

Expression estimation and eQTL mapping of HLA genes

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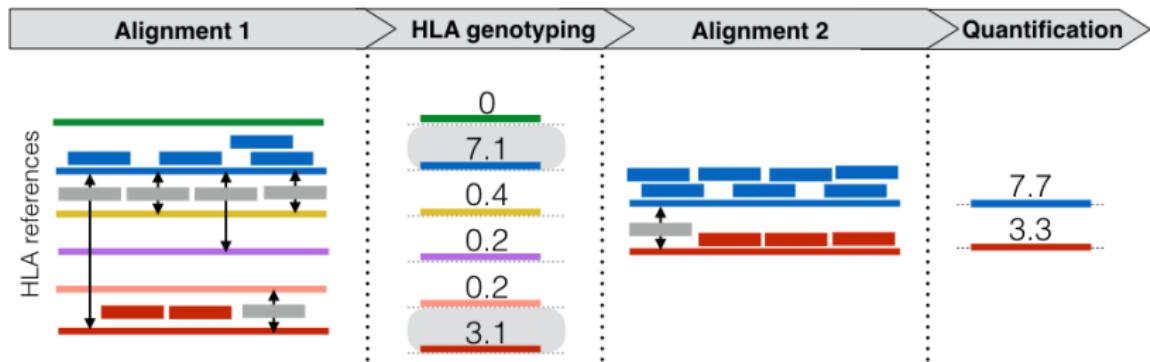
The importance of HLA expression phenotypes

- ▶ Association to cancer phenotypes
- ▶ Association to HIV/AIDS progression
- ▶ Transplantation

Importance of developing HLA expression pipeline

- ▶ Many datasets of genome-wide data are available, but HLA estimates may be inaccurate
- ▶ Better eQTL mapping
- ▶ HLA allele-level estimates
- ▶ Understand how the regulatory architecture is related to HLA lineages

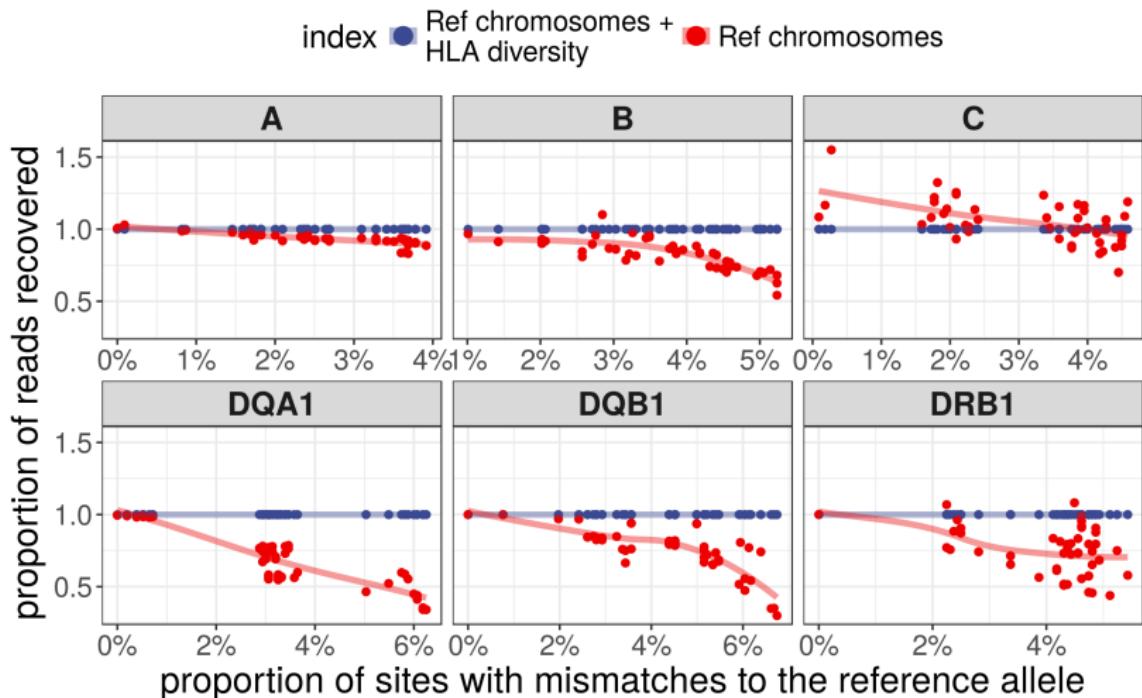
Strategy



*We explored approach using 3 tools: GEM, STAR (standard aligners) kallisto (kmer-based).

