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In-depth characterization of a hallmark for balancing selection: HLA heterozygote advantage against HIV-1

A hallmark for balancing selection in humans is the heterozygote advantage at genes of the Human Leukocyte Antigen (HLA), resulting in improved HIV-1 control. However, the actual mechanism through which heterozygotes obtain an advantage is still elusive. It may be conferred by the ability of HLA heterozygotes to present a broader array of viral peptides to immune cells, possibly resulting in more efficient cytotoxic T cell response. Heterozygosity may also simply increase the chance to carry the most protective HLA variants, as individual HLA alleles are known to differ substantially in their effect on HIV-1 control. Here we take advantage of available HLA genotype and set point viral load data from 6,311 HIV-1 patients of European ancestry and find a lower viral load for heterozygotes only at HLA-B ($P < 0.001$) and HLA-C ($P = 0.022$). Screening the entire HIV-1 proteome, we observed that patients heterozygous at HLA-B and HLA-C are predicted to bind a broader array of HIV-1 epitopes ($P < 0.001$ for both loci). Interestingly, a patient's viral load was negatively correlated with the breadth of HIV-1 epitopes bound by patient's HLA-B (tau = -0.15, $P <$ 10-16), but not for HLA-C (tau = 0.01, $P = 0.09$) alleles, suggesting that heterozygote advantage at HLA-B is mediated by a quantitative cytotoxic T cell response and a different mechanism could be involved at HLA-C. We also analyzed autologous HIV-1 sequence data and observed a significantly higher divergence of HIV-1 strains among HLA-B heterozygous patients compared to homozygotes, suggesting stronger evolutionary pressure from HLA heterozygosity.