Identifying causal variation in studies of disease associations with MHC genes

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Workshop on SJS/TEN

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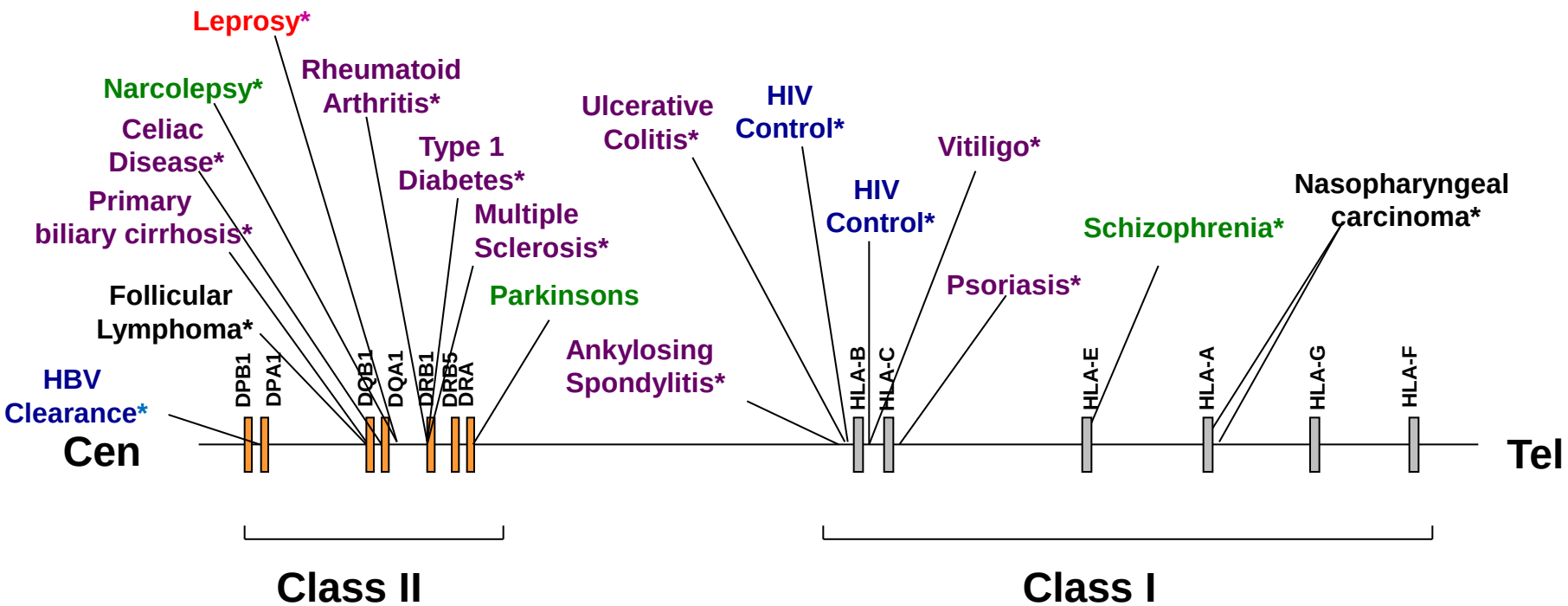
The human MHC: epicenter of disease association as determined by GWAS



Autoimmune
Cancer
Viral
Bacterial
Others

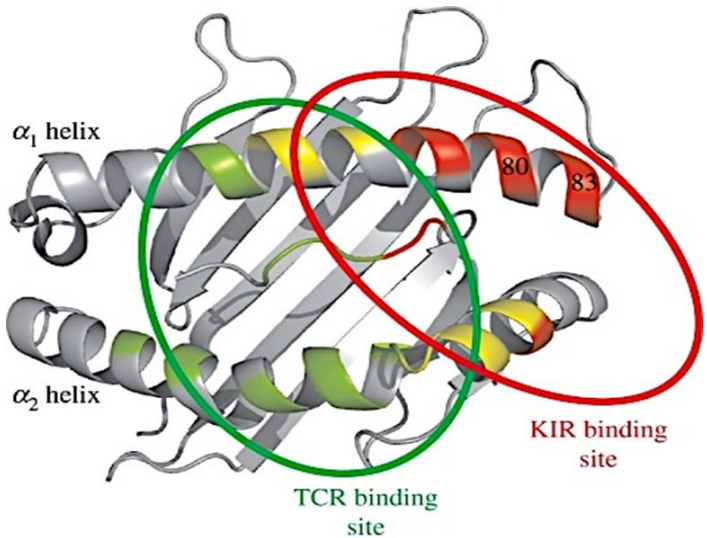
* Top Hit

HLA variation influences disease in a multifaceted manner through both acquired and innate immunity

