Genetic determinants of severe cutaneous adverse reactions associated with the use of antiepileptic drugs in Asian population

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Abstract

Severe cutaneous adverse reactions (SCARs) are a type of delayed hypersensitivity reaction to drugs that is idiosyncratic, unpredictable and dose independent. Common drugs causing SCARs include antiepileptic drugs (AEDs), particularly carbamazepine (CBZ), phenytoin (PHT) and lamotrigine (LGT). Recent advances in pharmacogenetic studies demonstrated that genetic factors have contributed to these SCARs, most significantly the specific alleles of human leukocyte antigen (HLA) genes. Apart from this HLA genes, polymorphisms in genes encoding for drug transporter proteins (e.g. P-glycoproteins) and drug-metabolizing enzymes might also play a role in the risk of SCARs associated with antiepileptic use. However, the associations vary between different ethnic populations. This review summarizes the literature on the associations between AED-induced SCARs and these genetic variations in Asian population. Studies have shown a strong association between CBZ-induced SCARs with HLA-B*15:02 allele among Han Chinese and was subsequently replicated in other populations in Southeast Asia including Thai, Malays, Indians, Vietnamese, Indonesian populations. Other HLA alleles found to increase the risk of SCARs with the use of AEDs include HLA-A*31:01 and HLA-B*15:11 alleles in Japanese, Koreans and Han Chinese populations, HLA- B∗15:08 among the Indians and HLA-B*15:13 among the Malays. For *ABCB1* gene, patients with single nucleotide polymorphisms *C3435T* and *G2677T/A* were found to have a low plasma level of CBZ and PHT, which may affect the susceptibility to develop SCARs. Two of the CYP2C19 polymorphic alleles, CYP2C19*2 and CYP2C19*3, were identified to be relevant in the changes in drug metabolism among patients treated with CBZ and PHT. It is shown that CYP2C19*2 variant increases the likelihood to develop SCAR as compared to wild type. In conclusion, variations in HLA alleles, P-glycoprotein and CYP2C19 are potential biomarkers for SCARs among Asian patients taking AEDs.

Keywords: HLA, cutaneous adverse drug reaction, SCAR, antiepileptics