

## Update on pharmacogenetics in epilepsy: a brief review

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Recent developments in the pharmacogenetics of antiepileptic drugs provide new prospects for predicting the efficacy of treatment and potential side-effects. Epilepsy is a common, serious, and treatable neurological disorder, yet current treatment is limited by high rates of adverse drug reactions and lack of complete seizure control in a significant proportion of patients. The disorder is especially suitable for pharmacogenetic investigation because treatment response can be quantified and side-effects can be assessed with validated measures. Additionally, there is substantial knowledge of the pharmacodynamics and kinetics of antiepileptic drugs, and some candidate genes implicated in the disorder have been identified. However, recent studies of the association of particular genes and their genetic variants with seizure control and adverse drug reactions have not provided unifying conclusions. This article reviews the published work and summarises the state of research in this area. Future directions for research and the application of this technology to the clinical practice of individualising treatment for epilepsy are discussed.

### The promise of pharmacogenetics in clinical practice

Pharmacogenetics encompasses the principle of testing for how genetic variation among individuals affects variation in response to medicine, both in terms of efficacy and adverse drug reactions. It provides the ability to identify potential adverse drug reactions or lack of effectiveness of a drug before administration. Therefore, pharmacogenetics holds the promise to deliver safe and effective drug treatment for various prevalent diseases by allowing individual prescribing based on patient genotype, but so far it has been implemented in clinical practice in only a few isolated examples.

Differences in treatment outcomes for various disorders are seen in patients with apparently identical diagnosis and treatment. These differences have been examined biochemically from drug concentrations in serum to assess the distribution of metabolites from individual drugs, which can guide some treatments. The completion of the human genome project has promoted studies on gene expression and genetic sequence variation between individuals, and enabled investigation of the genetic control of the individual variation seen in clinical practice.

The treatment of epilepsy offers a model opportunity for the application of pharmacogenetics into clinical practice in view of the high prevalence of this disorder,<sup>1,2</sup> the wide variety of individual responses to antiepileptic drugs, the readily quantified outcomes of seizure control, and the availability of validated scales to classify both seizures<sup>3</sup> and adverse effects.<sup>4,5</sup> These validated scales are used widely in clinical trials although not so commonly in clinical practice. The definition used to classify patients as being pharmacoresistant has varied in different studies investigating pharmacogenetics of antiepileptic drugs. The goal of epilepsy treatment should be complete seizure control, as this is what is needed for the patient to be able to drive, operate machinery, and have an optimum quality of life. Therefore the most appropriate definition of pharmacoresistance is the inability to achieve complete seizure control despite trials of at least three appropriate antiepileptics, taken at therapeutic doses, excluding

seizures due to drug non-compliance or extraordinary provoking events. However, although complete seizure control is eventually achieved in most newly treated patients,<sup>6</sup> this outcome is uncommon in patients treated in chronic epilepsy clinics. Because these populations have been used in all previous pharmacogenetic studies, a less strict definition of pharmacoresistance has been applied (most commonly the occurrence of more than three seizures despite trials of three or more antiepileptic drugs).<sup>7-9</sup>

Pharmacogenetics holds the potential for a significant reduction in the 40–50% of patients treated with an antiepileptic drug who currently have an adverse drug reaction<sup>10</sup> or inadequate seizure control (pharmacoresistance)<sup>6</sup> or both. Individual patients with similar epilepsy syndromes who are taking similar, or even the same, doses of medication can have vastly different responses.<sup>11</sup> Genetic differences among patients are likely to make some contribution to this variation. Current treatments for epilepsy are not curative; the goal of treatment is seizure freedom without side-effects. A third of a typical unselected epilepsy population remains refractory to conventional medication,<sup>12</sup> and even for those who eventually respond to treatment a quarter will have sufficient negative effects to warrant withdrawal of the drug.<sup>10,13</sup> Finally, there are particular epilepsy syndromes that often remain persistently refractory to current available treatments, such as Lennox-Gastaut and symptomatic focal epilepsies.

Traditionally, antiepileptic drugs have been developed through screening large numbers of compounds in a few animal seizure models. In the past two decades, however, the discovery of channelopathies in human epilepsy has provided novel mechanisms of epileptogenesis, which are now directing drug development according to a specific neurobiochemical approach. Insights into the genetic basis of some seizure disorders<sup>14</sup> have expanded our current understanding of epilepsy with significant implications for its treatment.