Individual allelic effects

Trans-eQTL for unlinked genes

Diversity of HLA function



Expression levels modify allelic responses in acquired immunity

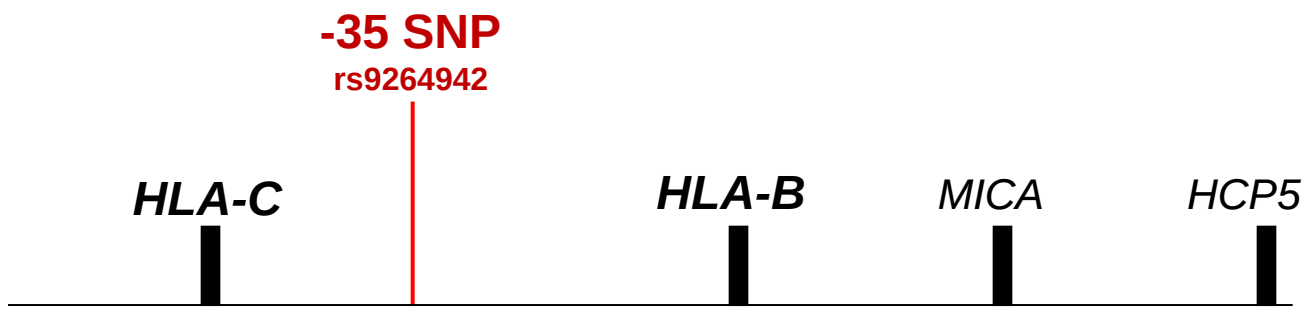
Allotype-specific binding to LILRB and KIR on leukocytes

HLA-B shows the strongest allelic associations with HIV control (relative to HLA-A and –C alleles)

HLA-B*57 protection
HLA-B*27 protection
HLA-B*35(Px) susceptibility

The strong allelic effects of HLA-B alleles on HIV control and the close location of HLA-B to HLA-C make it difficult to determine whether there are true effects of HLA-C variation on HIV control.