Simulation: Indices covering HLA diversity recover more reads

Typing accuracy: 100%



Quality assessment

Gene	not aligned	aligned to different ref	false positive reads
HLA-A	0	1.66	0
HLA-B	0	0.2	0
HLA-C	0	0	0
HLA-DQA1	0	0.4	0
HLA-DQB1	0	0	0
HLA-DRB1	0	0.4	0

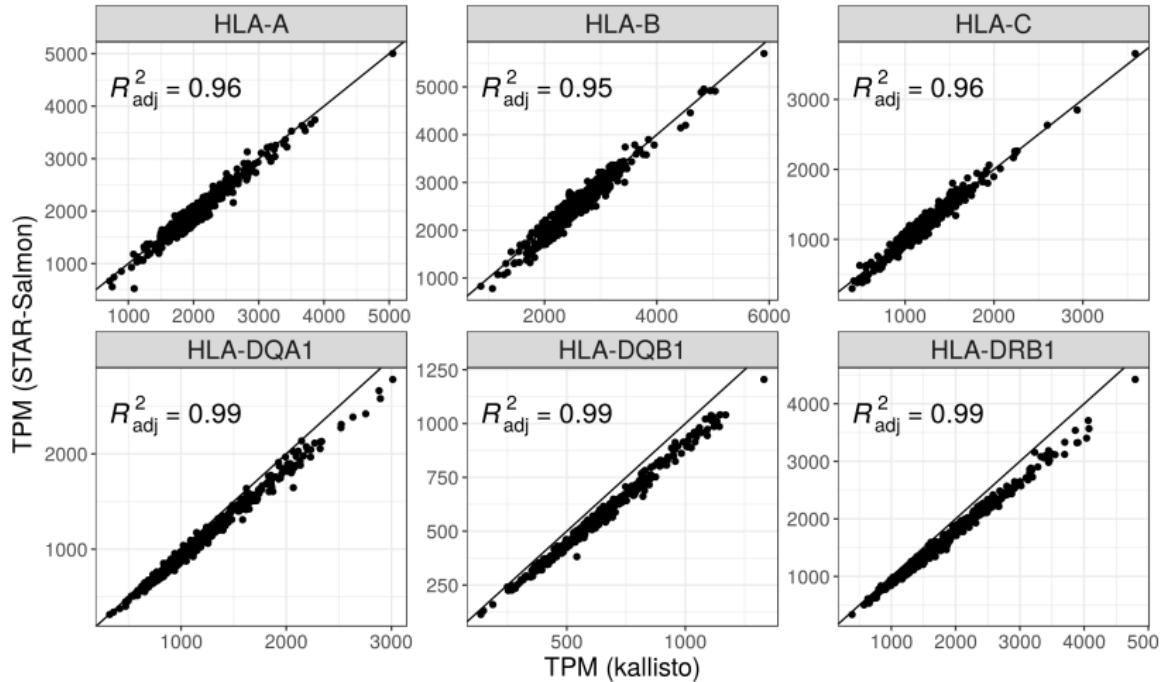
Geuvadis Data

