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Review

Newly diagnosed epilepsy and pharmacogenomics research: A step in the right direction?☆

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ABSTRACT

Pharmacogenomics holds the promise of selecting the right drug at the right dose for the right person. Its research and application in epilepsy are in their infancy. Although advances have been made in identifying genetic markers of adverse effects in terms of severe cutaneous reactions, there has been little progress in predicting efficacy. Most studies have been retrospective and case–control in design, despite the associated problems of recall bias and a usually undefined relationship between genotype and outcome. We describe the epidemiological framework necessary to detect genetic influences on antiepileptic drug response, and propose an ambitious prospective outcome study of newly diagnosed epilepsy across all age ranges, countries, and continents, which would provide the template for a global pharmacogenomic project. Other epidemiological considerations and statistical constraints and issues related to study design, databases, and ethics that are critical for advancement in the field are also discussed.

"A journey of a thousand miles begins with a single step."
Laozi (ca. 4th century BC Chinese philosopher)

1. Newly diagnosed epilepsy: Long-term outcome and predictive factors

Understanding the natural history of treated epilepsy must begin with a judicious diagnosis and the prescription of a first antiepileptic drug (AED) appropriate to the seizure type(s) and/or epilepsy syndrome, introduced at an acceptable dose and titrated carefully according to tolerability and response. A small number of prospective cohort studies have attempted to define the long-term outcome of newly diagnosed epilepsy [1–9]. In the Glasgow cohort of mainly adult patients followed for up to 26 years, the prognosis slowly improved over three consecutive time periods pertaining to 470, 780, and 1098 newly diagnosed patients, respectively [1,2,10]. The seizure freedom rate in the first analysis, 64%, increased marginally to 68.4%, at 10 years. This difference may be explained by a small improvement in successful combinations (mostly of two AEDs) rising from 3 to 6.4%, or a natural tendency for a small proportion of seemingly refractory epilepsy to remit over time. Whether this observation can be attributed to the introduction of newer AEDs with novel mechanisms of action is unclear, although it remains apparent that patients whose seizures fail to respond to two appropriate regimens at adequate dosing are likely to have drug-resistant seizures [11].

Many studies have attempted to identify factors predicting pharmacoresistance which would allow early consideration of nondrug therapies [3,12–15]. A large number of pretreatment seizures are universally associated with a poorer outcome [1,16,17]. In the Glasgow cohort, high seizure density within a few months of starting AED therapy was a better predictor of subsequent pharmacoresistance [2]. These observations could help explain the poorer prognosis in some localization-related epilepsy syndromes, such as in patients with hippocampal atrophy or cortical dysplasia, where pretreatment seizure frequency and, in particular, seizure density are often high [18–20]. Recently, Sillanpää and Schmidt [21] added seizure clusters to the list of seizure patterns that predict pharmacoresistance. Other clinical factors associated with poor outcome in the Glasgow patients with newly diagnosed epilepsy include family history, febrile convulsions, traumatic brain injury, and psychiatric comorbidity [15]. Interestingly, Kanner and co-workers reported that a lifetime psychiatric history was the sole predictor of disabling seizures in patients with refractory epilepsy failing temporal lobectomy [22]. These two concordant observations of

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different patient populations suggest that the deleterious neurobiological processes underpinning depression and, perhaps, other psychiatric disorders may overlap with those producing pharmacoresistant seizures [23].

Despite these recent advances in identifying the clinical factors associated with pharmacoresistance, their predictive power remains limited. For instance, some patients with hippocampal atrophy will have a good outcome [20], whereas others with the usually drug-responsive juvenile myoclonic epilepsy can prove resistant to all available pharmacological options [24]. These observations imply the presence of other factors influencing drug response beyond those contributing to the etiology of the epilepsy, and genetics has been postulated as one such factor [25]. Genetic factors may also play a role in predicting adverse effects, particularly idiosyncratic reactions [26].

2. Personalized medicine and pharmacogenomics

In the past few years, the discovery of genetic markers of susceptibility to diseases as well as response to medications ("pharmacogenomics") has become one of the fastest growing fields in clinical and translational biomedical research [27]. By leveraging the knowledge of an individual's genetic makeup, it is now possible to predict susceptibility to diseases and response to particular treatments, and match patients with the right medications given at the right doses. Indeed, pharmacogenomics is already making an impact in clinical practice. Notably, regulators, such as the U.S. Food and Drug Administration [28], recognize a growing list of genetic variants as valid biomarkers that should be tested before prescribing certain medications because of their role in predicting drug efficacy or safety (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm). Pharmacogenomics is at the heart of the clinical application of personalized medicine, which extends beyond molecular diagnostics and targeted therapeutics to include application of personalized medical care (e.g., telemedicine, electronic medical records, disease management services) and genomic-based nutrition and wellness services. Although still at an early stage, this strategy is steadily emerging as the new health care paradigm. The U.S. personalized medicine market is estimated at about US$232 billion and is projected to grow by 11% annually, nearly doubling in size by 2015 to more than US$450 billion [29].