-35 promoter region SNP upstream of *HLA-C* associates with VL setpoint



31300K **31541K**

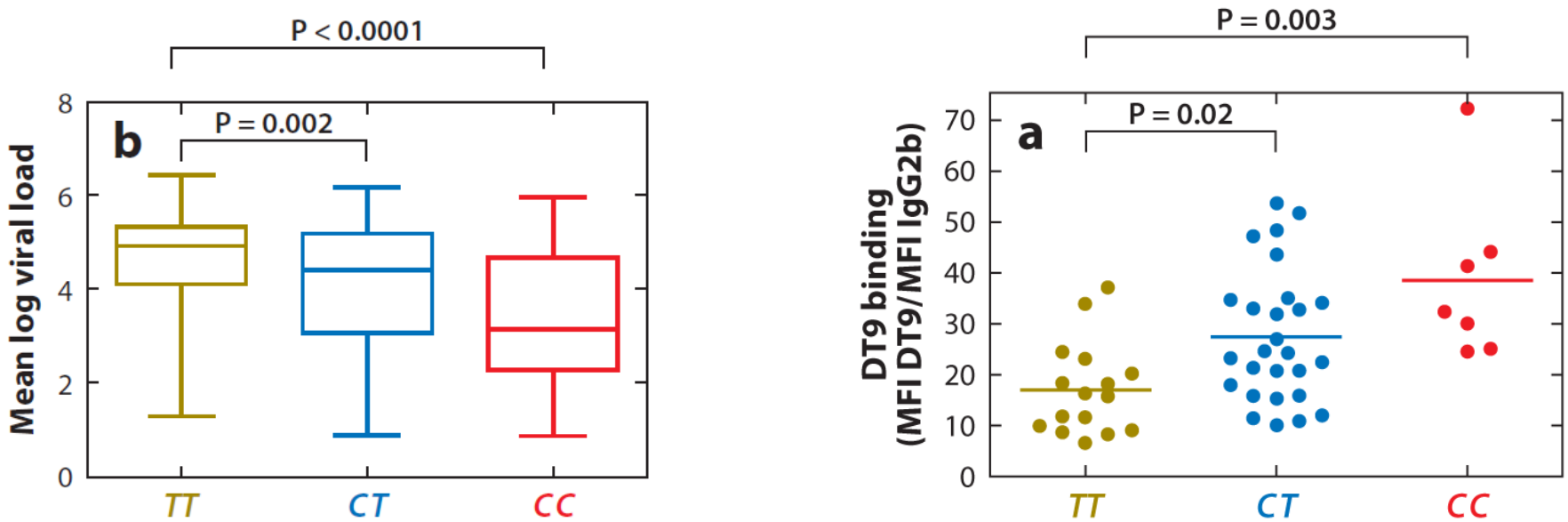
Chromosome 6

-35	
C	protective
T	susceptible

Fellay et al., *Science*, 2007

HLA-B and HLA-C map 150Kb from one another

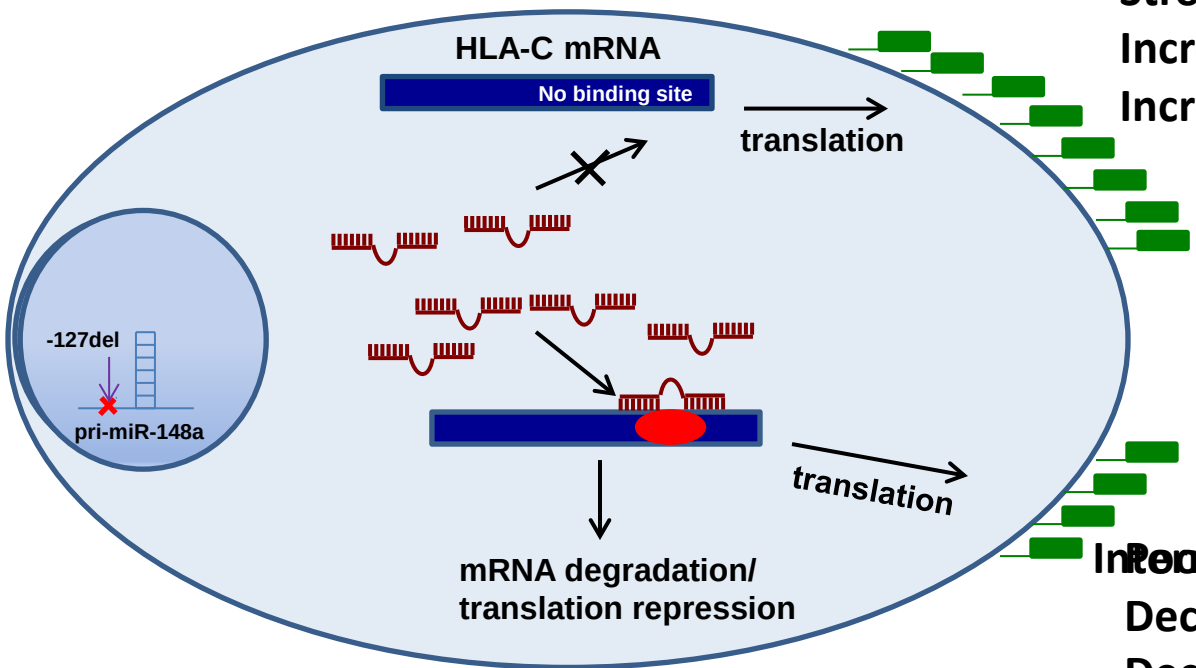
-35 correlates with VL and HLA-C expression levels in whites, but not blacks



The -35 SNP is unlikely to be "causal" for an effect on HIV control and for differential expression of HLA-C. What are the causal variants?