Typing accuracy

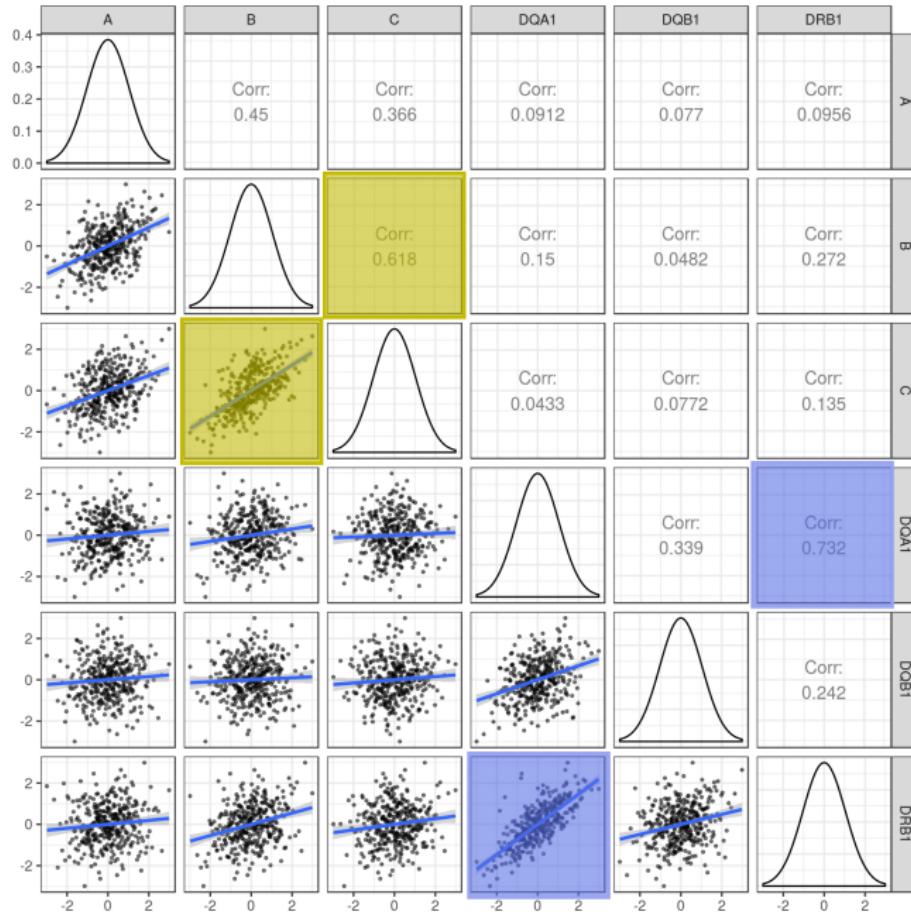
Gene	accuracy
HLA-A	97%
HLA-B	98%
HLA-C	96%
HLA-DQB1	95%
HLA-DRB1	98%

*Gold standard: 1000 Genomes individuals HLA-typed by Gourraud et al. (2014). PLoS ONE 9(7): e97282.

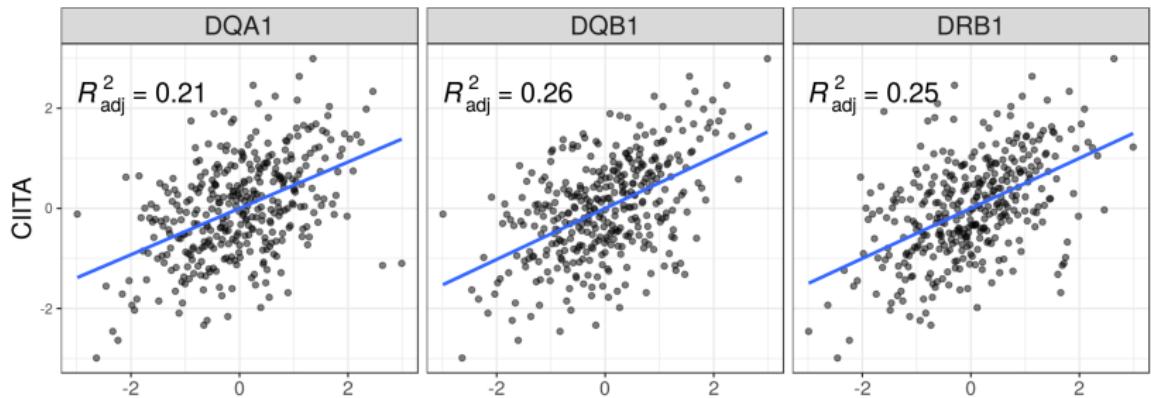
Aligner choice does not influence expression estimate



