil, while *BCHE* variant carriers experienced similar long-term treatment effects with both agents [13]. This result probably reflects the ability of rivastigmine to inhibit both enzymes (BCHE and AChE) as compared to donepezil which is a relatively specific AChE inhibitor.

A recent genome-wide association study performed in a cohort of 176 AD patients with extreme phenotype of response to cholinesterase inhibitors reported two polymorphisms associated with drug response and replicated in 198 additional AD-treated patients [33]. One variant mapped to the intron region of *PKRCE*, coding a protein kinase involved in several cellular functions, and the other variant has been suggested to act as a cis-regulator of *NBEA*, an A kinase-anchoring protein playing a role in the maturation of the nervous system.

Overall, the results from pharmacogenetic studies in AD suggest a role of genetic variants affecting drug metabolism or drug target enzymes in the response to cholinesterase inhibitors. However, further studies are needed to demonstrate the benefit of genetic testing for patient management in clinical practice. The *APOE* gene seems to play an important role in disease susceptibility and disease progression rather than a specific effect on the response to these drug in AD.

Parkinson's disease

The treatment of Parkinson's disease (PD) is essentially based on dopamine replacement therapy with levodopa, dopamine agonists, and/or dopamine metabolism inhibitors. Considering the high inter-individual variability observed in terms of motor response, development of complications or adverse events, several studies have investigated the genetic factors related to drug response in PD. Dopamine is synthesised from levodopa by the Aromatic L-Amino acid Dopa Decarboxylase (AADC) and subsequently metabolised by two major pathways, via C-O-methyltransferase (COMT) and via monoamine oxidase B (MAOB). Dopamine and dopamine agonists act through the dopamine receptor sub-types (DRD1, DRD2, DRD3, DRD4, DRD4). The *COMT* gene has a functional and frequent (minor allele frequency, minor allele frequency = 0.5) Val158Met polymorphism which confers to the protein a high (Val allele, or *COMT^H*) or a low (Met allele, or *COMT^L*) enzymatic activity. This gene has been extensively studied in PD with conflicting results. The *COMT^L* allele has been associated with PD risk in a Chinese population but not in a Caucasian population [34]. The *COMT* Val158Met polymorphism was not associated with differences of pharmacokinetic or the motor response to levodopa during an acute drug challenge [35; 36]. However, daily doses of levodopa were found higher in high metabolisers in some studies suggesting a lower response to the drug [37; 38]. Some genetic association studies have suggested that *COMT^L* carriers are more at risk in developing motor complications, including dyskinesia [39; 40], but others [38; 41; 42]

have failed to confirm this result. The COMT Val158Met polymorphism was linked with the motor response to entacapone, a COMT inhibitor, during an acute challenge [36] but appeared to have no significant effect when it or another COMT inhibitor tolcapone were administered repeatedly [43; 44]. This COMT polymorphism was also associated with the motor response to pyridoxine [45] and methylphenidate [46] when co-administered with levodopa. An association has been found between the motor response to levodopa and AADC [47] and one study showed a correlation between one polymorphism of the Organic Cation Transporter 1 gene (OCT1) and doses of anti-parkinsonian drugs [48] but these studies require replication. The DAT gene does not appear to modify the motor response to levodopa during an acute challenge [49] but two studies have suggested an association with a shorter delay of dyskinesia onset [50; 51]. The monoamine oxidase genes (*MAOB* and *MAOA*) were not associated with the motor response to levodopa or the risk of dyskinesia in PD [37; 38; 42].

Although dopamine and dopamine agonists are presumed to act through dopamine receptors, no association has been found between *DRD2* and *DRD3* and the motor response or the daily doses of dopaminergic drugs [52; 53]. Only one study found an association between the motor response to pramipexole, a dopamine agonist, during an acute challenge in a PD and the *DRD3* Ser9Gly polymorphism, but not with the *DRD2* gene, in a population of Chinese origin [54]. By contrast, discontinuation of non-ergoline dopamine agonists was suggested to be associated with *DRD2* and *DRD3* genetic determinants [55]. Several studies found an association between dyskinesia and the *DRD2* gene [56-59] or motor fluctuations [60] although this has not been replicated by others [50; 51; 61]. This discrepancy may be due to the different polymorphisms tested or to differences in the clinical definition of dyskinesia. Interestingly, one study found a specific association between the *DRD3* Ser9Gly polymorphism and dystonic dyskinesia but a lack of association with peak-dose dyskinesia [61]. Levodopa-induced dyskinesias are supposed to be due to the over-stimulation of the dopaminergic pathway but also to other neurotransmitter systems triggering the basal ganglia circuit towards an aberrant neuronal plasticity. Based on this hypothesis, genes from other pathways were tested for their association to dyskinesia in PD and found significant for the opioid receptor [58] and the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism [62]. However, the latter result was not replicated in two studies [38; 51] and no significant association were found with the glutamate receptor GRIN2B or the serotonin receptor [61].