3. Pharmacogenomic research in epilepsy: Next steps

The first impact of pharmacogenomics in clinical epileptology was the discovery of HLA-B*1502 as a strong predictor of carbamazepine-induced Stevens–Johnson syndrome (SJS) in people of Chinese and south Asian ancestry [26]. Testing for HLA-B*1502 in at-risk ethnic populations is now recommended by regulators globally, including in the United States, United Kingdom, and Canada. However, little progress has been made in predicting AED efficacy. We believe this is partly because of our inadequate knowledge of the natural history of epilepsy in response to treatment, which has been derived from a plethora of limited data available from an increasing number of databases. Many studies were retrospective and of relatively small sample size and/or short duration. Clarity has been further compromised by the heterogeneity of the epilepsy syndromes with their variable causes and prognoses.

High-quality long-term follow-up studies that identify the patterns of outcome and delineate the different phenotypes are essential for valid pharmacogenomic investigations. What is needed is an ambitious prospective epidemiological study of newly diagnosed epilepsy across all age ranges, countries, and continents, which would provide the template for a global pharmacogenomic project [30]. Possible endpoints of such a study are listed in Table 1. With improved epidemiological documentation must come a better understanding of the biological mechanisms underpinning pharmacoresistance. This is a challenging task as response to and adverse effects of individual drugs reflect the complex multifunctional interplay among acquired and genetic factors and may also vary for different drugs or drug groups with varying mechanisms of action. In the following sections of this article, Dr. Michael Johnson and Dr. Nigel Tan, who are among the most active investigators in the field, will draw from their own research to deliberate the complexities of these issues and propose approaches to addressing them.

Table 1
Variables from a proposed global epidemiological outcome study.

1. Phenotypes and genotypes of patients either seizure free on initial treatment or refractory from the outset
2. Proportion of patients remaining free from seizures for 1, 2, 3, and 5 years on drugs in different mechanistic categories for comparison with nonresponders to the same drugs
3. Time to reach 6 months and 1, 2, 3, and 5 years of remission for each cohort on each antiepileptic drug or mechanistic group
4. Proportion of patients seizure free for at least 1 year but later showing a relapsing/remitting pattern of response
5. Outcome of each epilepsy syndrome for each identified phenotype and genotype
6. Proportion of patients discontinuing each drug or mechanistic group because of inefficacy or side effects
7. Proportion of patients already treated for or developing comorbid psychiatric disorders
8. Mortality from any cause, including suicide and sudden unexpected death in epilepsy

4. Promising Areas of Research and Young Investigators

4.1. Michael Johnson

Epidemiological considerations and statistical approaches to genomic prediction

The prediction of outcome following an intervention requires the development of a multivariable prognostic model which itself entails three research stages [31]. The first stage, and the stage we are currently at in epilepsy, is the stage of "development." Developmental studies aim to identify important predictors (genomic and clinical), assign relative weights to each predictor, and estimate the model's discriminatory performance. The next stage is to validate the model in a data set different from that used in its development, and the final stage is to quantify whether the predictive model has clinical utility using "impact studies." In this section, we consider the epidemiological framework to detect genetic effects on AED response, the potential for genomic information to contribute increased precision to prediction, and the obstacles that will need to be overcome to develop clinically useful tools that inform optimal choice of therapy for the individual person with epilepsy.

4.1.1. Epidemiological framework

4.1.1.1. Defining drug response. Clinical outcome of epilepsy is a composite measure confounded by the joint effects of therapeutic response to medication and the natural history of the disease. For example, several childhood epilepsies may appear drug resistant only to remit in later life [32]. In such cases, cross-sectional measurement of "AED response" shortly after the onset of epilepsy would classify the patient's seizures as "drug resistant," but measurement some years later following spontaneous remission of epilepsy might classify the person's seizures as "drug responsive" (if they were still taking medication), yet that patient's genotype would be unaltered. A similar situation arises in adult epilepsy, where the natural tendency for some types of epilepsy to remit spontaneously over time inflates the estimate of "drug responsiveness" [33,34]. Thus, the category "seizure free" comprises a heterogeneous group of patients with epilepsy, some of whom are seizure free because of a pharmacological response to AEDs (i.e., their seizures are suppressed by medication—"drug responders") and some who are seizure-free because their epilepsy