The effect of genetic polymorphisms on the metabolism of drugs is significant. Many of the main drug-

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metabolising enzymes have well-characterised functional variants. For example, patients with variant genotypes of CYP2D6 (homozygote, two null [non-functioning] alleles) are associated with poor metaboliser status<sup>15,16</sup> compared with those with two wild-type (normal) alleles who are extensive metabolisers. Multiple copies of a normal gene can give ultra rapid metaboliser status.<sup>17</sup> This variable rate of metabolism alters serum drug and metabolite concentrations, and the clinical effect of this is dependent on the activity and toxic effects of the drug and its metabolites, and in particular the size of the difference between a therapeutic and a toxic dose. These variants are not rare, with the prevalence of CYP2D6 poor metabolisers being 6–10% in white populations. Therefore, an important clinical application of this technology would be dosage schedules according to genotype.

Genetic polymorphisms can alter drug metabolism at various sites. There is potential for alteration in absorption, distribution, transport, metabolism, clearance, and sites of action. Antiepileptic drugs are not only substrates, but can also inhibit or induce genes implicated in metabolism,<sup>18,19</sup> which can then affect not only the antiepileptic drug taken by the patient, but also the metabolism of concurrently prescribed medication. The rate of metabolism can also be affected by gene–gene interactions. There are several genes whose function is the regulation of other genes. These include PXR (pregnane X receptor)<sup>20</sup> and CAR (constitutive androstane receptor).<sup>21</sup> The products of these genes induce members of the cytochrome p450 family and consequently have the potential to increase the rate of metabolism.<sup>20,21</sup> Therefore, phenotype can be affected by both target genes and genes connected with regulation.

## Genetic variation and response to antiepileptic drugs

The importance of genetics on the effect of antiepileptic drugs was initially shown by selective breeding programmes in animals (basic genetic manipulation) that resulted in a strain of rats with resistance to the antiepileptic effect of phenytoin.<sup>22</sup> In human beings, an example of the role of genetics is the variation in individual susceptibility to the occurrence of neural tube defects in the offspring of women taking similar doses of valproic acid, which suggested that genetic factors could be contributing.<sup>23,24</sup>

Substantial evidence from studies of the pharmacokinetics of antiepileptic medication indicates that genetic variation probably affects the clinically effective drug dose in any given patient. The potential application of pharmacogenetics to clinical practice has been investigated in genetic association and expression studies. Association studies have been undertaken for genes implicated in drug transport (*MDR1/ABCB1*),<sup>7–9,25</sup> end-organ drug targets (sodium channel *SCN1A*),<sup>26,27</sup> and integral components of the immune response system (TNF $\alpha$  and *HLA-DR*, *HLA-DQ*, *HLA-B*).<sup>28,29</sup> Data show gene expression effects for genes associated with drug transport (*MDR1/ABCB1*, *MDR2/ABCB2*)<sup>30–42</sup> and metabolism by the cytochrome p450 system (*CYP3A4*, *CYP2C9*, *CYP2C19*, *CYP2D6*).<sup>43–49</sup> The effect of linkage disequilibrium is an important consideration in some of these observations.<sup>50</sup> Linkage disequilibrium refers to the non-random association among variant alleles at different polymorphic sites in the genome (though often not exclusively among sites that are physically near one another in the genome). For this reason when a variant is associated with a phenotype the variant studied might not be causal, but could simply serve as a marker for a causal variant that it is in linkage disequilibrium with. Therefore the association identified with a polymorphism could suggest an effect exerted by another polymorphism in that gene or another gene that is located nearby. The actual causal variant might be identified by further genetic or functional analysis, but in general, the precise localisation of casual variants is proving to be a difficult obstacle in genetic association studies.

Metabolic studies have led to several genes being implicated in the individual variability in the pharmacology and metabolism of antiepileptic drugs (*PXR*, *OCT2N*, *CYP2D6*, *CYP1A2*, *CYP2A6*, *CYP2B6*, *CYP2E1*, *UGT1A6*, *UGT1A9*, *UGT2B7*).<sup>16,51–56</sup> New technology, including oligonucleotide microarray, is available to study gene expression after antiepileptic treatment.<sup>57</sup> Expression microarray analysis has the potential to identify genes that function differently between two samples thus providing candidate genes for further analysis.