Most of the non-motor features in PD can be related to the disease itself or to adverse effects of dopaminergic drugs. They are thus potentially subjected to disease or pharmacogenetic modifiers. Hallucinations were not found to be associated with *DRD1*, *DRD2*, *DRD3*, *DRD4* [50; 63-65], but

consistent findings suggest an association with cholecystokinin (CCK) and its receptor (CCKAR) [66; 67] and controversies remain for an effect of polymorphisms of the DAT [50; 65]. No association was found between hallucinations and polymorphisms of the ApoE [63], the serotonin transporter (5HTT), or its receptor 2A (5HT2AR) although the latter was associated with delusions [68; 69]. An interaction effect was found between the executive functions of patients, levodopa-therapy and the COMT genotype in agreement with the major role played by COMT in the prefrontal cortex in dopamine availability [70; 71]. Sleepiness or sleep attacks were found associated with DRD4, and COMT genes but not with the DRD2 or the 5-HTT genes [53; 72]. More recently, impulse control disorders association studies has been performed in PD showing significant associations with DRD3, GRIN2B [73], and a dose-dependent association with the 5HT2AR [74]. No association was found for COMT, DAT, DRD2 or 5-HTT [73; 75]. However, these studies remain to be replicated to draw definitive conclusions [76].

In conclusion, despite the intensive efforts made in the field of pharmacogenetics in PD, the majority of the reported associations have not been replicated resulting in a lack of consistent and useful results. This discrepancy probably reflects the heterogeneity of the disease, inadequate design or sample size of the studies, or insufficient genome coverage. Better studies will be needed in the future to allow the development of a genetic-based personalisation of drug therapy in PD.

Other movement disorders

Tardive dyskinesia occurs in about 25% of patients treated with antipsychotics, particularly with the first-generation of antipsychotics, suggesting the primary involvement of dopamine receptor blockade in their physiopathology. Familial occurrence suggests a genetic influence on tardive dyskinesia [77]. Several genetic association studies and meta-analyses have been performed to identify genetic factors of this adverse event. Meta-analyses have shown that the most consistent findings are related to the association with the DRD3 Ser9Gly polymorphism, the Ser allele being protective [78]. Some meta-analyses also found significant association with the *DRD2* gene although there were more negative studies than positive ones [79; 80]. Association with genes from the serotonergic system were also reported and one meta-analysis showed an association with the 5HT2AR [81]. Others from the dopaminergic (COMT, DRD4), serotonergic (HTR2C) or other neurological or non-neurological systems have occasionally been found to be associated with tardive dyskinesia [82]. A genome wide association study has been performed exploring genetic susceptibility to tardive dyskinesia and found no SNP reaching statistical significance [83]. However, the trend found with the GLI family zinc finger 2 (GLI2), encoding a transcription factor that participates in dopaminergic neuron development, was replicated in an independent sample.

Tetrabenazine is effective in the treatment of hyperkinetic movement disorders. Tetrabenazine is metabolised by CYP2D6 into its active metabolites. One pharmacogenetic study has suggested that CYP2D6 genotypes are associated with different patterns of response to tetrabenazine with a longer titration phase and higher daily doses for ultrarapid metabolisers than other patients [84]. Adverse effects of tetrabenazine were not affected by the different genotypes.

Domperidone is a dopamine receptor D2 antagonist that is used in gastroparesis. Because the blood-brain barrier is virtually impermeable to this drug, it has been used in PD to counteract the nausea induced by dopaminergic drugs. Although age was the most important factor predicting domperidone effects, the response to the drug in this small cohort of 48 subjects was considered significantly associated with the potassium channel gene *KCNH2* and its dose was associated with the drug transporter gene *ABCB1* genes [85]. No association was observed with the *DRD2* gene, and no significant association was found with the adverse effects of domperidone. Although needed to be taken with caution because of the small sample size, these results suggest that pharmacogenetics may be of help in determining which patients might respond to domperidone and avoid treatment in those who might develop side-effects.

Multiple sclerosis

Over the last 20 years, the number of clinically tested drugs available to treat patients with multiple sclerosis (MS) has increased considerably. Most of the drugs approved by the FDA and/or the EMEA for the remitting-relapsing form of MS are immune modulators (interferon beta (IFN- β), glatiramer acetate, natalizumab, laquinimod, fingolimod, teriflunomide, alemtuzumab, dimethyl fumarate, mitoxantrone). However, response to treatment is highly variable in MS, a good response being obtained for 40-60% for each individual drug, and serious adverse events can occur, particularly with the more recent drugs. So far, the most extensive research in pharmacogenetics has been performed for interferon and glatiramer acetate therapies which look for biomarkers in the move towards a personalised management of patients.

