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Poster presentation

P08-06 LB. A genome-wide association study of host genetic determinants of T cell responses to the MRKAd5 HIV-1 gag/pol/nef vaccine in the STEP trial

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Background

HIV-1 specific T cell responses induced by the MRKAd5 HIV-1 gag/pol/nef vaccine are highly variable, and human genetic variation is likely to play a role in the inter-individual differences. Contemporary genomic analyses make it possible to comprehensively assess associations of common genetic variants with phenotypes. We here combine whole-genome genotyping and HLA Class I typing results to provide a global survey of the host mechanisms associated with variability in T cell responses to the vaccine.

Methods

All male vaccinees who were HIV seronegative 4 weeks after the 2nd vaccination (week 8) were included. Genotyping data were obtained using Human 1 M BeadChips. IFN-γ ELISpot assays using Gag, Pol and Nef peptide pools were run on PBMCs collected at week 8. Positive responses were analyzed in regression models including age and eigenstrat values as covariates. Only Gag responses and the sum of Gag/Pol/Nef responses were considered, because preliminary data indicate that those measures may associate with HIV viral load in infected vaccinees.

Results

792 individuals had complete results. No genetic variant reached genome-wide significance. However, the strongest determinants of Gag responses (p = 1E-06) were observed in the MHC region. We therefore also tested individual HLA alleles: B*2705, B*5101 and B*5701 associated with higher Gag responses, whereas B*0801 and B*4501 associated with lower responses. Together, these HLA alleles accounted for 13.6% of the observed variability. Nested regression models demonstrated that they can explain most of the association signals detected in the genome-wide scan.

Conclusion

Genetic variants located in the MHC region strongly associate with Gag responses in individuals vaccinated in the STEP trial. HLA-B alleles known to associate with differences in HIV-1 control are essential contributors to the observed signal. This suggests that the host genetic background modulates individual responses to T cell vaccines and should be considered in the design and analysis of future studies.