Table 1 lists the potential genes implicated in the variable response to antiepileptic medication and

	Product	Function
<i>MDR1/ABCB1</i>	P-glycoprotein	Transmembrane transport Associated with <i>CYP3A</i>
<i>SCN1A</i>	$\alpha$ 1 subunit sodium channel	Movement of sodium ions across membrane
<i>GABBR1</i>	Gamma-aminobutyric acid receptor B	Membrane receptor
<i>GABA-B</i>		
<i>TNF<math>\alpha</math></i>	Subunit of tumour necrosis factor	Associated with the inflammatory pathway
<i>HLA</i>	HLA	Associated with immune response. HLA alleles allow for different peptide presentation on T cells
<i>CYP3A</i>	Cytochrome p450 enzyme	Associated with hydroxylation
<i>CYP2C19</i>	Cytochrome p450 enzyme	Associated with hydroxylation
<i>CYP2C9</i>	Cytochrome p450 enzyme	Omega oxidation pathway
<i>CYP2A6</i>	Cytochrome p450 enzyme	Associated with oxidation
<i>MRP</i>	Multidrug resistance-associated protein	Transmembrane transport
<i>OCTN2</i>	Organic cation transport protein	Transmembrane transport
<i>UGT 1A6</i>	Uridine diphosphate glycosyltransferase	Associated with glucuronidation pathway
<i>CYP1A2</i>	Cytochrome p450 enzyme	Associated with hydroxylation
<i>CYP2D6</i>	Cytochrome p450 enzyme	Associated with hydroxylation
<i>CYP2C8</i>	Cytochrome p450 enzyme	Associated with hydroxylation
<i>PXR</i>	Pregnane X receptor	Associated with indirect metabolism in hydroxylation pathway
<i>PRNP</i>	Cellular prion protein	Associated with neuron protection

**Table 1: Potential candidates, and their known functions, associated with pharmacogenetics of antiepileptic drugs**

summarises their known function. Table 2<sup>58-69</sup> summarises the evidence for variant genotypes in candidate genes associated with the metabolism and effect of antiepileptic drugs in human beings. Here we review the work to date, focusing on the different categories of candidate genes implicated in drug transport, sodium channel function, and immunological regulation.

### Drug transporters

The membrane transporter genes encode for proteins that actively extrude drugs from cells, with the potential to affect both toxicity and efficacy. They were initially described in tumour cells resistant to chemotherapy drugs.<sup>70,71</sup> P-glycoprotein, a drug efflux transporter, was associated with multi-drug resistance gene (*MDR1*)