Interferon-beta

IFN- β was the first treatment approved in remitting-relapsing MS. Although IFN- β was consistently demonstrated in clinical trials to decrease the relapse rate of MS patients, up to 60% of patients will continue to experience clinical or brain imaging signs of disease activity. This failure has been supposed to be partly related to the development of IFN- β neutralising antibodies since early clinical trials. However these antibodies develop within months of treatment initiation – thus are not an early

predictor of response - and explains probably only a small proportion of non-responders. Interestingly, the development of these antibodies has been suggested to be HLA-class II mediated [86; 87], the major genetic risk factor for MS.

Intensive research has been done in MS to identify genetic predictors of IFN- β response. A traditional candidate gene approach has first been used in several studies, investigating genes related to the disease or to the supposed biological mechanism of action of IFN- β (for a review, [88]). Altogether these studies had limited success, leading to contradictory or inconclusive results, and failed to identify reliable determinants of IFN- β response in MS. Of note, studies investigating human leukocyte antigen (HLA) class II, the major genetic susceptibility factor for MS, were negative. The two genome-wide association studies performed so far both confirm that the response to IFN- β is most likely a multi-gene response in MS [89; 90]. Both studies used pooled patient samples for the discovery stage with a certain cost advantage but with other limitations related to the lack of individual data. Nevertheless, the two studies found significant association with drug response implicating genes related to central nervous system activity, such as glutamate- or GABA-related genes, rather than genes involved in the immunological pathways by contrast to that found in genetic association studies for MS susceptibility [91] and to what might be expected for the mechanism of action of IFN- β . Two polymorphisms have been replicated in subsequent independent studies, one in the glypican 5 gene (*GPC5*) a heparin sulphate proteoglycan that have important functions in the extracellular matrix [92], and another SNP located in the interferon regulatory factor 5 gene (*IRF5*) [93; 94]. However, none of these associations were confirmed in a recent study [95]. Altogether, these results suggest that the response to IFN- β in MS is related to polygenic factors, and reflect MS pathophysiology involving a complex interaction between the CNS, the extracellular matrix and the immunological system. Finally, several studies using microarray experiments have also looked for gene expression profiles induced by IFN- β and/or predictive of its therapeutic response in MS. Although a clear molecular signature can be detected in blood cells after IFN- β therapy, the pattern and number of modulated genes were different suggesting an individual drug-response fingerprint that will probably be difficult to translate into a reliable tool in clinical practice [96].

Glatiramer acetate

Glatiramer acetate (GA) was the second drug to be approved in MS. GA is a random polymer of amino acids initially developed to resemble the myelin basic protein and to reproduce the disease when injected in animal models. GA has proven efficacy in relapsing remitting MS patients with a response rate of around 50%. The mechanism of action of GA is not fully understood but is suggested to have multiple effects on both the innate and adaptive immune system. Compared to IFN- β , only a few studies have

investigated genetic markers for response to GA and with inconclusive results. One study has suggested an association with HLA Class II [97] but this was not replicated in a subsequent study [98] in which a significant association with polymorphisms in the T-cell receptor beta and Cathepsin S genes were found. By using a bioinformatics algorithm for the identification of composite allele sets, a recent study proposed markers to discriminate between GA and IFN- β responders [99]. However, all these findings will have to be validated.

Other treatments for MS

Although it is probably too early to draw definitive conclusions, a few studies have emerged addressing genetic determinants for the clinical response to more recently approved drugs in MS. Natalizumab is a monoclonal antibody directed towards alpha-4 integrins that has shown its efficacy in reducing MS relapse. To date studies have failed to find genes associated with the response to natalizumab in MS patients [100]. However, a genetic variant of the anti-apoptotic protein Akt predicted natalizumab-induced lymphocytosis and post-natalizumab multiple sclerosis reactivation in one study [101]. The expression levels of three miRNAs were later suggested as possible biomarkers for individual progressive multifocal leukoencephalopathy (PML) risk assessment [102] although JCV antibody status, immunosuppressive pre-treatment, and duration of natalizumab therapy remain the main risk factors for PML. The antineoplastic mitoxantrone (MTX) has been established as second-line treatment for RR or secondary progressive MS. ABC-transporter gene-polymorphisms (*ABCB1* and *ABCG2*) have been found to be potentially associated with MTX response in MS [103]. In addition, the case of a patient treated with MTX who showed severe cardiotoxicity and rare polymorphisms of these genes, was reported [104]. A clinical trial using MTX is currently ongoing to investigate the role of ABC-transporter genes in the response to MTX (ClinicalTrials.gov Identifier: NCT01627938). In addition, increased susceptibility to the development of acute promyelocytic leukemia, another rare adverse effect of MTX, may be linked to genetic variants in DNA repair and drug-metabolising enzymes [105].

