Carriage of HLA-B*5701 and a Haplotype Hsp70-Hom Variant is Associated with a Class I MHC-Restricted Hypersensitivity Response to Abacavir

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Background
Sustainability is a clinically significant drug hypersensitivity syndrome associated with abacavir use has a significant component. We have shown that the presence of HLA-B*5701 strongly predicts abacavir hypersensitivity (ABC HSR), particularly in combination with other allele markers specific to the 7.1 ancestral haplotype (AH), and identified a potential susceptibility locus within a 300kbp region between MEGCG and C4G loci in the central MHC. Here we used fine recombinant haplotype mapping to identify the susceptibility locus.

Methods
248 consecutive abacavir-exposed individuals were studied, representing full ascertainment of abacavir use in the Western Australian HIV Cohort study. 18 cases of definite ABC HSR and 230 controls were identified, utilizing an updated clinical classification that included correlative clinical and patch test patients. Patients were typed for genetic markers using standard molecular techniques. Immunofluorescence measurement of TNF (green) and immunohistochemical localization of HLA-B and HLA-A/B (red) were undertaken on abacavir exposed ex vivo lymphocytes to examine ABC HSR. 11.7% of controls (OR 6.9, p=0.0001). A haplotype non-synonymous polymorphism of Hsp70-Hom (HspM57, M493T) was found in combination with HLA-B*5701 in 94.4% of hypersensitive cases and 22.2% of controls (OR 31.6, p<0.0001).

RESULTS
Exposure to abacavir is accompanied by a rare and sometimes lethal hypersensitivity reaction that typically involves multiple organs and rapid and more severe recurrence on re-exposure. The positive predictive value of the presence of each of the risk markers was 17.6% for HLA-B*5701 and 18% for Hsp70-Hom M493T. Individuals with ABC HSR exhibited a significantly higher proportion of monocytes expressing TNF in response to abacavir stimulation, which was abrogated on depletion of CD8+ T cells from whole blood.

Conclusions
These data indicate that the presence of HLA-B*5701 and Hsp70-Hom M493T are predisposing factors in the development of ABC HSR, and implicate them in the generation of a Class I-restricted pathogenic immune response.

REFERENCES