	Design	Population	Gene/protein	Findings
<b>Membrane transporters</b>				
Tan, 2004 <sup>7</sup>	Retrospective, case control	609 epilepsy patients (401 PR and 208 PS)	<i>MDR1</i>	No significant association of <i>MDR1</i> 3435 CC genotype with PR
Siddiqui, 2003 <sup>8</sup>	Retrospective, case control	200 PR, 115 PS, and 200 controls	<i>MDR1</i>	Homozygous <i>MDR1</i> 3435 CC associated with increased PR compared with TT alleles
Zimprich, 2004 <sup>9</sup>	Retrospective, Case control	193 epilepsy patients (44 PS, 83 intermediate sensitivity, 66 PR) and 228 controls	<i>MDR1</i>	<i>MDR1</i> 1236C-2677G-3435C haplotype found to have an increased frequency in poor responders compared with those that responded best to antiepileptic medication
Giessmann, 2004 <sup>20</sup>	Biochemical case series	Seven patients intestinal mRNA expression	<i>MRP1</i> , <i>MRP2</i> , <i>MDR1</i>	Carbamazepine induced intestinal <i>MDR1</i> mRNA, <i>MRP2</i> mRNA, and <i>MRP2</i> protein content
Aronica, 2004 <sup>31</sup>	Histological case series	24 patients with epilepsy	Pgp, <i>MRP1</i> , <i>MRP2</i> , and MVP	Increased expression was seen in a hippocampus specimen from patients with refractory mesial temporal lobe epilepsy compared with expression levels in normal hippocampus sections
Tishler, 1995 <sup>35</sup>	Histological case series	19 patients intractable epilepsy	<i>MDR1</i>	Increased mRNA and protein expression of Pgp in capillary endothelium in postoperative brain specimens from patients with intractable epilepsy
Owen, 2001 <sup>41</sup>	Histological	Cell lines and lymphocyte cells	Pgp	Carbamazepine is not a substrate for Pgp in intestinal Caco cells and lymphocytes
Lazarowski, 2004 <sup>38</sup>	Histological case series	Three patients with tuberous sclerosis and refractory epilepsy	<i>MDR1</i> , <i>MRP1</i>	Increased protein expression of <i>MDR1</i> and <i>MRP1</i> in epileptogenic cortical tubers of patients with tuberous sclerosis and refractory epilepsy
Sills, 2005 <sup>59</sup>	Case series	400 epilepsy patients	<i>MDR1</i>	No association was seen with C3435T polymorphism and drug response
Hung, 2005 <sup>60</sup>	Case control study	108 drug resistance and 223 seizure free epilepsy patients plus 287 healthy controls	<i>MDR1</i>	Association was seen between the haplotypes of C1236T, G2677T, and C3435T and both the drug-resistant epilepsy patients and the seizure-free patients
<b>Sodium channel</b>				
Tate, 2005 <sup>26</sup>	Retrospective case series	706 epilepsy patients (425 carbamazepine and 281 phenytoin)	<i>SCN1A</i>	<i>SCN1A</i> polymorphism in intron 5 (-91) associated with increased maximum dose of carbamazepine and phenytoin
Remy, 2003 <sup>61</sup>	Electrophysiological	Ten temporal lobe epilepsy and three control patients	<i>SCN</i>	In hippocampal sections patients pharmacoresistant to carbamazepine the block of the Na <sup>+</sup> channel is lost
<b>HLA</b>				
Pirmohamed M, 2001 <sup>28</sup>	Retrospective case control	60 carbamazepine sensitive patients (37 non-serious, 23 serious), 313 controls (63 carbamazepine patients no adverse reactions, 250 healthy volunteers)	<i>TNFα</i>	<i>TNF</i> 308 variant allele ( <i>TNF2</i> ) frequency was higher in patients with serious hypersensitivity reaction than in controls. They also showed a higher frequency of DR3, DQ2, and <i>TNF2</i> -DR3-DQ2 haplotype
Chung, 2004 <sup>29</sup>	Retrospective case control	44 epilepsy patients on carbamazepine and 101 controls	<i>HLA-B</i>	<i>HLA-B</i> *1502 associated with Stevens-Johnson syndrome with carbamazepine
<b>Neurotransmitter receptors</b>				
Gambardella, 2003 <sup>62</sup>	Prospective case control	141 patients with temporal lobe epilepsy and 372 healthy controls	<i>GABA B</i> (G1465A polymorphisms)	The variant A polymorphism showed an increased risk of developing temporal mesial lobe epilepsy as well as a higher risk of pharmacoresistance
<b>Prion protein</b>				
Walz, 2003 <sup>63</sup>	Prospective case control	100 patients with mesial temporal lobe epilepsy operated on because of monthly seizures compared with 180 healthy controls	<i>PNRP</i>	Patients with the Asn171Ser variant were shown to be five times more likely to still have seizures after a temporal lobectomy than those without
<b>Cytochrome 2C19</b>				
Mamiya, 1998 <sup>65</sup>	Biochemical case series	134 epilepsy patients treated with phenytoin	<i>CYP2C19</i>	Japanese patients with epilepsy treated with phenytoin had serum concentrations of phenytoin metabolites assessed with respect to <i>CYP2C9</i> and <i>CYP2C19</i> genotypes. Hydroxylation capacity of phenytoin was impaired in those with mutations of <i>CYP2C9</i> and <i>CYP2C19</i>
Mamiya, 2000 <sup>64</sup>	Biochemical case series	74 epilepsy patients	<i>CYP2C19</i>	Participants classified as having two poor metaboliser alleles ( <i>CYP2C19</i> *2 or <i>CYP2C19</i> *3 or combination of these two) have reduced clearance of phenobarbital compared with patients who have at least one wild-type allele
Odani, 1997 <sup>65</sup>	Biochemical case series	44 epilepsy patients treated with phenytoin	<i>CYP2C19</i>	Samples with at least one copy of the mutant <i>CYP2C19</i> <sub>102</sub> allele had decreased elimination rate of phenytoin compared with the wild type samples
Xiao, 1997 <sup>66</sup>	Biochemical case series	303 epilepsy patients	<i>CYP2C19</i>	<i>CYP2C19</i> <sub>102</sub> and <i>CYP2C19</i> <sub>103</sub> show reduced metabolism rate of 5-mephenytoin compared with the wild type allele
Hung, 2004 <sup>67</sup>	Biochemical case series	169 epilepsy patients treated with phenytoin	<i>CYP2C19</i>	Variant genotyping at <i>CYP2C9</i> and <i>CYP2C19</i> were shown to affect the pharmacokinetics of phenytoin. Lower doses were recommended depending on the number of poor metabolisers' alleles at either or both of these two genes
Taguchi, 2005 <sup>68</sup>	Biochemical case series	20 epilepsy patients	<i>CYP2C19</i>	Genotyping of <i>CYP2C19</i> and <i>CYP2C9</i> has an effect on the dose of phenytoin needed to achieve the therapeutic drug concentration range, but between patients with the same genotype additional factors still play a part