Azathioprine (AZA) is occasionally used in MS and is more commonly used in other neuroimmunological disorders such as myasthenic syndromes, chronic inflammatory demyelinating polyneuropathies and polymyositis. Thiopurine S-methyltransferase (TPMT), the enzyme catalysing S-methylation of AZA, has a genetic polymorphism in 10% of Caucasians, with 1/300 individuals having complete deficiency. Patients with intermediate or deficient TPMT activity are at higher risk of toxicity after receiving standard doses of AZA, and a recent retrospective study of 7,360 patients referred for TPMT phenotype/genotype determination in France has confirmed a strong genotype-phenotype correlation and illustrates the

usefulness of pharmacogenetics in clinical practice [106]. TPMT testing is recommended by the FDA to identify patients who are at increased risk of myelotoxicity and recommendations have been published to adapt the starting doses of AZA [107]. AZA is thus a good example of the potential impact of pharmacogenetics in clinical practice including cost- and clinical-effectiveness uncertainty that may be a challenge to decision makers [108].

Stroke

Most of data available for pharmacogenetics in stroke come from studies investigating the response to oral anticoagulants and antiplatelet agents, except for a few studies performed on the genetic determinants of the response to rtPA that would need replication.

Thrombolysis

The beneficial effect of treatment with recombinant tissue plasminogen activator (t-PA) given at the acute stage of ischemic stroke has been clearly demonstrated. However, only 45% of patients will be alive and independent after treatment, symptomatic haemorrhagic events occur in 8%, and mortality is about 9% [109]. The main predictors of thrombolysis outcome (good or bad) are age of the patient, time to treatment after stroke onset, baseline NIHSS score, blood pressure, glycaemia, and radiological early ischemic sign. A few candidate gene association studies have investigated genetic determinants of the outcome post-thrombolysis suggesting a polygenic effect: recanalisation or good clinical outcome was associated with genetic polymorphisms of the thrombin-activatable fibrinolysis inhibitor (TAFI), plasminogen activator inhibitor-1 (PAI-1), coagulation factor XIII (FXIII), cyclo-oxygenase-2 (COX-2), angiotensin conversion enzyme (ACE), interleukin-1 beta (IL1B), and Willebrand factor (WF) [110-112]; the re-occlusion was associated with MDP, CD40 and PAI-1 [113; 114]; and haemorrhagic transformation or death with Alpha-2-macroglobulin (A2M) and coagulation factor XII (F12). Although increased plasma concentration of metalloproteinase-9 (MMP9) was associated with haemorrhagic transformation [115], no significant genetic link was found with the *MMP9* gene [116]. Importantly, none of these results were obtained from randomised controlled trials or compared to a control group not treated with thrombolysis, which severely limits the interpretation of the results. Algorithms combining clinical and genetic variables have been proposed to predict stroke outcome in patients treated with rtPA [113], which would need replication before being introduced into clinical practice.

Anticoagulants

Vitamin K antagonists, which target vitamin K epoxide reductase (VKOR), are the most widely used oral anticoagulants in the world used in stroke prevention. There is high interindividual variability in dose requirements of anticoagulants, monitored by the international normalised ratio (INR), with a risk of thrombosis with underdose and haemorrhagic events with overdose. Several pharmacogenetic studies has clearly shown that this variability is partly explained by genetic factors, particularly polymorphisms in genes coding their metabolizing enzyme (CYP2C9), and the gene coding their target (VKORC1). However, randomised clinical trials testing the hypothesis that genotyping might be useful in clinical practice to optimise anticoagulant therapy have only been published recently. Indeed, three randomised clinical trials addressing this issue for warfarin [117; 118], or acenocoumarol and phenprocoumon [119] were published in the New England Journal of Medicine in December 2013. All three trials investigated the benefit of CYP2C9 and KOKC1 genotyping at the initiation of vitamin K antagonist initiation, using the percentage of time in the therapeutic range (INR) during the first 4-12 weeks as their primary endpoint. Two of these trials failed to demonstrate a benefit of genotyping as compared to an algorithm based on clinical variables [117; 119], and one trial found a significant - although marginal - benefit of genotyping when compared to a initial fixed dose based only on age (67.4% vs. 60.3% in therapeutic range) [118]. However, the time to reach a therapeutic INR occurred significantly earlier in 2 trials and fewer adverse events occurred in the 3 trials in the pharmacogenetic group although there was insufficient statistical power to detect a significant difference. Recent meta-analyses including these trials have been published suggesting that genetic testing might indeed be useful for fixing preventative doses and adverse event prevention [120-122].