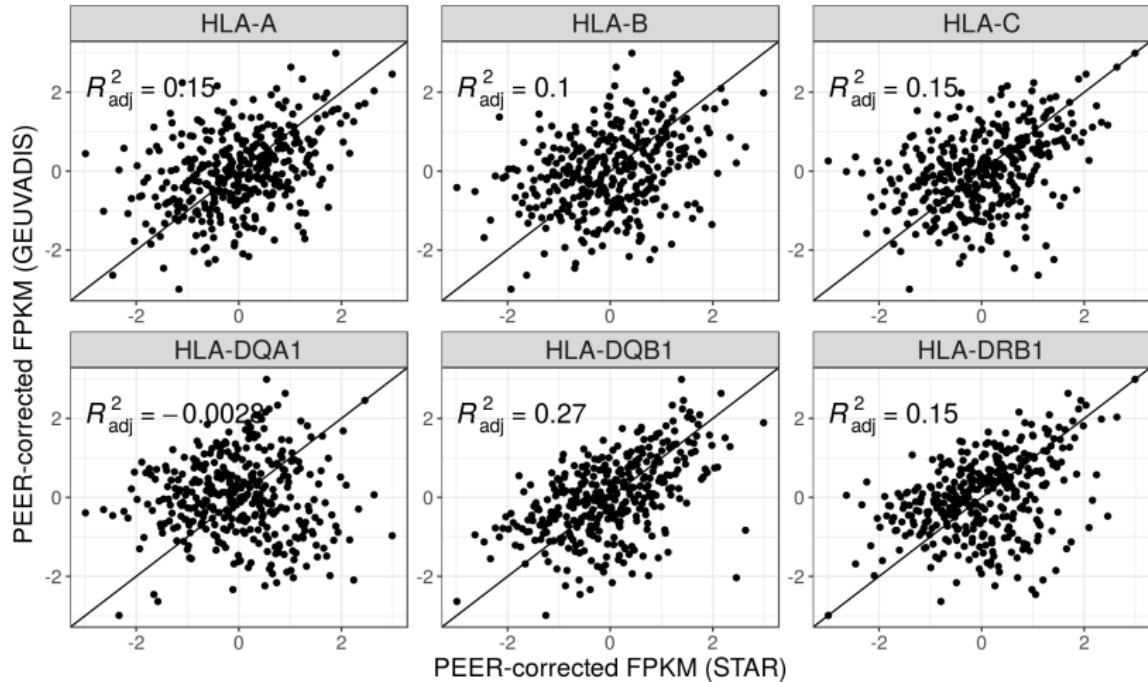
Validation 1: Correlation of expression



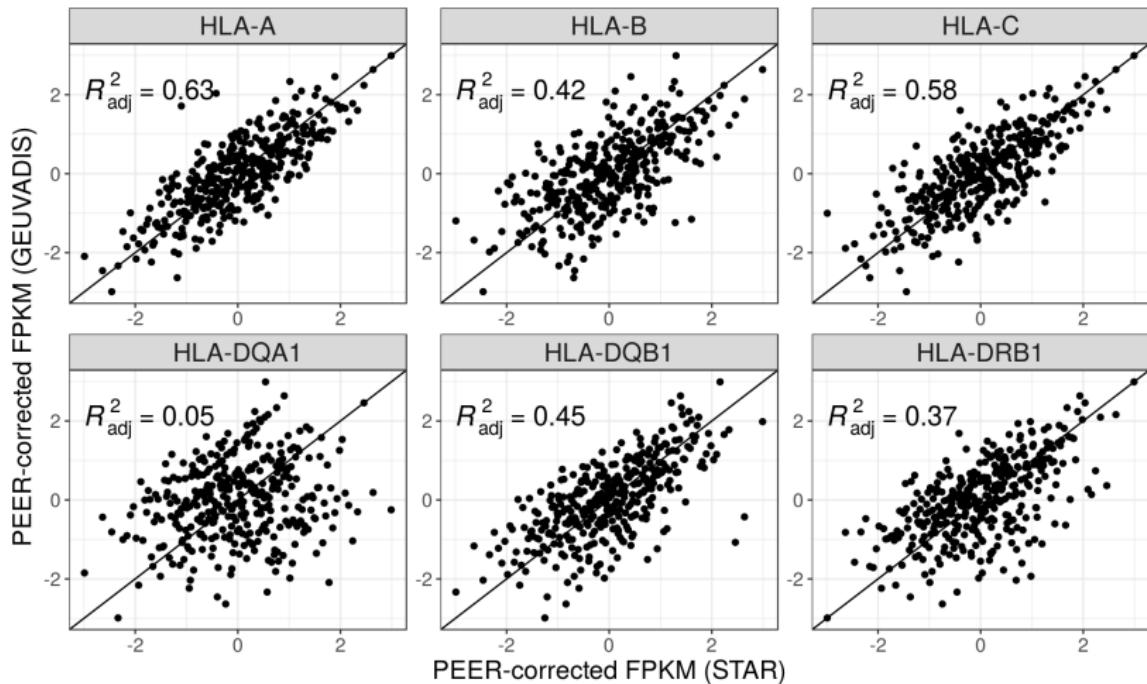
Validation 2: Class II genes and their transactivator