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	Design	Population	Gene/protein	Findings
<b>Cytochrome 2C9</b>				
Tate, 2005 <sup>26</sup>	Retrospective case series	281 epilepsy patients	CYP2C9	CYP2C9 polymorphism associated with increased maximum dose of phenytoin
Mamiya, 1998 <sup>45</sup>	Biochemical	134 Japanese epilepsy patients treated with phenytoin	CYP2C9	Serum concentrations of phenytoin metabolites assessed with respect to CYP2C9 and CYP2C19 genotypes. Hydroxylation capacity of phenytoin was impaired in those with mutations of CYP2C9 and CYP2C19
Ho, 2003 <sup>48</sup>	Biochemical	39 epilepsy patients	CYP2C9	CYP2C9*2 and CYP2C9*3 have reduced efficiency for biotransformation of valproic acid to 4-ene-VPA, 4-OH-VPA, and 5-OH-VPA
Odani, 1997 <sup>65</sup>	Biochemical	44 epilepsy patients treated with phenytoin	CYP2C9	Samples heterozygous for the wild-type and Leu <sup>359</sup> had a 33% lower elimination rate of phenytoin than wild type samples
Hung, 2004 <sup>67</sup>	Biochemical case series	169 epilepsy patients	CYP2C9	Variant genotyping at CYP2C9 and CYP2C19 were shown to an effect on the pharmacokinetics of phenytoin. Lower doses were recommended depending on the number of poor metabolisers' alleles at either or both of these two genes
Van der Weide, 2001 <sup>69</sup>	Biochemical case series	60 epilepsy patients	CYP2C9	Patients with at least one mutant CYP2C9 allele had a lower dose of phenytoin to achieve a therapeutic serum drug concentration than did patients with two normal alleles
Taguchi, 2005 <sup>68</sup>	Biochemical case series	20 epilepsy patients	CYP2C9	Genotyping of CYP2C19 and CYP2C9 has an effect on the dose of phenytoin needed to achieve the therapeutic drug concentration range, but between patients with the same genotype additional factors still play a part

PR=pharmacoresistant; PS=pharmacosensitive; MRP=multi resistance-associated protein; MDR=multi drug resistance; MVP=major vault protein; Pgp=P-glycoprotein; SCN=sodium channel; CYP=cytochrome.