What can we conclude from these results? First, that genetic determinants are clearly involved in the individual variability of the response to vitamin K antagonist. The clinical benefit of genetic testing appears marginal in randomised clinical trials as compared to algorithms based on clinical variables with frequent INR measurements. However, in clinical practice, INR measurements are commonly not performed as often as required in all patients. The added value of genetic testing as a starting point for clinical management of patients clinically treated with anticoagulants remains to be evaluated. Most pharmacogenetic studies have been performed on Caucasian populations although “minority” populations might have different response profiles [123]. Pharmacogenetic studies have been performed mostly on warfarin, the most widely used oral anticoagulant in the world but not in France where fluindione is prescribed in 80% of patients (ANSM report 2014). The positive balance of cost-effectiveness found for genetic testing as compared to the classic algorithms [124] will have to be re-

evaluated when considering the new oral anticoagulant therapies that have emerged in the last few years [125].

Antiplatelet agents

Antiplatelet therapy is indicated for both the management of acute ischemic stroke and the prevention of stroke [126]. Among the different antiplatelet agents, aspirin (with or without extended-release dipyridamole) and the thienopyridine clopidogrel are recommended as first-line agents. Different studies have reported a wide variability in response to antiplatelet therapy causing a large number of patients to have high platelet reactivity (HPR) and experience new thrombosis events under treatment [127]. Several pharmacogenetic studies have shown that the variability in response to clopidogrel is partly explained by genetic factors, particularly polymorphisms in genes coding for the metabolising enzyme CYP2C19 [128; 129]. Clopidogrel is a pro-drug that requires bioactivation to form an active metabolite that blocks the platelet receptor to ADP (named P2Y₁₂). The CYP2C19 enzyme is directly involved in both steps of the hepatic bioactivation of clopidogrel to its active metabolite, supporting the association between CYP2C19 loss-of-function alleles (e.g., *2-*8) and reduced formation of active metabolites and existence of HPR, typically measured by *ex vivo* ADP-induced platelet aggregometry. Importantly, these pharmacokinetic and pharmacodynamic links translate into increased risks for adverse cardiovascular outcomes (e.g., cardiovascular death, myocardial infarction, stroke, stent thrombosis) among coronary patients who are CYP2C19 loss-of-function allele carriers compared to CYP2C19*1 homozygotes [130-137]. The risk seems particularly great in high-risk coronary patients who undergo coronary angioplasty and stenting, but have been inconsistently reported in lower risk patient populations. A limited number of observational studies suggest that in stroke survivors treated with clopidogrel, CYP2C19 loss-of-function allele carriers have a higher risk of recurrence [138; 139]. A second consideration relates to the gene dose effect. Reduced response to clopidogrel can be improved by increasing the clopidogrel dosing regimen in heterozygous carriers (around 20% of Caucasians) of CYP2C19 loss-of-function allele but not in homozygous carriers (3-5% of Caucasians) [140] suggesting that the use of clopidogrel should be avoided in these latter patients. Unfortunately algorithms for the guidance of antiplatelet therapy with the use of pharmacogenetic data are currently unavailable.

Headache

A few pharmacogenetics studies have investigated the response to triptans in migraine patients and have been reviewed elsewhere [141]. So far, most of these studies have failed to identify significant genetic association with drug response particularly with the serotonin receptor 5HT_{1B}, one of the targets

of these drugs. However, most of these studies include only a small number of patients and may be underpowered. The positive associations found with genetic variants in the serotonin transporter have recently not been replicated [142]. A few studies have also considered medication overuse headache as a potential pharmaco-genetic interaction and have found association between this disorder and genetic polymorphisms in the dopamine neurotransmitter system (*DAT*, *MAOA*, *DRD4*, *DRD2*) and the *BDNF* [143-145] known to predispose patients to drug abuse behaviour. Monoamine oxidase A (*MAOA*) has also been associated with triptan overuse [146].

Epilepsy

Epilepsy is one of the most common neurological disorders, affecting 1-2% of the world population. There are numerous pharmacogenetic studies which assess the extent to which gene variants may influence individual responses to antiepileptic drugs (AED). However, the findings are consistently investigated for only two old AED, phenytoin and carbamazepine, and have led to clinical recommendations. The association of the *2 and *3 alleles of *CYP2C9* was found to modify phenytoin metabolism [147]. The HLA-B*1502 was associated with serious hypersensitivity reactions (i.e. Stevens Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN)) in Asiatic populations [148]. More recently, HLA-A*3101 has also been associated with an even broader range of carbamazepine hypersensitivity reactions, including mild maculopapular exanthema, hypersensitivity syndrome and SJS/TEN in European populations [149]. Very recently, *CYP2C* variants, including *CYP2C9**3, known to reduce drug clearance, have been related to phenytoin-related severe cutaneous adverse reactions in populations from Japan and Malaysia [150].

