

Scientific Report:

Association of HLA with predisposition to nevirapine hypersensitivity

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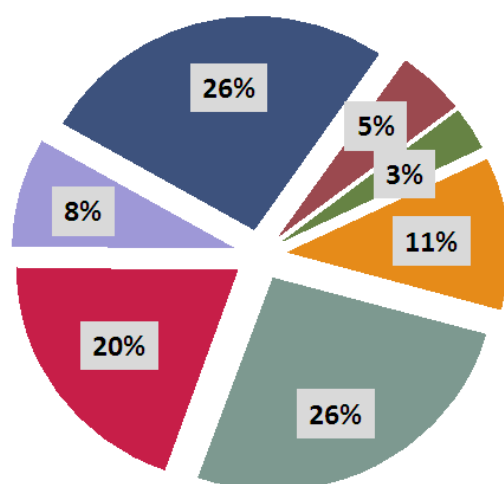
1. Study aims

Up to one third of patients treated with nevirapine experience a rash and around 1% develop serious reactions including Stevens-Johnson and Lyell-syndromes (1). Although a genetic predisposition to nevirapine hypersensitivity reactions (NVP-HSR) has been suspected, no genetic variants have been consistently associated with the disease. Because a previous report suggested an association with a specific HLA Type II allele (*HLA DRB1*0101*) (2), we assessed the association of HLA alleles with NVP-HSR in 61 study participants.

2. Results

We first evaluated the clinical phenotypes. The clinical information was extracted from patient charts using a structured questionnaire. We evaluated 61 individuals who had stopped NVP due to presumed HSR according to the SHCS database. Thirty-eight (62%) participants were male, the median age was 44 years. The clinical evaluation revealed that the syndrome *NVP-HSR* is characterised by multiple, partially overlapping clinical phenotypes (Figure).

Clinical phenotypes in 61 individuals who stopped NVP due to presumed HSR in the SHCS



The most common phenotypes in patients who had stopped NVP due to presumed HSR were rash and fever (26%) and a rash without further symptoms (26%). A severe rash (grade 3) occurred in 11% of these patients. In 20% of cases, there was insufficient information for a reliable classification. Taken together, there was a broad spectrum of clinical phenotypes summarized with the label NVP-HSR. The clinical picture reached from mild rashes to severe, life-threatening Stevens-Johnson syndromes. Even the most common clinical phenotypes occurred in only 16 individuals.

We next performed sequenced-based HLA typing in all study participants and compared the allele frequencies with SHCS participants who tolerated NVP for more than 6 weeks. Neither HLA-class I nor class II alleles were significantly associated with NVP-HSR. Because of the low numbers of clinical phenotypes, it remained unclear whether this negative result was due to insufficient statistical power, or because genetic variants outside the MHC region determine NVP-HSR.

To date, there were no reports that convincingly identified genetic variants associated with NVP-HSR. This points to more complex genetic determinants of NVP-HSR compared to the mono-genetic trait of abacavir hypersensitivity reactions. It is therefore very probable that only very large studies could reveal whether genetic variants play a major role in the pathogenesis of NVP-HSR. As our study was clearly underpowered to assess this issue, we decided to not pursue the investigations further. If promising candidate genes are identified in the future, we will reconsider a genetic association analysis based on the clinical phenotypes defined in this study.

Reference List

1. R. B. Pollard, P. Robinson, K. Dransfield, *Clin. Ther.* 20, 1071 (1998).
2. A. M. Martin *et al.*, *AIDS* 19, 97 (2005).