class I and class II, function in complement, hormone and intracellular peptide processing.

The hypersensitivity reactions of an antiretroviral drug, abacavir, had been extensively studied and its association to the HLA-B*5701 allele in Caucasians have been strongly implicated with odds ratios 117, negative predictive value more than 90% in every ethnic studies, but highly variable positive predictive value due to variability of HLA-B*5701 allele frequencies in each population. (Mallal et al., Lancet 2002; Hetherington et al., Lancet 2002; Martin et al., Proc Natl Acad Sci 2004).

Association study in hypersensitivity to nevirapine by Martin et al had reported that HLA-DRB1*0101 in patient with high CD4 level may determine susceptibility to nevirapine hepatitis with 40% positive predictive value and 96% negative predictive value (Martin et al., AIDS 2005). However this result had never been confirmed and no single HLA allele were associated with cutaneous adverse reactions from nevirapine in the study.

SUMMARY OF INVENTION

The present disclosure~~invention~~ provides a method of predicting the risk of a patient for developing cutaneous adverse drug reactions induced by NNRTIs. It was discovered that an HLA-B allele, HLA-B*3505 and/or variations on CCHCR1 gene are associated with skin rash that is induced by non nucleoside reverse transcriptase inhibitors such as nevirapine.

Accordingly, the present application provides a method of assessing the risk of a patient for developing a cutaneous adverse drug reaction

comprising maculopapular (MP), erythema multiforme (EM), urticaria, angioedema, fixed drug eruption, Steven Johnson's Syndrome (SJS) and Toxic Epidermal Necrosis (TEN) induced by NNRTIs such as nevirapine. The present application provides a method of screening the risk of a patient for developing a cutaneous adverse drug reaction in response to a drug, comprising performing genotyping of an allele HLA-B*3505 or variations on gene CCHCR1 using a biological sample from the patient. Patients with HLA-B*3505 and/or variations on CCHCR1 gene are at risk of development of cutaneous adverse drug reaction from NNRTIs such as nevirapine. Avoidance of nevirapine in these patients is preferable. HLA-B*3505 and/or variations on CCHCR1 are important for understanding the pathogenesis of cutaneous adverse drug reaction in Thais HIV infected patients. The HLA-B*3505 allele and/or variations on CCHCR1 are supposed to be important in other population where these alleles presented.

In one aspect, there is provided a method of assessing the risk of a patient for developing a cutaneous adverse reaction to non-nucleoside reverse transcriptase inhibitor such as nevirapine by using HLA- B * 3505 allele wherein the presence of HLA-B*3505 allele is indicative of a risk for a cutaneous adverse drug reaction to nevirapine.

Specifically, one embodiment~~aspect~~ of the present disclosure~~invention~~ provides a method of assessing the risk of a patient for the developing a cutaneous adverse drug reaction in response to a drug, comprising determining the presence of HLA-B*3505 alleles by determination of Deoxyribonucleic acid (DNA) or Ribonucleic acid(RNA) or protein or by mean of molecules interacting with HLA-B. The allele and genetic markers can be detected by using any method known in the art. For example, the presence of the allele can be determined by using an oligonucleotide that specifically hybridizes with the nucleic acid coding for the allele. The genetic markers can be selected from the group of genetic marker of the variations consisting of rs1140412, rs4997054, rs9461684, rs3179865 and rs707912, which is the proxy of HLA-B*3505.

The presence of the allele of interest can also be determined by detecting an equivalent genetic marker of the allele, which is a genetic marker that is in linkage disequilibrium to the allele. An equivalent genetic marker can be, e.g., an SNP (single nucleotide polymorphism), microsatellite marker or any genetic polymorphisms. For example, the markers of HLA-B*3505 allele haplotype include, without being limited to, rs1140412, rs4997054, rs9461684, rs3179865 and rs707912. In other words, the presence of the rs1140412, rs4997054, rs9461684, rs3179865 and rs707912.haplotye, rather than the alleles *per se*, is indicative of a risk for cutaneous adverse drug reactions.

One embodiment~~aspect~~ of the present disclosure~~invention~~ provides a method of assessing the risk of a patient for the developing a cutaneous adverse drug reaction in response to a drug, comprising determining the presence of variation in CCHCR1 gene by determination of Deoxyribonucleic acid (DNA) or Ribonucleic acid(RNA) or protein or by mean of molecules interacting with HLA-B. The allele and genetic markers can be detected by using any method known in the art. For example, the presence of the allele can be determined by using an oligonucleotide that specifically hybridizes with the nucleic acid coding for the allele. The genetic markers can be selected from the group of genetic marker of the variations consisting of rs746647and rs1265112, of which is indicative of a risk for cutaneous adverse drug reactions.

The presence of the allele of interest can also be determined by detecting an equivalent genetic marker of the allele, which is a genetic marker that is in linkage disequilibrium to the allele. An equivalent genetic marker can be, e.g., an SNP (single nucleotide polymorphism), microsatellite

marker or any genetic polymorphisms. For example, the markers of at risk CCHCR1 allele and haplotype include, without being limited to, rs746647and rs1265112. In other words, the presence of the rs746647 and rs1265112, rather than the alleles *per se*, is indicative of a risk for cutaneous adverse drug reactions.

One embodiment~~aspect~~ of the present disclosure~~invention~~ provides a method of assessing the risk of a patient for the developing a cutaneous adverse drug reaction in response to a drug, such as nevirapine. The cutaneous adverse drug reaction comprised of maculopapular (MP), erythema multiforme (EM), urticaria, angioedema, fixed drug eruption, Steven Johnson's Syndrome (SJS) and Toxic Epidermal Necrosis (TEN). HLA-B*3505 or variations in CCHCR1 or variations in TCF19 or variations in POLR3G or rs9461681 or rs6545803 is indicative of nevirapine induced cutaneous adverse drug reaction.

Further provided is a method of screening and/or identifying medicines that can be used to treat drug-induced cutaneous adverse drug reactions by determining the presence of HLA-B*allele and/or variation in CCHCR1, TCF19, POLR3G gene as a target in drug development. For example, cells expression any of the alleles or genes can be contacted with medicine candidates, and the candidates that binds to the allele are likely to inhibit the function of the allele. The efficacy of the allele-binding candidate in treating drug induced reactions can then be further tested.

BRIEF DESCRIPTION OF DRAWINGS

7. The method of any of claims 14 wherein the presence of the allele is determined by using DNA prepared from the peripheral blood of the patient.

8. The method of any of claims 1-4 wherein the presence of the allele is determined by using RNA, protein, cells or any biomolecular products prepared from the peripheral blood of the patient.

9. The method of any of claims 1-3 wherein the presence of non nucleoside reverse transcriptase inhibitors is comprised of nevirapine, efavirenz and delavirdine.