Genetic Susceptibility and Pharmacogenomics of Cutaneous Adverse Drug Reactions

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Adverse drug reactions (ADRs) account for 6-7 % of all hospital admissions and remain a major clinical problem. Cutaneous adverse drug reactions (cADRs) are ADRs primarily involve skin, ranging from mild maculopapular eruption (MPE), with increasing severity, to hypersensitivity syndrome (HSS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The latter still carries 30% mortality rate. SJS/TEN can be caused by over 100 drugs; in Taiwan the incidence is estimated to be 8 cases per million person-years and the most common offending drugs are carbamazepine (CBZ), followed by phenytoin (PHT) and allopurinol. The genetic factors that determine susceptibility of various cADRs are unclear in most cases. MALDI-TOF mass spectrometry was used to screen more than 1,000 single nucleotide polymorphisms in genes related to drug metabolism and immune response, followed by sequence-based typing of the HLA loci A, B, C, and DRB1, using a case control association study design. We found striking associations of HLA-B alleles with severe cADRs induced by CBZ and allopurinol; specifically, HLA-B*1502 was strongly associated with CBZ-SJS/TEN ($p=1.06 \times 10^{-36}$, odds ratio 2286), HLA-B*5801 was associated with HSS/SJS/TEN induced by allopurinol ($p=1.22 \times 10^{-29}$, odds ratio 580.3) *(Nature 428:486, 2004, PNAS 102: 4134, 2005)*. PHT, which has a chemical structure resembling CBZ, when causing SJS/TEN, was also associated with HLA-B*1502, ($p<0.001$, odds ratio: 7.1), despite a weaker association when compared to CBZ-SJS/TEN. The CBZ-MPE/HSS, however, was not associated with HLA-B; instead MPE was associated with HLA*3101 and HSS with SNPs in the motilin gene located terminal to the MHC class II genes *(Pharmacogenetics & Genomics, 16:297, 2006)*. Our results indicated that genetic susceptibility to drug-induced cADRs is both drug-specific and to some extent phenotype-specific. Global gene expression profiles of the blister fluid cells from SJS/TEN patients revealed more than 200 differentially expressed genes, including genes involved in the granule-mediated cytotoxicity. These genetic markers have potential to be used for further development of tests to identify individuals at risk for these drug-related life-threatening conditions, as well as for an increased understanding of the pathogenesis of these clinical syndromes (*Personalized Med.* 2:225, 2005).