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Personalizing Approaches in Selecting AEDs

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As other field of medicine the concept of individualized therapy in epilepsy is becoming increasingly important in the treatment of patients with epilepsy, however the predictive markers for disease prognosis and treatment outcome are still limited. As the identification of genetic markers is increasing, we may divide the genetic biomarkers into three parts; 1) for prognosis of the epilepsy syndrome, 2) for the response to medication, and 3) for the risk for side effects for selected AEDs.

Key Words: Pharmacogenetics; Anticonvulsants; Personalized medicine

The identification of valid biomarkers for predicting the outcome of diseases or improvement of drug response, as well as avoidance of side effects is an emerging field of interest in medicine. As other field of medicine the concept of individualized therapy in epilepsy is becoming increasingly important in the treatment of patients with epilepsy, however the predictive markers for disease prognosis and treatment outcome are still limited. Traditionally, the clinical decision process for selection of an antiepileptic drug (AED) is trial and error fashion predominately based on the patient's epileptic syndrome and side effect profiles of the AEDs. Although standard dosages of AEDs are used, the response of an individual patient to a specific AED is generally unpredictable. Furthermore, there are only few clues to predict the occurrence of side effects from AEDs on clinical background. Therefore, there is an urgent need for valid predictive biomarkers to guide patient-tailored individualized treatment strategies in epilepsy. As the identification of genetic markers is increasing, we may divide the genetic biomarkers into three parts; 1) for prognosis of the epilepsy syndrome, 2) for the response to medication, and 3) for the risk for side effects for selected AEDs. Although an increasing number of cases with epileptic encephalopathy with mutations of KCNQ2 has been described, the identification of a mutation in KCNQ2 or KCNQ3 in the case of benign familial neonate/infantile seizures is associated with a positive prognosis. The identification of a mutation in PRRT2 indicates a good prognosis with normal psychomotor development and mostly seizure freedom without medication in the long term. Hence, the identification of biomarkers can help to predict outcome in the benign familial epilepsies of childhood. SCN1A is the gene with the most frequent mutations in epilepsy published to date, comprising a large spectrum of epilepsy phenotypes. At the benign end of the spectrum, patients with generalized epilepsy with febrile seizures plus (GEFS+) and even simple familial febrile seizures have been described. Whereas point mutations in SCN1A are found in GEFS+ families, many of the severe myoclonic epilepsy of infancy (SMEI) carry de novo nonsense muta-

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tions predicting truncated proteins without function. Concerning clinical management and prognosis, truncating or other deleterious mutations in SCN1A serve as biomarkers to predict an unfavorable prognosis and a bad response to sodium channel blockers. The prediction of AED efficacy is particularly important for approximately 30 % of pharmacoresistant patients who do not respond to the first or second AED. About 15 % of pharmacoresistant patients become seizure-free after responding to the third, fourth, or later AED that is tried in the course of systematic treatment. To predict such late responses, genetic biomarkers would avoid long periods of trial and error until the right drug is found. Among the different drug efflux transporters, MDR1 [P-glycoprotein (Pgp)], which is encoded by the ABCB1 gene, is the best characterized. The first study, in 2003, suggested that the 3435C 〉 T polymorphism of ABCB1 gene may explain resistance to AED therapy in epilepsy, but several other association studies, as well as meta-analyses, have clearly demonstrated that the impact ofABCB1genetics on the pharmacoresistance of AEDs is inconsistent. The clinical relevance, however, is still controversial as some studies have shown a positive and some a negative association between ABCB1 variants and response to AEDs. However, the concept that Pgp expression and function may be directly associated with pharmacoresistant temporal lobe epilepsy in patients has been very recently corroborated by a highly attractive approach investigating Pgp activity in patients with epilepsy using positron emission tomography technology. Most of the AEDs are metabolized hepatically, and several phase 1 and 2 drug-metabolizing enzymes are involved. In particular, cytochrome P450 (CYPs) enzymes are of interest as several genetic variants in CYP isozymes have been identified in the past, substantially altering enzyme expression and function with clinical consequences. Phenytoin (PHT) is predominantly metabolized by CYP2C9 and, to a lesser extent, by CYP2C19. Loss-of-function polymorphisms in both of these liver enzymes result in impaired PHT metabolism and, consequently, to elevated plasma levels of PHT. Poor metabolizers who are carrying homozygous loss-of-function variants are particularly at risk for the development of side effects as PHT is a drug with a narrow therapeutic window. Severe allergic skin reactions, such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can appear upon treatment with carbamazepine (CBZ). The human leucocyte antigen (HLA) allele HLA-B*1502 is strongly associated with SJS or TEN upon CBZ therapy in the Chinese population. HLA-B*1502 does not seem to be a predictive marker for CBZ-induced skin reactions in the Korean and Japanese populations, while HLA-B*1511 is a predictor in these Asian subgroups. In a prospective study with more than 4000 patients considered for treatment with CBZ in Taiwan it was shown that genetic testing completely prevents SJS and TEN when all patients carrying the HLA-B* 1502 allele (7.7 %) are treated with other AEDs. In the European population, an association of HLA-A*3101 was found for all hypersensitivity syndromes with CBZ treatment.

References

1. Biervert C, Schroeder BC, Kubisch C, et al. A potassium channel mutation in neonatal human epilepsy. Science 1998;279:403-406.
2. Weckhuysen S, Mandelstam S, Suls A, et al. KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. Ann Neurol 2012;7:15-25.
3. Heron SE, Ong YS, Yendle SC, et al. Mutations in PRRT2 are not a common cause of infantile epileptic encephalopathies. Epilepsia 2013;54:e86-89.
4. Gambardella A, Marini C. Clinical spectrum of SCN1A mutations. Epilepsia 2009;50(Suppl. 5):20-23.
5. Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet 2000;356:1638-1642.
6. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069-1077.
7. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Ann Neurol 2007;62:375-381.
8. Löscher W, Klotz U, Zimprich F, Schmidt D. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia 2009;50:1-23.
9. Siddiqui A, Kerb R, Weale ME, et al. Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. N Engl J Med 2003;348: 1442-1448.
10. Haerian BS, Roslan H, Raymond AA, et al. ABCB1 C3435T

polymorphism and the risk of resistance to antiepileptic drugs in epilepsy: a systematic review and meta-analysis. Seizure 2010;19:339-346.
11. Feldmann M, Asselin MC, Liu J, et al. P-glycoprotein expression and function in patients with temporal lobe epilepsy: a case-control study. Lancet Neurol 2013;12:777-785.
12. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther 2013;138:103-141.
13. Hung CC, Huang HC, Gao YH, et al. Effects of polymorphisms in six candidate genes on phenytoin maintenance therapy in Han Chinese patients. Pharmacogenomics 2012;13:1339-1349.
14. Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics 2006;16:297-306.
15. Kim SH, Lee KW, Song WJ, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. Epilepsy Res 2011;97:190-197.
16. Kaniwa N, Saito Y, Aihara M, et al. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. Epilepsia 2010 ;51:2461-2465.
17. Chen P, Lin JJ, Lu CS, et al. Taiwan SJS Consortium, Carbamazineinduced toxic effects and HLA-B*1502 screenin gin Taiwan, N Engl J Med 2011;346:1126-1133.
18. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med 2011;364:1134-1143.