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Review article

Pharmacogenomics in epilepsy

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HIGHLIGHTS

- Genetic variation can influence response to antiepileptic drug (AED) treatment through various effector processes.
- Metabolism of many AEDs is mediated by the cytochrome P450 (CYP) family; some of the CYPs have allelic variants that may affect serum AED concentrations.
- 'Precision medicine' focuses on the identification of an underlying genetic aetiology allowing personalised therapeutic choices.
- Certain human leukocyte antigen, *HLA*, alleles are associated with an increased risk of idiosyncratic adverse drug reactions.
- New results are emerging from large-scale multinational efforts, likely imminently to add knowledge of value from a pharmacogenetic perspective.

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ABSTRACT

There is high variability in the response to antiepileptic treatment across people with epilepsy. Genetic factors significantly contribute to such variability. Recent advances in the genetics and neurobiology of the epilepsies are establishing the basis for a new era in the treatment of epilepsy, focused on each individual and their specific epilepsy. Variation in response to antiepileptic drug treatment may arise from genetic variation in a range of gene categories, including genes affecting drug pharmacokinetics, and drug pharmacodynamics, but also genes held to actually cause the epilepsy itself.

From a purely pharmacogenetic perspective, there are few robust genetic findings with established evidence in epilepsy. Many findings are still controversial with anecdotal or less secure evidence and need further validation, e.g. variation in genes for transporter systems and antiepileptic drug targets. The increasing use of genetic sequencing and the results of large-scale collaborative projects may soon expand the established evidence.

Precision medicine treatments represent a growing area of interest, focussing on reversing or circumventing the pathophysiological effects of specific gene mutations. This could lead to a dramatic improvement of the effectiveness and safety of epilepsy treatments, by targeting the biological mechanisms responsible for epilepsy in each specific individual.

Whilst much has been written about epilepsy pharmacogenetics, there does now seem to be building momentum that promises to deliver results of use in clinic.

Contents

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1. Introduction

The response, in terms both of seizure control and adverse reactions (ADRs), to antiepileptic drugs (AEDs) varies greatly across individuals [1]. Moreover, AED treatment in epilepsy is complicated because there are many different syndrome and seizure types within epilepsy, the biology of almost all of which is largely unknown. Response rates do seem to vary in relation to epilepsy syndrome, underlying cause, and other factors [2,3]. The broad phenotypic spectrum and heterogeneous aetiology make the choice of treatment both challenging and empirical: evidence-based information guiding clinicians on the most effective drug and dose for individual patients is lacking. Furthermore, AEDs can have many associated ADRs, some of which are severe and life-threatening [4]. A cross-sectional survey of 809 patients showed that 36.5% experienced one or more ADRs; these events were not related to the number of AEDs, but rather to individual susceptibility, the specific AED used and physicians' skills [5].

There is established evidence that genetic factors certainly contribute to this variability [6]. However, few robust findings have clearly emerged in epilepsy. Progress since the most recent comprehensive reviews [6,7] has been limited. The increasing application of massively-parallel genetic sequencing and results of collaborative projects (such as EpiPGX, http://www.epipgx.eu/and CPNDS, http://cpnds.ubc.ca/) may soon expand knowledge in this area.

Recent advances in the genetics and neurobiology of the epilepsies are establishing the basis for a new era in the treatment of epilepsy, focused on each individual and their particular epilepsy. Testing for gene variations that might predict drug response and ADRs will hopefully soon improve the efficacy and safety of epilepsy therapies, targeting the best drug from those available for each individual patient. Increasing knowledge of the biology of the epilepsies may also lead to the re-purposing for epilepsy of drugs not originally intended for use in epilepsy, and may also direct discovery of rational new therapies. Moreover, as more is becoming understood, it is also clear that in some cases, there is important overlap between disease causation and the profile of response to AEDs.

There remains much to be learnt about epilepsy pharmacogenomics: any classification is necessarily arbitrary. Here, we distinguish the influence of genetic factors on response to AEDs from those affecting adverse drug reaction. We further classify the former according to the mediating mechanisms: pharmacokinetics and pharmacodynamics, or genes mutations which are recognised as capable of causing epilepsy ('epilepsy genes'). This should be considered as an evolving classification. Despite ongoing progress in the field, only some findings are accepted within the community so far, whilst many results have not been replicated, and might be specific to certain populations. Below, we present the state of the art, by reporting first the findings with the best established evidence, followed by those with less certain status.

1.1. Influence of genetic factors on response to AEDs

Genetic variation can influence response to AEDs through various mediating effector systems, including pharmacokinetics and pharmacodynamics (e.g. polymorphism in gene encoding drug metabolizing enzymes or putative brain AED targets, such as receptors or ion channels), and mutations in 'epilepsy genes'; and by modifying the expression of enzymes and other molecules involved in the pathogenesis of pharmacoresistance or adverse drug reactions [8,9]. A key problem is that the mechanistic basis of pharmacoresistance, especially resistance to multiple AEDs, is not understood in the vast majority of cases; nor is the overlap between drug resistance and disease causation well understood [10].

1.2. Pharmacokinetics and pharmacodynamics

In humans, metabolism of those AEDs that undergo such processes is mostly mediated by the cytochrome P450 (CYP) family. Some of the CYPs have genetic (allelic) variants, encoding isoforms of differing activity, which in turn may affect serum AED concentrations, or alter flux through paths for drug metabolism, with subsequent potential risk of drug toxicity.

2. Established evidence

There is established evidence of an effect of polymorphic *CYP2C9* and *CYP2C19* genes: variant alleles can lead to significant differences in AED serum concentrations [11]. CYP2C9 accounts for about 90% of the metabolism of phenytoin. *CYP2C9* polymorphisms are an important determinant of the rate of phenytoin metabolism. Individuals carrying *CYP2C9* alleles encoding variant enzymes (allozymes) with reduced activity metabolize phenytoin at a considerably slower rate compared with individuals homozygous for the wild-type (*CYP2C9*1*; rs1057910(A)) allele, and therefore have a greater risk of developing concentration-dependent neurotoxicity: *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910(C)) are the best documented [12,13]. The maximum dose of phenytoin reported in a series of people with epilepsy was about 50 mg less per *CYP2C9*3* allele [14].

A genome-wide association study of cases with phenytoin-related severe cutaneous adverse reactions and 412 population controls from Taiwan discovered a cluster of 16 single nucleotide polymorphisms in *CYP2C* genes at 10q23.33 that reached genome-wide significance. Direct sequencing of *CYP2C9* identified missense variant rs1057910 (*CYP2C9*3*) as showing significant association with phenytoin-related severe cutaneous adverse reactions [15]. The mechanism underlying this association has yet to be established. Despite the available evidence, pre-treatment pharmacogenetic testing for *CYP2C9* variants is not routine practice, with monitoring for clinical signs of toxicity and serum drug level being the standard approach.

3. Less robust evidence

Few, and mostly preliminary, data are available on genetic factors influencing the metabolism of other AEDs.

Studies investigated the association between *CYP2C19* genotypes and the pharmacokinetics of clobazam and N-desmethylclobazam (N-clobazam), a pharmacologically active

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