**Table 2: Studies of pharmacogenetics specific to antiepileptic drugs in human beings**

expression, which is alternatively known as ATP-binding cassette, sub-family B, member 1 (*ABCB1*).<sup>72</sup> The families of membrane transporters, of which the gene product of *MDR1/ABCB1* is the best-studied example, could act to limit the accumulation of antiepileptic drugs in the brain since their primary function is to cause efflux of potential toxins.<sup>73,74</sup> The function and biochemistry of P-glycoprotein with respect to antiepileptic drugs has been reviewed elsewhere.<sup>75</sup>

There is evidence to suggest that antiepileptic drugs interact with the *MDR1/ABCB1* gene product. Carbamazepine has been shown to increase the transport of the P-glycoprotein substrate talinol (a marker of *MDR1/ABCB1* mRNA expression).<sup>30</sup> In-vitro studies show that phenytoin, lamotrigine, and valproic acid inhibit P-glycoprotein transporter expression in calcein assay (used to determine the effect of compounds on the function of P-glycoprotein in live cells).<sup>40</sup> P-glycoprotein is thought to transport various antiepileptic drugs,<sup>76</sup> making it a potential contributor to pharmacoresistance, although the evidence for carbamazepine is conflicting.<sup>41</sup> Further studies have shown that P-glycoprotein mRNA and protein concentrations in tissue resected from patients with drug-resistant epilepsy are increased compared with tissue from control subjects.<sup>31–36,42,61,77</sup>

The question as to whether an increase in P-glycoprotein activity is related to a genetic polymorphism in the *MDR1/ABCB1* gene has been assessed. A common single nucleotide polymorphism identified within exon 26 of the *MDR1/ABCB1* gene (T/C) has been shown to be associated with a differential function of P-glycoprotein.<sup>71</sup> The homozygote T is found in about 25% of the white population.<sup>78</sup> This variation results in a silent substitution (no amino acid change) at position 3435 and is closely linked to a polymorphism

within intron 26. This *MDR1/ABCB1* polymorphism is located within an extended block of linkage disequilibrium and thus it might not be a causal variation but a marker of a causal polymorphism in a gene nearby.<sup>50,26</sup> Clinical studies of this gene have thus far been done only on retrospective cohorts and in patients with chronic epilepsy undergoing treatment at tertiary centres. The relation between the *MDR1/ABCB1* polymorphisms and the association with pharmacoresistance in epilepsy is unclear with three of the published studies documenting an association of pharmacoresistance with the 3435CC genotype of the *MDR1/ABCB1* gene,<sup>8,9,60</sup> whereas other studies were unable to identify an association.<sup>7,59</sup> These discrepancies could be explained by many factors, including sample size, sample homogeneity, sample bias, and diagnosis of the epilepsy syndromes and pharmacoresistance definitions. If the *MDR1/ABCB1* 3435 polymorphism has an effect (or is in linkage disequilibrium with a variant that does) it does not seem to have a substantial effect on the final phenotype. There are polymorphisms of other transporter proteins (*MRP1*, *MRP2*, *OCTN2*) that have a potentially important role in the metabolism of antiepileptic drugs<sup>51,79</sup> and need further investigation.

### Drug metabolism

Table 3 summarises the role of the pathways in the metabolism of antiepileptic drugs with particular reference to carbamazepine and valproic acid, which are the most commonly prescribed initial antiepileptic drugs in developed countries.<sup>80</sup>

### The cytochrome p450 system

The cytochrome p450 mono-oxidases (CYP450) are an important family of liver enzymes, which metabolise

#### Enzymes associated with major metabolic pathways\*

Carbamazepine	CYP3A4, CYP1A2, CYP2A6, CYP2C8, CYP2C19, CYP2D6, UGT1A6, UBG2B
Valproic acid	50% by UGT, CYP2C9, CYP2C19
Phenytoin	CYP2C9, CYP2C19, UGT
Phenobarbital	CYP2C9, CYP2C19
Primidone	CYP2C9, CYP2C19,
Gabapentin	95% excreted unchanged by kidney, rest by transaminase and vitamin B6
Tiagabine	CYP3A4, UGT
Topiramate	80% excreted unchanged by kidney, rest CYP2C9, CYP2C19
Felbamate	CYP2E1, CYP3A4, CYP2C19
Lamotrigine	More than 70% UGT1A4, 10% excreted unchanged, the rest currently unknown
Leviteracetam	60% excreted unchanged, 24% hydrolysis of acetamide group by CYP450 independent process, 2-5% via p450 enzymes

\*Alteration in any enzyme important in metabolism can alter the metabolite population formed affecting efficacy and adverse event profile.

