Background: Multiple class I and II HLA associations have been described in association with nevirapine (NVP) hypersensitivity reaction (HSR) phenotype. We hypothesized that the peptide binding (PB) properties may be shared across alleles within the HLA-A or -B loci.

Methodology: HLA-A, B, C DR typing was performed on stored DNA from a retrospective case control analysis of NVP-related HSR (P<0.05) using the Roche 454 FLX platform. Universals and multivariates analyses stratified by race were performed according to HLA class III alleles, HLA superotypes and HLA alleles according to PB. Kir ligands were used for peptide binding predictions. A haplotype of significant importance was identified using HLA-A*02:07 and HLA-B*57:01 binding to NVP was performed with the highest ranked candidate.

Results: PB analysis revealed to four-digit (20mers, 80mers) and triplet (10mers) motifs were shared among alleles within the HLA-A or -B loci. PB analysis identified a top association with NVP cutaneous HSR among populations of African, Asian and European descent.

Conclusions: NVP is a non-nucleoside reverse transcriptase inhibitor (NNRTI) associated with a hypersensitivity syndrome (HSR) in approximately 5% of patients who begin therapy and is characterized by any combination of fever, rash, hepatitis or cutaneous reaction. HLA is the limiting treatment toxicity of NVP which is otherwise well tolerated without known short or long-term CNS, metabolic or renal toxicities. The evidence from human and animal models is that NVP HSR is dependent on both CD4 and CCR5 T cell responses. NVP HSR has been associated with Class I and Class II alleles that appear to be either phenotype and ethnicity specific. Eg. HLA-DRB1*01:01 with rash-associated hepatitis in Caucasians or HLA-B*35:09 with rash in Asian populations.

We did an extensive analysis to look at peptide binding properties of HLA alleles associated with risk of various NVP cutaneous HSR. With our hypotheses control has been to test the hypothesis that peptide binding properties may be shared amongst different HLA risk alleles and explain in part the apparent complexity of these associations across different ethnicities.

Patients samples were taken from a case control analysis of NVP HSR (ClinicalTrials.gov NCT01303104). Tolerant cases had NVP for 18 weeks, while NVP HSR was defined as those who experienced cutaneous or hepatitis toxicity above the median value.

NVP HSR was associated with Class I and II alleles that appear to be either phenotype and ethnicity specific. Eg. HLA-DRB1*01:01 with rash-associated hepatitis in Caucasians or HLA-B*35:09 with rash in Asian populations. HLA is the limiting treatment toxicity of NVP which is otherwise well tolerated without known short or long-term CNS, metabolic or renal toxicities. The evidence from human and animal models is that NVP HSR is dependent on both CD4 and CCR5 T cell responses. NVP HSR has been associated with Class I and Class II alleles that appear to be either phenotype and ethnicity specific. Eg. HLA-DRB1*01:01 with rash-associated hepatitis in Caucasians or HLA-B*35:09 with rash in Asian populations.

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