Thomas et al. Nature Genetics 2009

Variants at the unlinked loci, HLA-C and miR-148a, interact in disease pathogenesis, eliminating the possibility that their effect on HIV control is due to the neighboring HLA-B gene



Strong HIV control
Increased risk of Crohn's
Increase risk of GVHD

Intermediate control
Decreased risk of Crohn's
Decreased risk of GVHD

HLA-C

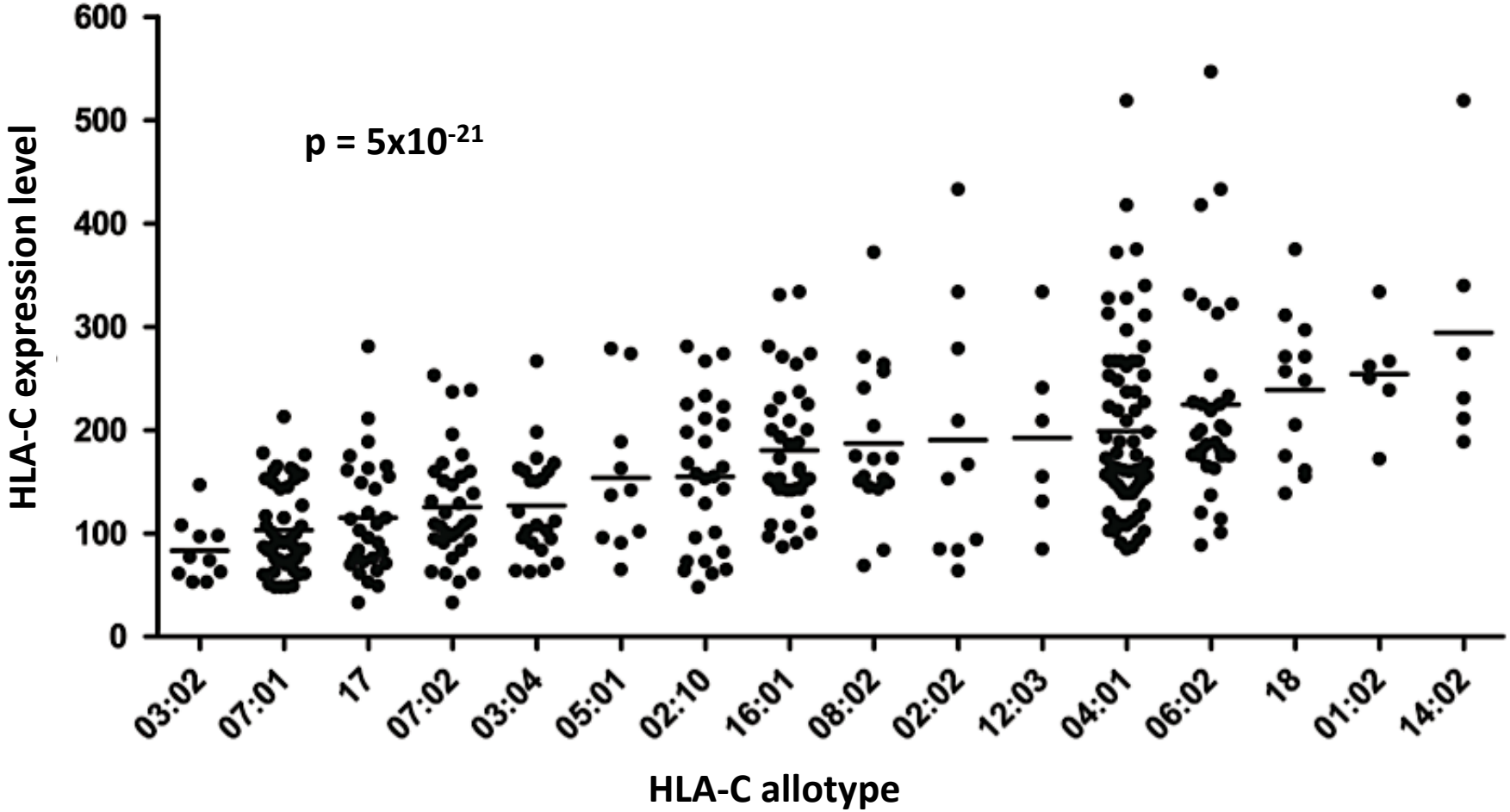
mature miR-148a

HLA-B alleles are fixed for the escape variant and there is no effect of miR-148a on HLA-B expression.