The other studies provided negative or inconsistent results. This research is mainly directed towards reducing drug resistance. Despite more than 25 AED, resistance remains stable at around 30%. Indeed, AED in epilepsy is often compromised by the unpredictability of efficacy and safety and inter-individual variability among patients. In order to find an explanation for refractoriness, several hypotheses on pharmacodynamics (i.e. drug target) and pharmacokinetic parameters (i.e. transportation and metabolism) have been suggested. One of the potential mechanisms is over-expression of P-glycoprotein (P-gp, also known as ABCB1 or MDR1) in endothelial cells of the blood-brain barrier (BBB) in epilepsy patients. P-gp plays a central role in active transport of xenobiotics and thus drug absorption and distribution in many organisms. Whether variants in the ABCB1 gene influences resistance to AEDs remains widely debated. The expression of P-gp has been shown to be greater in drug-resistant than in drug-responsive patients and over-expressed in tissue from patients with focal epilepsy [151]. One study demonstrated that refractory patients were more likely to possess the CC genotype at the C3435T region

of the *ABCB1* gene and to be resistant to multiple antiepileptic drugs. In another study, 210 European patients with temporal lobe epilepsy, clustered by seizures/year, exhibited a relationship between the CGC haplotype at the regions C1236T, G2677T and C3435T, showing resistance to several antiepileptic drugs, and they also showed an increase in drug resistance of up to six times in homozygous CGC patients with medial temporal lobe epilepsy [152; 153]. In a recent study on 115 patients treated by phenytoin and/or phenobarbital and/or carbamazepine, the response to AED appeared also modulated by C3435T in *ABCB1* or P-gp activity [154]. However, a very recent meta-analysis of 8 studies of pharmaco-resistance to antiepileptics, including 634 drug-resistant patients, 615 drug-responsive patients and 1,052 healthy controls found no allelic association of *ABCB1* C3435T with risk of drug-resistance in overall and in the subgroup analysis by ethnicity [155]. Another meta-analysis of eight reports on the possible role of the *ABCC2* transporter at the blood brain barrier in altered drug response including 1,294 good responders and 1,529 poor responders observed an overall significant association of high activity promoter variant c.-24C>T with drug response. However, all the associations were lost after testing for multiple corrections [156]. To conclude, variants in the *ABCB1* and *ABCC2* transporter genes could influence resistance to AEDs with a lower plasma level of related antiepileptic drugs and some lower efficacy of specific drugs but further studies are warranted (in different ethnic groups with layered analysis on the basis of different phenotypic covariates) to investigate whether these variants could help avoid or limit the drug resistance seen in the everyday practice.

Genetic variants influencing the sensitivity of targets to AEDs (i.e. pharmacodynamics) are also being investigated, for example, the presence of rs3812718 polymorphism in the 1A subunit of the sodium channel (*SCN1A*) has been observed in association with high doses of carbamazepine in epileptic patients [157]. Similarly, a mutation was detected in the sodium channel 3A subunit (*SCN3A*-K354Q) in paediatric patients with partial epilepsy who were refractory to single drug therapy with carbamazepine or oxcarbazepine [158]. Another recent but negative example of research has concerned levetiracetam, a broad-spectrum antiepileptic drug that binds to the membrane protein SV2A. Non synonymous coding variation within *SV2A* gene was extremely rare in 158 patients with focal or generalised epilepsies, suggesting that rare variation is not likely to account for the individual differences in response to levetiracetam [159].

Finally, one of the most extensive fields of research has concerned the influence of the superfamily of cytochrome P450 (CYP450). Among the polymorphic enzymes that metabolise xenobiotics, class I enzymes are well preserved and show low polymorphism but are active in the metabolism of drugs and pre-carcinogens, and they include CYP1A1, CYP1A2, CYP2E1 and CYP3A4. The class II enzymes on the