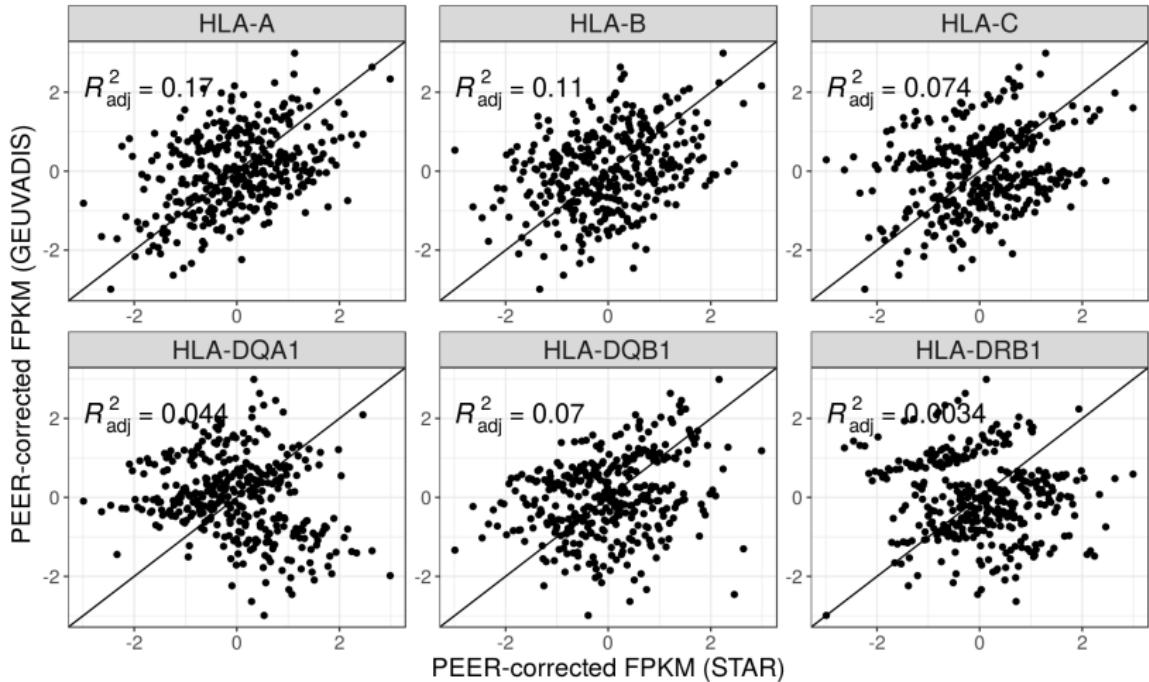
Correlation with Geuvadis published estimates



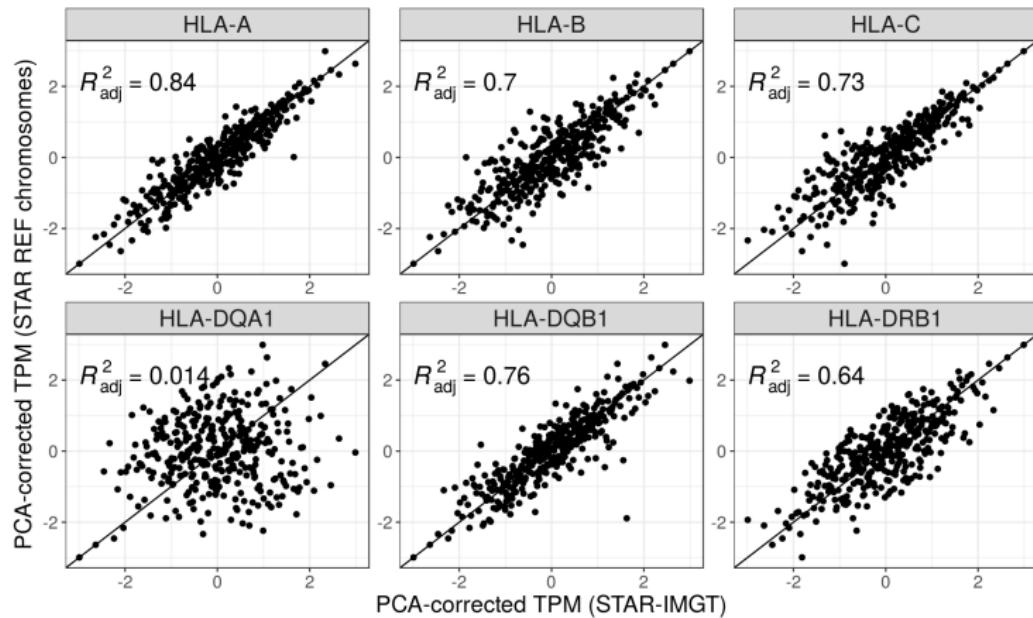
Taking the uncorrected Geuvadis data and running myself the correction