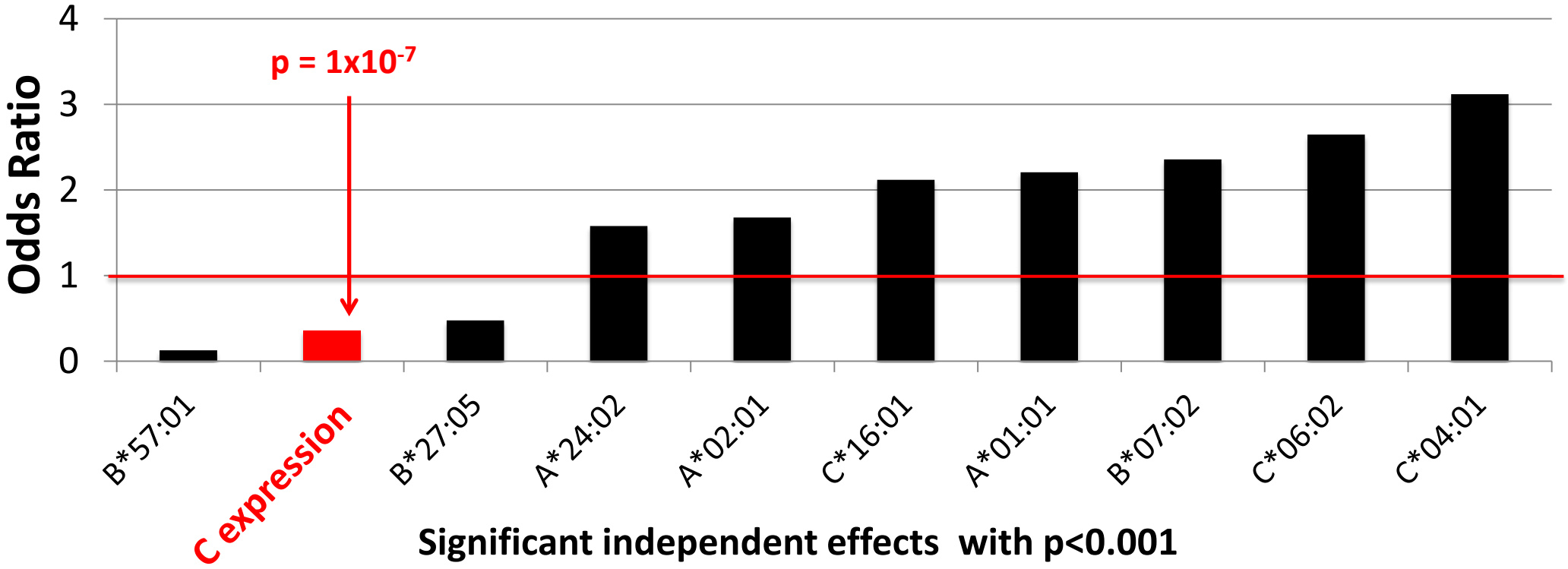
Kulkarni et al, Nature, 2011
Kulkarni et al, PNAS, 2013

- **The -35 SNP associated with HIV control in GWAS in whites, not blacks, and this SNP also associates with HLA-C expression in whites, not blacks (-35 SNP effect is inconsistent across populations, so this SNP is unlikely to be causal).**
- **Variation in the 3' UTR of HLA-C (in LD with -35 in whites) that determines miRNA regulation affects HLA-C expression levels and associates with HIV control in whites among those with HLA-C alleles that are regulated by the miRNA.**
- **A variant in the miRNA gene interacts with the 3'UTR variant of HLA-C in HIV control. This strengthens the "causal" effect of the HLA-C 3'UTR variant in HIV control and rules out the possibility that the association is simply marking an effect of the closely mapping HLA-B locus, as no HLA-B allele binds the miRNA.**