other hand, are highly polymorphic and active in the metabolism of no pre-carcinogenic drugs; this group includes CYP2B6, CYP2C9, CYP2C19 and CYP2D6 [160]. From 1945 to 2005, 1200 drugs were reviewed, 121 of which had pharmacogenetic importance, but only 69 were associated with polymorphisms in cytochromes CYP2D6, CYP2C9, CYP2C19 and CYP3A4. These genetic biomarkers could be excellent molecular tools to predict the outcome of drug treatments (see review of [161]). For example, individuals possessing certain alleles of the *CYP2C9* gene have significantly reduced rates of phenytoin metabolism and require a low maintenance dose [147]. CYP2C19 and its variants influence the metabolism of barbiturates and CYP2D6 variants influence carbamazepine [162]. Schematically, poor metabolisers of these enzymes have a higher risk of adverse events and high metabolisers require higher doses to avoid inefficacy. Although single drug therapy remains the mainstay in the treatment of epilepsy, combinations of AEDs are frequently used in patients who do not respond to a single drug. When combination therapy is used in patients, drug interactions become clinically relevant for numerous reasons: the AEDs (carbamazepine, valproic acid, phenytoin and phenobarbital) have significant effects on the activity of enzymes that metabolise most existing drugs and most of the old and new generations of AEDs are substrates of CYP450, including CYP1A2, CYP2C9, CYP2C19 and CYP3A4, and glucuronyl transferase and epoxide hydrolase [163; 164]. For example, valproic acid within the therapeutic range induces the expression of CYP3A4 by the direct activation of constitutive androstane receptor (CAR). Other antiepileptic drugs metabolised by this enzyme are ethosuximide, tiagabine, zonisamide and carbamazepine. Carbamazepine (CBZ) undergoes first-pass metabolism in the gut wall mucosa and the liver with the initial pathways being catalysed by the enzymes CYP3A4 and CYP2C9/19, respectively, with minor participation of CYP2C8 and CYP3A5 [165; 166]. An attempt has been made to avoid the involvement of CYP450 metabolism for the new third generation AEDs. However, there frequently remains an association between AEDs and CYP 450 metabolism. Moreover, the new AEDs are often metabolised by the less known glucuronidation by hepatic UDP-glucuronosyltransferase, which could also strongly influence drug resistance. For instance glucuronidation of eslicarbazepine results from the contribution of UGT1A4, UGT1A9, UGT2B7, and UGT2B17, UGT2B4 (high affinity), the latter isozyme plays a major role at therapeutic plasma concentrations of unbound eslicarbazepine. To conclude, pharmacogenetic studies have recommended the assay for the *HLA-B*1502*, *HLA-A*3101* and *2 and *3 alleles of *CYP2C9* before initiating carbamazepine and phenytoin to avoid severe adverse effects. However, most of these suggestions to better tailor the antiepileptic treatment remain hypothetical and have not confirmed in clinical practice. Large studies taking into account all the

pharmacodynamic and pharmacokinetic parameters and coupled with AED concentration monitoring will be required.

Conclusion

Over the past few decades, many studies have investigated the genetic factors associated with drug response in neurological disorders, showing the growing interest for pharmacogenetics in this field. However, the effects of only a few genes have been replicated and demonstrated to have a clinically relevant pharmacogenetic effect. In an effort to provide information to clinicians, the PharmGKB database has annotated drug labels containing pharmacogenetic information for drugs approved by drug agencies. Information available from this database for drugs commonly used for neurological disorders are listed in Table 1. Guidelines for these drugs are also available on the pharmacogenomics website (<http://www.pharmgkb.org/>). Despite these recommendations, genotyping is not systematically performed for these drugs in clinical practice because accessibility to genotyping laboratories are not yet widely available and because clinicians are not aware of their usefulness. Most of other associations identified for other genes in clinical studies lack replication and the benefit of genotyping in clinical practice remains to be demonstrated. Pharmacogenetics in neurology is confronted with the usual problems in the field, particularly the weak predictive effect at a single gene level, the variability of drug response being multigenic and mostly explained by other clinical or drug-interaction factors. The nonlinear relationship between blood and brain drug concentrations increases the complexity of modelling drug responses in the field of Neurology. Algorithms taking into account clinical, pharmacological and genetic factors will be necessary to allow personalised medicine at the individual level. For that purpose, randomised clinical trials having as principal objective the evaluation of the benefits of genotyping prediction as compared to the usual methods will be necessary, an effort rarely supported by drug industries. A research effort by large international consortia of clinicians and researchers will thus need to be pursued in order to move towards a more personalised medicine for neurological diseases in the future.

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Disclosure of interest

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D.D. served on the Scientific Advisory Board for Novartis and Aguetant and has received PHRC grants from the French Ministry of Health and research funding from the ARSLA charity. He has received various honoraria from pharmaceutical companies for consultancy and lectures on Parkinson’s disease at symposia.

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L.L. received honoraria for clinical trials from GSK, Trophos , Biogen; received grants from AFM, ARSLA, Agence National pour la Recherche (ANR), served on the Scientific Advisory Board for Novartis and received travel grants from Merck-Serono.