**Table 3: Enzymes involved in the metabolism of commonly prescribed antiepileptic drugs**

various drugs into substances with altered activity and ease of clearance. Most prescribed drugs are metabolised by the cytochrome p450 system and several genetic polymorphisms in genes that correspond to the cytochrome enzymes have been identified.<sup>81,82</sup> However, no large clinical association studies have been reported up to now.

Genetic variation in these genes can affect metabolism, leading to the altered phenotypes discussed earlier. Individuals with poor metaboliser alleles of *CYP2C9* or *CYP2C19* genes were shown to have a reduced metabolism of phenobarbital, phenytoin, and valproic acid compared with those with wild-type (normal) alleles.<sup>26,45,48,64–66,83</sup>

The discovery of polymorphisms that alter the rate of drug metabolism has led to investigation of drug dose concentrations and maximum drug doses. Several studies of phenytoin have shown that variations in the genes for *CYP2C9* and *CYP2C19* correlate with the maximum dose of drug needed by patients to control their seizures. Patients with the poor metaboliser alleles at these genes needed lower doses of phenytoin to achieve the therapeutic serum drug concentrations than did those with the normal extensive metaboliser alleles.<sup>26,67,69</sup> The identification of the genotype of patients before drug administration could prevent high serum drug concentrations. Table 2 summarises the evidence on the effects of cytochrome p450 polymorphisms.

#### Glucuronidation

The uridine diphosphate glucuronosyltransferase enzymes are responsible for the glucuronidation of various endogenous substances in addition to common drugs.<sup>84</sup> Most of the metabolism of valproic acid and lamotrigine occurs via this glucuronidation pathway at therapeutic doses for antiepileptic treatment. Genetic polymorphism has been shown to affect the

glucuronidation pathway<sup>85</sup> thereby altering the metabolite populations responsible for the efficacy and adverse event profiles.

#### End-organ targets

Many of the antiepileptic drugs, especially carbamazepine, phenytoin, and lamotrigine, are thought to exert their primary antiepileptic action by use-dependent blockage of neuronal sodium channels. This mechanism is also believed to contribute to the actions of valproic acid and topiramate. Mutations in the alpha unit of the sodium channel gene, *SCN1A*, are associated with familial and sporadic epilepsies,<sup>86</sup> and another study showed that patients with epilepsy had a higher proportion of variations in the *SCN1A* gene than did control patients.<sup>27</sup> An *SCN1A* polymorphism has been investigated in a cohort of patients with chronic epilepsy. The AA genotype was associated with patients being prescribed higher maximum doses of carbamazepine and phenytoin than those patients who had the *SCN1A* Intron 5(-91) GG genotype.<sup>26</sup> The importance of the neuronal sodium channel to pharmacoresistance was also suggested by findings of a study linking clinical pharmacoresistance to carbamazepine with loss of the expected use-dependent block of sodium channels by carbamazepine in human hippocampal slices.<sup>61</sup> Further studies are needed to confirm these findings.

#### Immunogenetic background

Inflammatory mediators, such as *HLA* genes and tumour necrosis factor (TNF), are important in adverse reactions to antiepileptic drugs. HLA association studies suggest that immunological mechanisms might contribute to the cause of some epilepsies. However, there has been only one clinical association study of immunological mediators. *HLA-DR4*, *HLA-DQ2*, and *HLA-DR7* groups were identified more often in patients with hippocampal sclerosis-related temporal lobe epilepsy than in healthy controls.<sup>87</sup> This study did not directly assess pharmacoresistance, and association studies might simply reflect the effects of linkage disequilibrium. Therefore the importance of these factors in the pathogenesis and treatment of epilepsy is yet to be clarified.

