Genetic variations and response to antiepileptic drug

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Summary

Despite the state-of-the-art medical treatment with antiepileptic drugs (AED), at least one-third of newly diagnosed epilepsy patients may show poor response to AED. Although the biological mechanism of diverse responses to AED is poorly understood, it is likely that multifactorial factors could be responsible for the different responses. Clinical factors such as etiology of epilepsy and pre-treatment seizure frequency can predict the different responses to AED, whereas the role of genetic variations in individuals contributing to variation in response to AED is still conflicting. The inconsistency in proving the genetic roles in different responses to AED may be partly explained by (1) diversity of the definition of response to AED, (2) heterogeneity of the subjects, and (3) lack of multigenetic approach. While we hypothesize that the genetic variations in individuals may independently contribute to different responses to AED, multigenetic interactions including both the genetic variations of pharmacokinetics and pharmacodynamics may take place.
Genetic variations in individuals that may be associated with response to antiepileptic drug

Epilepsy is a prevalent chronic neurological disease affecting at least 50 million people worldwide. The response to antiepileptic drugs (AED) in newly diagnosed epilepsy is different among individuals. Many of the newly diagnosed epilepsy cases show very favorable response to initial AED, whereas at least 1/3 of the newly diagnosed epilepsy patients reveal poor response to their initial AED [1].

Why is the response to AED in individuals so different, even though with the same disease? Although the biological mechanism of diverse responses to AED is poorly understood, it is likely that multifactorial factors could be responsible for the different responses. The clinical factors influencing response to AED is well known but the genetic variations in individuals contributing to the diverse responses to AED are still unclear. From a traditional point of view, one of the useful ways of predicting response to AED is looking at the clinical background of each individual. In clinical practice, choosing AED is dependent on the type of seizures and etiology of epilepsy. Clinical factors such as the etiology of epilepsy and the neurobiology of epilepsy itself may contribute to the different responses to AED. Symptomatic etiology including hippocampal sclerosis is one of the robust clinical factors predicting poor response to AED [2, 3].

Do the genetic variations in individuals result in different responses to AED? There is a possibility that the genetic variations in individuals may be associated with the response to AED independent of clinical factors. The response to AED is dependent on each pharmacological process of AED [4]. AED should be absorbed from the gastrointestinal tract and transported to the brain. Then, the AED has to act on the receptor site in the brain where it works. Slightly different pharmacodynamic and pharmacokinetic functions may result from each pharmacological process that is controlled by genetic variations in individuals [5-9]. Because the genes coding transporters or receptors are polymorphic, genetic variations in individuals may contribute to different responses to AED. If genetic variations in individuals are associated with response to AED, they are multigenetic interactions rather than monogenetic trait. A reasonable approach is to look at the genetic variations such as single nucleotide polymorphism (SNP) in individuals for each pharmacological process of AED.

Genetic variations in individuals that may affect pharmacodynamics

Pharmacodynamics is the mechanism at the receptor site where AED act. To modify the excitability of neurons, AED act selectively on diverse molecular targets so that seizure related firing is blocked without disturbing non-epileptic activity. The pharmacodynamics of AED is based largely through effects on voltage-gated sodium and calcium channels, or by promoting inhibition mediated by γ-aminobutyric acid (GABA) receptors [4].

One study using patch-clamp recordings in human hippocampus showed that the mecha-
nism of action of carbamazepine (CBZ), which is use-dependent block of voltage-dependent sodium channels, is completely lost in CBZ-resistant patients [10]. Decreased AED sensitivity resulting from loss of sodium channel may contribute to a novel mechanism underlying the development of drug resistant epilepsy. Genetic variations of the sodium channel may also be associated with the variation in response to sodium channel blockers such as CBZ and phenytoin (PHT) in individuals. Because the genes coding voltage-sensitive sodium channel type 1, alpha-subunit (SCN1A), are polymorphic, a few studies have researched the association between SNP of SCN1A and the response to AEDs. The original study by Tate et al. [11] successfully showed a positive association between SNP at IVS5-19 G>A and the maximal dose of CBZ or PHT. A subsequent study conducted in Caucasians failed to reproduce the positive association between SNP at IVS5-19 G>A and the maximal dose of CBZ [12]. However, another study conducted in Japanese revealed a positive association between the genetic variation of IVS5-19 G>A and CBZ resistance [13]. In addition, a study has reported a positive association between SNP of SCN2A IVS7-32 G>A and AED resistance in Hong Kong Chinese [14]. Nevertheless, there is as yet no definite evidence suggesting the association between the genetic variation of SCN1A and the different responses to AED.