HLA-C allotypes are expressed at differing levels on the cell surface in an allotype-dependent manner and the 3'UTR variant cannot completely account for this differential expression



Higher HLA-C expression associates with better HIV control in EA (n=2527)



Confirmation across independent cohorts, differing outcomes:

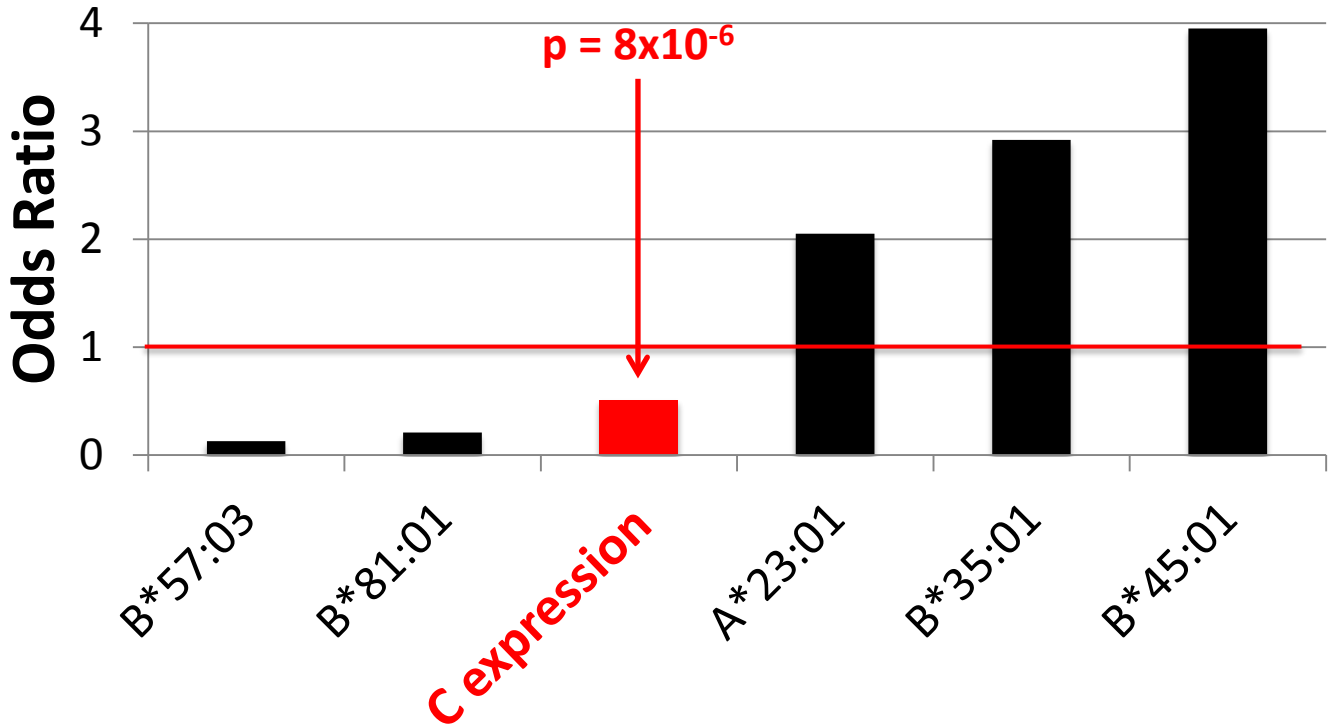
Viral load in chronic infection

Viral load at set point

Time for progression to AIDS

224 unit change; C07 vs C06

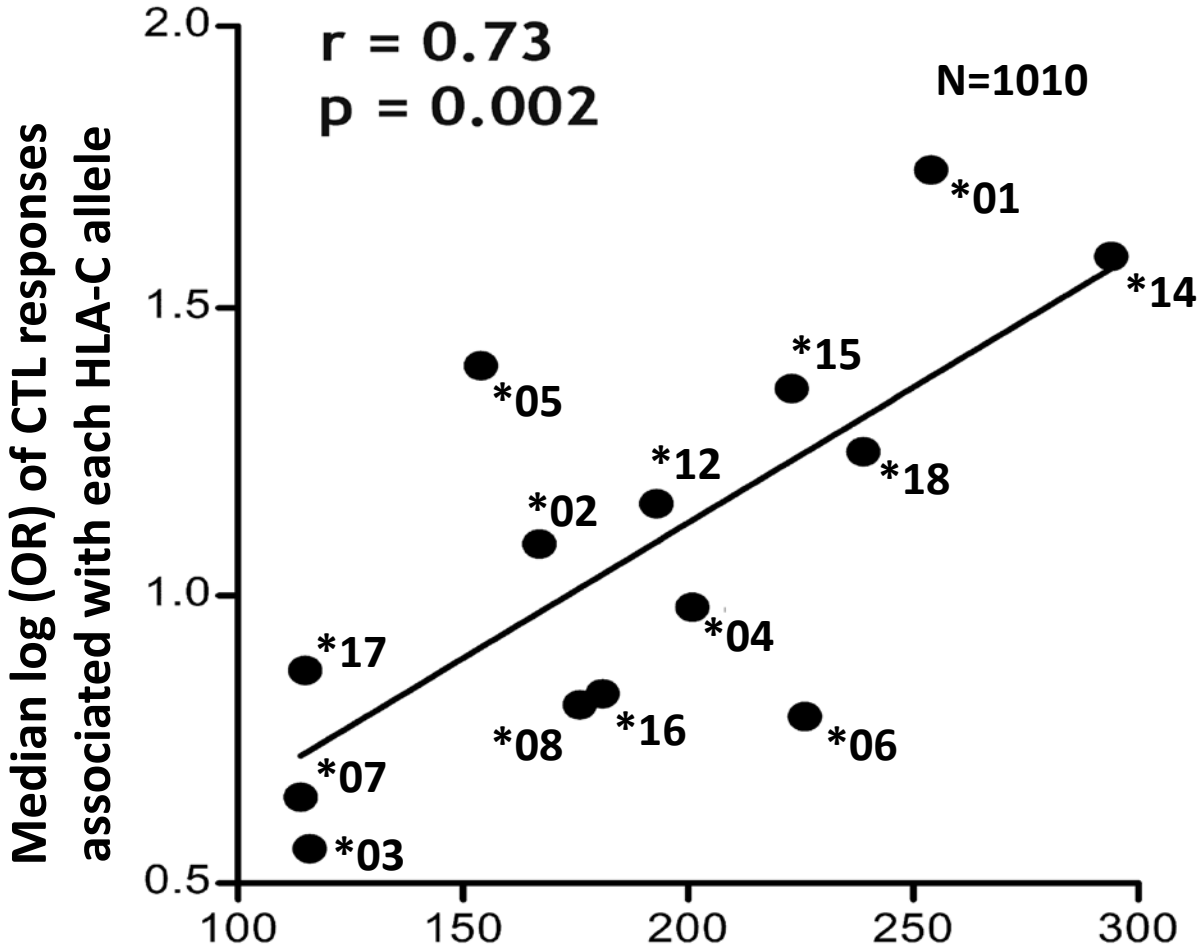
Higher HLA-C expression associates with better HIV control in AA (n=1209)



Significant independent effects with p<0.001

Confirmation across populations: HLA allele frequencies and linkage disequilibrium between HLA loci differ between AA and EA.

Functional data are invaluable for attributing causation to a genetic association: The frequency of HLA-C restricted CTL responses to HIV peptides correlates positively with the level of HLA-C expression



Apps et al, Science, 2013

- **Measurement of HLA-C expression levels across alleles allowed a direct test for an association between HLA-C expression levels and HIV control, rather than involving the -35 SNP proxy or a variant that accounts for only part of the differential expression (3'UTR).**
- **The effect of HLA-C expression levels was consistent in black and white cohorts, and across different HIV outcomes.**
- **Functional data explain/support an effect of HLA-C expression on HIV control through enhanced CTL activity among those with high expression levels of HLA-C.**

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