Table

Title

Current recommendations from drug agencies concerning pharmacogenetics on drugs used for the treatment of neurological diseases

Drug	Gene	FDA	EMA
azathioprine	<i>TPMT</i>	<p>Genetic testing recommended</p> <p>The azathioprine (Imuran) FDA-approved drug label recommends testing for TPMT genotype or phenotype to identify patients who are at increased risk of myelotoxicity: those with low or absent TPMT activity</p>	ND
carbamazepine	<i>HLA-B</i>	<p>Genetic testing required</p> <p>The FDA-approved label for carbamazepine (Tegretol) states that screening of patients with ancestry in genetically at-risk populations (patients of Asian descent) for the presence of the HLA-B*1502 allele should be carried out prior to initiating treatment with Tegretol due to a high risk of serious and sometimes fatal dermatological reactions</p>	ND
clobazam	<i>CYP2C19</i>	<p>Actionable pharmacogenetics</p> <p>In patients known to be CYP2C19 poor metabolisers, the drug label states that the initial dose of clobazam (ONFI) should be 5 mg/day. Patients can be titrated initially to 10 - 20 mg/day, and then titrated further to a maximum daily dose of 40 mg, if tolerated. This is due to an increase in levels of N-desmethylclobazam, the active metabolite of clobazam.</p>	ND
clopidogrel	<i>CYP2C19</i>	<p>Genetic testing recommended</p> <p>CYP2C19 poor metabolisers may have diminished effectiveness of the drug, leading to higher cardiovascular event rates following acute coronary syndrome or transcatheter coronary intervention, as compared to patients with normal CYP2C19 function. The drug label suggests that alternative treatment or treatment strategies should be considered for patients identified as</p>	Actionable PGx

		CYP2C19 poor metabolisers.	
diazepam	<i>CYP2C19</i>	<p>Actionable pharmacogenetics</p> <p>The FDA-approved drug label for diazepam (Diastat) notes that the drug is metabolised by CYP2C19 and CYP3A4, and that inter-individual variation in clearance of the drug is probably attributable to CYP2C19 or CYP3A4 genetic variability.</p>	ND
galantamine	<i>CYP2D6</i>	<p>Informative pharmacogenetics</p> <p>Dosage adjustment of galantamine is not necessary in patients identified as CYP2D6 poor metabolisers as the dose is individually titrated to tolerability.</p>	ND
phenytoin	<i>HLA-B</i>	<p>Actionable pharmacogenetics</p> <p>A strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA B gene, in patients using carbamazepine. Limited evidence suggests that HLAB*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.</p>	ND
tetrabenazine	<i>CYP2D6</i>	<p>Genetic testing required</p> <p>Its primary metabolites are metabolised mainly by CYP2D6. Patients requiring doses above 50 mg per day should be genotyped for the drug metabolising enzyme CYP2D6 to determine if the patient is a poor metaboliser (PM) or an extensive metaboliser (EM). People with CYP2D6 poor metaboliser genotypes should be treated with lower doses.</p>	ND
valproic acid	<i>OTC, CPS1, POLG</i>	<p>Genetic testing required</p> <p>Treatment with valproic acid is contraindicated in patients with known urea cycle disorders (UCD), a group of uncommon genetic abnormalities, since these patients can experience sometimes fatal hyperammonemic encephalopathy following initiation of valproate therapy. UCD results from mutations in one of several genes, including</p>	ND

		ornithine transcarbamylase (OTC) deficiency and carbamoyl-phosphate synthetase 1 (CPS1) deficiency. Valproic acid is also contraindicated in patients with POLG mutations. POLG is a mitochondrial DNA polymerase and mutations in this gene are associated with hereditary neurometabolic syndromes such as Alpers Huttenlocher Syndrome. These patients are at an increased risk of liver failure and death.	
Vardenafil	<i>CYP3A4</i> , genetic degenerative retinal disorders	ND	Informative pharmacogenetics The EMA European Public Assessment Report (EPAR) for vardenafil (Levitra) contains genetic information regarding its contraindication in patients with hereditary retinal degenerative disorders. It also mentions that the drug is metabolised primarily by CYP3A4 and that concomitant use of potent CYP3A4 inhibitors is contraindicated, or dose adjustments should be made when prescribed with moderate CYP3A4 inhibitors.
warfarine	<i>CYP2C9</i> , <i>VKORC1</i>	Actionable PGx The FDA recommends genetic testing for CYP2C9 and VKORC1 variants prior to initiating treatment with warfarin. The guidelines are currently under review following recently published studies on warfarin pharmacogenetics.	ND

Legend

Drugs are listed in alphabetical order. FDA or EMA drug labels for gene of interest according to PharmGKB are shown for each drug (source : <http://www.pharmgkb.org>).

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