New quantifications

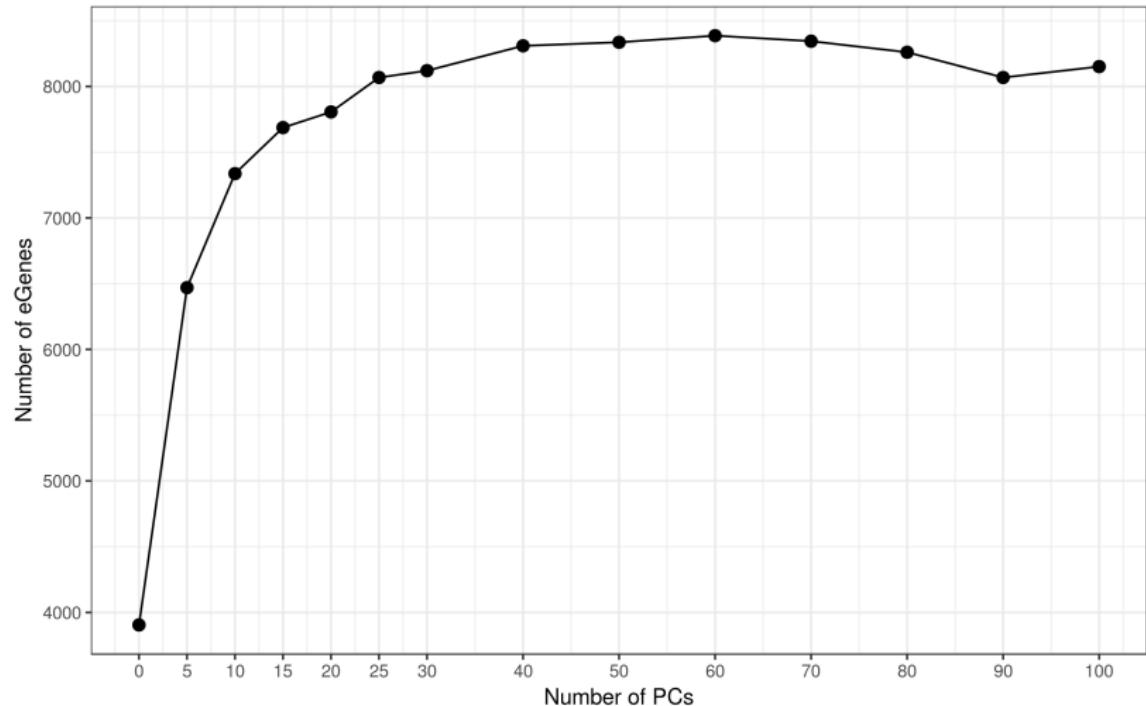


Mapping to REF chromosomes may be enough for gene-level estimates

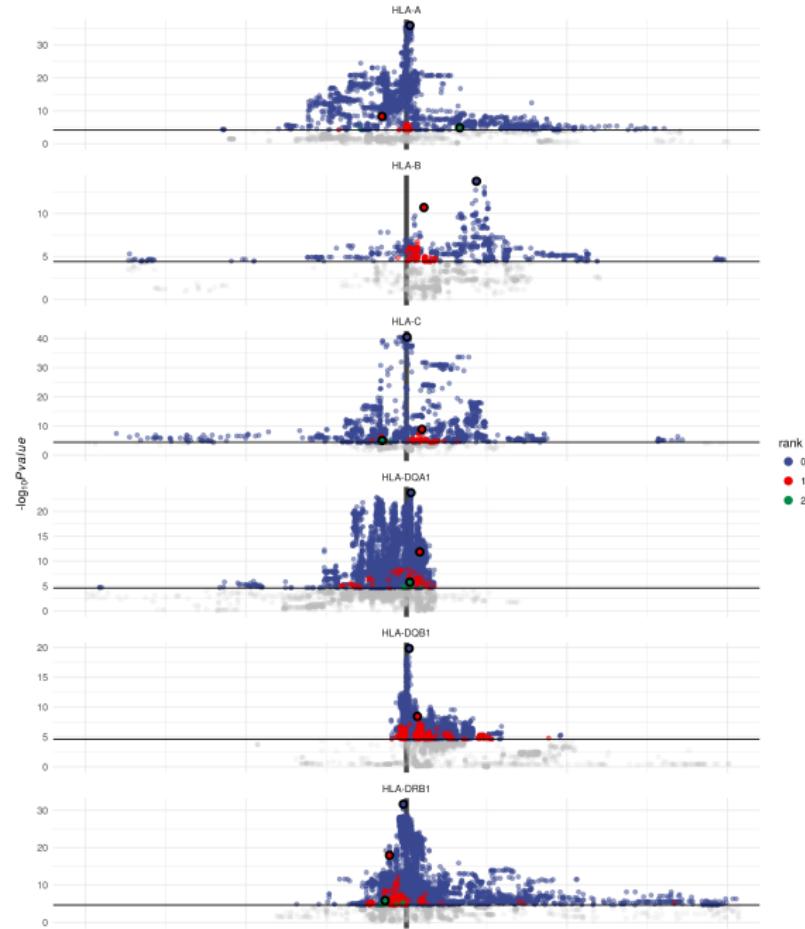


eQTLs

Number of eGenes



eQTLs at HLA genes



RTC with Geuvadis eQTLs

Gene	rank	variant	geuvadis gene	geuvadis variant	RTC
HLA-C	0	rs41561715	HLA-C	rs115899777	0.95
HLA-DQA1	0	rs373884000	HLA-DRB1	rs116405062	0.97