Other AED targets, where functional polymorphisms could possibly influence the clinical treatment response, are GABA<sub>A</sub> receptors. Nevertheless, there is little association study in human.

Genetic variations in individuals that may affect pharmacokinetics

Before acting on the receptor site in the brain, AED should be absorbed from the gastrointestinal tract and penetrate the brain through the blood-brain barrier (BBB). There are evidences that AEDs are transported by specific proteins. P-glycoprotein (P-gp) is an example of these proteins and the most researched molecule [8, 15-18]. P-gp is an efflux protein that can be found at the capillary endothelium in the BBB. Basically, P-gp is an efflux protein that can pull xenobiotics back from entering the parenchyma of the brain. P-gp plays a physiological role in preventing the brain from incidental intoxication by xenobiotics, but overexpressed P-gp is pathological and an obstacle to treatment resulting in poor response to AED.

To be a candidate factor responsible for different responses to AED in individuals, P-gp should satisfy at least two prerequisites. One is that P-gp should be overexpressed at the epileptic focus, and the other is that P-gp should be a substrate for AED. A few studies consistently showed overexpression of P-gp in brain capillary endothelial cells from patients with drug-resistant epilepsy [19, 20]. On the other hand, studies on whether AEDs are substrates for P-gp yielded conflicting results [16, 21-23]. However, a recent study using concentration equilibrium transport assay has successfully demonstrated that AEDs such as PHT, phenobarbital (PB), lamotrigine (LTG) and levetiracetam are substrates for P-gp [23].
Is genetic variation of the ATP binding cassette B1 gene (ABCB1) that encodes P-gp in individuals responsible for different responses to AEDs? Siddiqui et al. [24] were the first to show that the CC genotype of ABCB1 3435C>T was associated with poor response to AED. However, subsequent studies were controversial regarding the association between the genetic variations of ABCB1 in individuals and the response to AEDs [25-31]. Furthermore, both a prospective study and a study using whole genome approach failed to replicate the original report [32, 33].

Why were these association studies so conflicting? The author believes that the inconsistency in proving the genetic roles in response to AED may be partly explained by (1) diversity of the definition of AED-resistance, (2) heterogeneity of the subject, and (3) lack of multigenetic approach. The definitions of AED resistance were diverse among studies. One study classified patients into poor response group, whereas another study categorized the patients with the same response to AED into good response group [34]. In addition, some previous studies enrolled patients taking AEDs that are not the substrate for P-gp, such as CBZ and valproate [16, 21]. The impact of genetic role in the different responses to AED may be less than that of environmental factors such as clinical factors, and the interaction between multiple genetic variations in individuals may be responsible for the different responses to AED.

Do conflicting results mean that the role of genetic variations of ABCB1 is clinically irrelevant? Basic et al. [35] recently reported very convincing evidence for a positive association between the genetic variations of ABCB1 and response to AED. They studied prospectively whether the ABCB1 3435C>T polymorphism affects the brain uptake of PB in patients with generalized epilepsy on PB monotherapy. While the ABCB1 3435C>T polymorphism did not affect plasma levels of PB, the CC genotype of ABCB1 3435C>T was associated with significantly lower PB levels in cerebrospinal fluid (CSF) and a significantly lower CSF/plasma ratio than the CT or TT genotypes. The study of Basic et al. seems to confirm the association between the CC genotype at ABCB1 3435 and AED resistance originally described by Siddiqui et al. [24].

The author explored the contribution of genetic variations in individuals to LTG response by a multigenetic approach including the genes involved in pharmacokinetics (ABCB1, UGT1A4) and pharmacodynamics (SCN1A) of LTG. Patients carrying the specific diplotype of not only ABCB1 but also SCN1A were significantly associated with LTG response. Furthermore, there was an epistatic interaction; as the number of the risk alleles of ABCB1 or SCN1A increased, the risk of LTG resistance was significantly augmented. The LTG response may be partly associated with the multigenetic interaction between the genes for both ABCB1 and SCN1A.

In conclusion, predicting the response to AED before commencing on AED is not easy, but we can predict the response to AED. Although the biologic mechanism of diverse response to AED is poorly understood, it is likely that multifactorial factors could be re-
sponsible for the variation in response. The impact of genetic role on the varying response to AED may be less than that of environmental factors such as clinical factors, and the interaction between multiple genetic variations in pharmacokinetics and pharmacodynamics may be responsible for the different responses to AED.

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