Serious skin hypersensitivity reaction due to carbamazepine has been associated with a polymorphism at position 308 in the TNF $\alpha$  promoter region gene<sup>28</sup> and with variants of the *HLA* gene alleles *DR3* and *Q2*.<sup>1</sup> A larger study revealed a higher frequency of *HLA-B\*1502* in 44 patients taking carbamazepine, who developed Stevens-Johnson syndrome, than in controls.<sup>29</sup>

#### Limitations of current work

So far the published studies are limited by the absence of prospective data and by selection biases, with cohorts drawn from chronic epilepsy patients in tertiary medical centres. Furthermore, these reports have provided little information about the drugs and doses used by their

participants, who often took several antiepileptic drugs. Data for confounders,<sup>88</sup> such as ethnic origin,<sup>16,89</sup> diet,<sup>90</sup> and medication,<sup>21,81,91</sup> and for comorbidities are also sparse. Additionally, most studies did not stratify by epilepsy syndrome or seizure types, which are both known to affect the probability of pharmacoresistance to antiepileptic drugs.

Genetic association with phenotypes has been shown, but further research is needed to identify causal variants. An improved understanding of the pharmacokinetics and dynamics of antiepileptic drugs will enable a more rational focus on which candidate genes are likely to be associated.<sup>81</sup>

### Future directions

Although the evidence implies an important role for pharmacogenetics in the management of patients with epilepsy, the current published work does not include a multicentre prospective trial to answer the criticisms of previous work. Such a trial would need to account for the allele frequency differences that occur due to ethnic origin.<sup>92</sup> Concurrent medication use is an important factor for consideration, both in terms of side-effect profile and competitive metabolism.<sup>91</sup> For example, simple daily low-dose aspirin for 7 days and 14 days has been shown to induce in-vivo *CYP2C19* activity.<sup>93</sup> Other dietary factors, such as consumption of grapefruit juice, which alters liver metabolism and enzyme activity, should also be considered.<sup>90</sup>

The prospect of predicting drug response, and therefore directing treatment, on the basis of individual genotype<sup>94</sup> promises significant health and quality-of-life benefits to patients. Additionally, there is potential to advance the science of epilepsy with improved understanding of the complex pathophysiology of this group of disorders. This research could open other treatment avenues, such as targeted treatment and reversal of drug-transporter activity, which has been developed to some extent in cancer chemotherapy.<sup>72,95,96</sup>

The development of the pharmacogenetic approach to epilepsy treatment also provides substantial advantages in time and cost savings for both patients and communities by reducing patient–doctor contact time, seizure-related morbidity, drug side-effects,<sup>97</sup> medication alterations,<sup>98</sup> and polypharmacy.<sup>12</sup> The choice of appropriate medication for an individual could be influenced by use of a single, simple DNA test. Although the cost-effectiveness of introducing pharmacogenetics into clinical practice has been debated,<sup>99,100</sup> the diminishing costs of DNA typing suggest that a pharmacogenetic approach is affordable.

Various potentially valuable drugs have been removed from the market because of side-effects in a subset of the population. The best example of this, for antiepileptic drugs, is felbamate. Pharmacogenetic techniques, which identify susceptible individuals before treatment, could allow selection of those with a low risk of side-effects from these drugs. The US Food and Drug Administration is

### Search strategy and selection criteria

References for this review were identified by searches of PubMed in August, 2005, for research published between 1966 and the present, and from references from relevant articles; numerous articles were also identified through searches of the extensive files of the authors. The search terms “epilepsy”, “therapy”, “pharmacogenetics”, “MDR”, “CYTOCHROME”, “OCTN2”, “UGT”, “SCN”, “PXR”, “TNFalpha”, “HLA”, “MRP”, “carbamazepine”, “valproate”, “lamotrigine”, “pregabalin”, “phenobarbitone”, “gabapentin”, “tiagabine”, “topiramate”, “felbamate”, “leviteracetam”, “primidone” were used. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the topics covered in the review.

currently preparing guidelines for the role of pharmacogenetics in drug development and clinical practice.<sup>101</sup>

The potential advantages of pharmacogenetics offer a revolutionary approach to clinical practice and the treatment of epilepsy. The realisation of these potentials will need close liaison between clinicians and scientists to coordinate sound research design and implementation.

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### Authors' contributions

CS did the literature search, wrote the manuscript, and prepared the tables; MN wrote the manuscript; JW did the literature search and prepared the tables; DG, SB, LS, CS, TO, and MN contributed to the editing of the manuscript; and TO supervised the first author.

### Conflicts of interest

DG has a patent pending on the SCN1A genotype for prediction of dosage; however, any remuneration from this patent goes to the Institution for further research funding. We have no other conflicts of interest.

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