HLA-DQA1	1	rs9274722	HLA-DQA1/HLA-DQB1	rs9274660	0.92
HLA-DQB1	0	rs1770	HLA-DQA1/HLA-DQB1	rs9274660	0.98
HLA-DRB1	0	rs9270698	HLA-DQA1/HLA-DQB1	rs9274660	0.92
HLA-DRB1	2	rs145607970	HLA-DQA1/HLA-DQB1	rs9274660	0.93

How allele-level expression is estimated in the HLA field

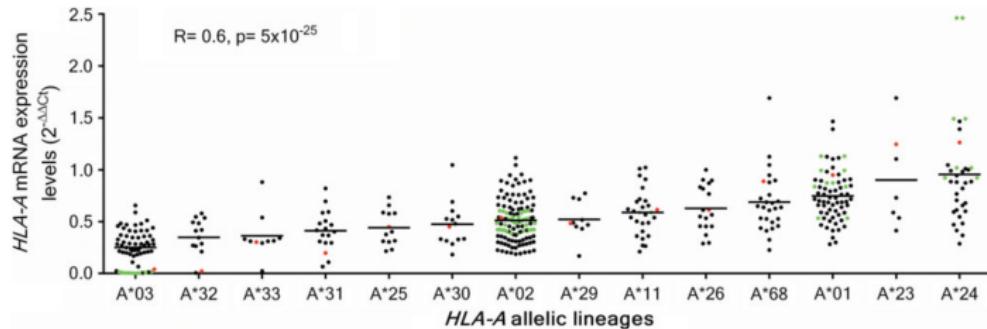
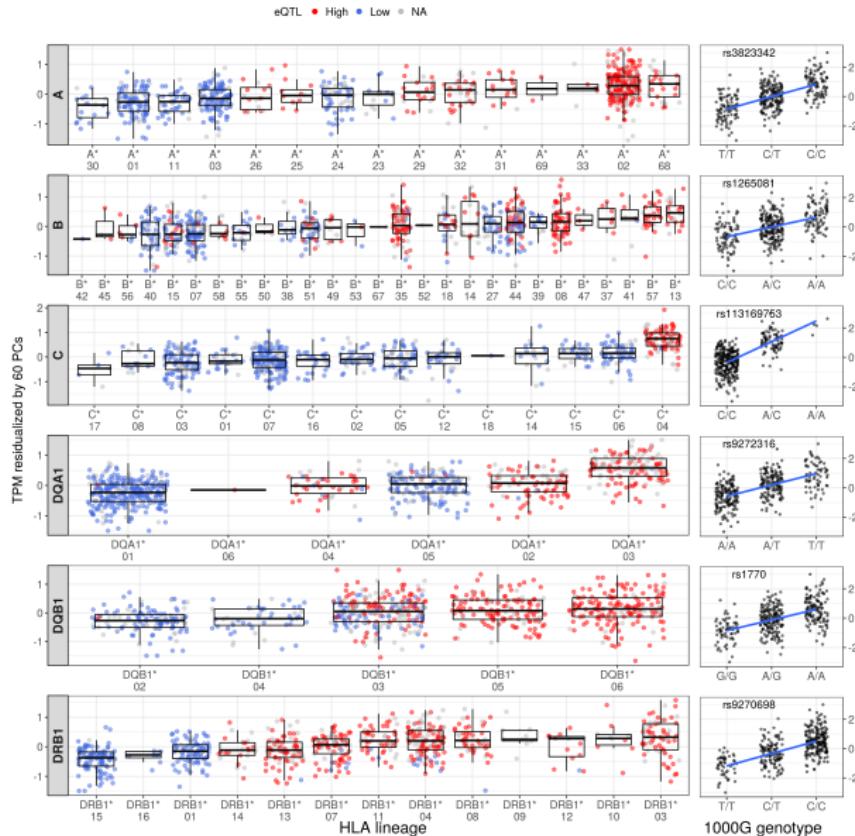


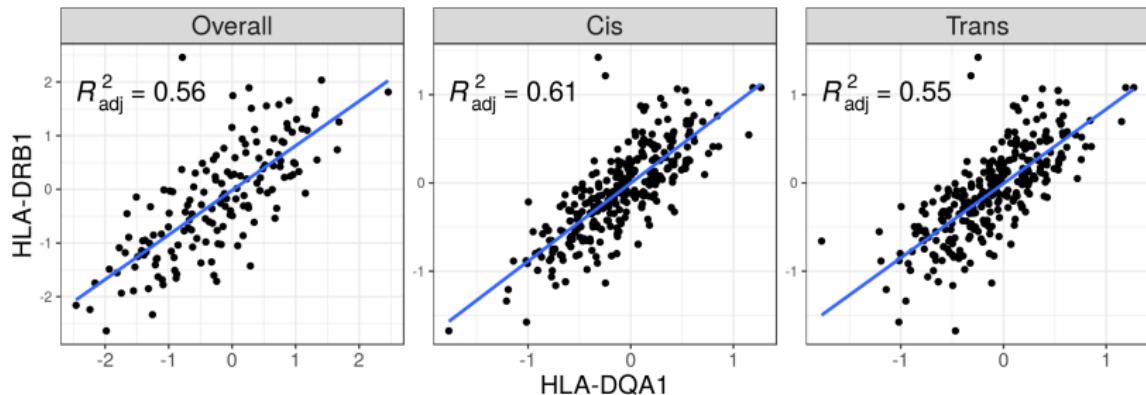
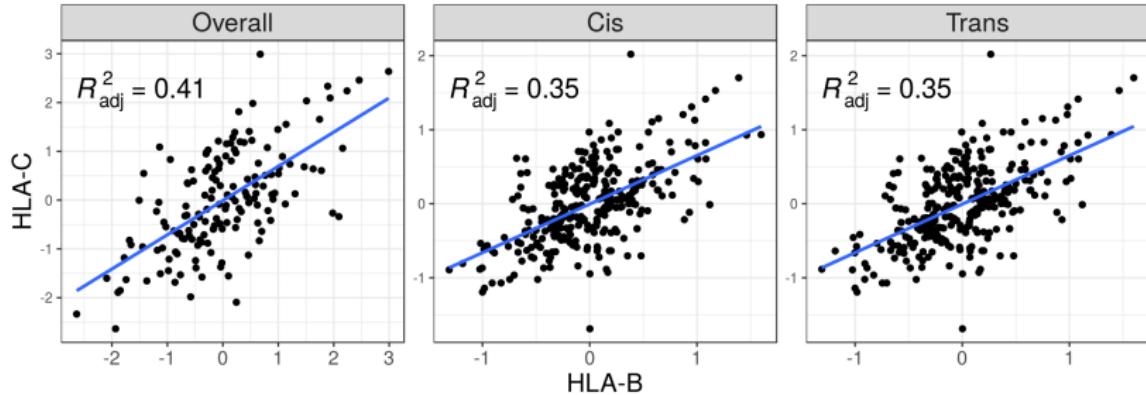
Figure 1. HLA-A gradient of expression across allelic lineages present in EAs. HLA-A mRNA expression level in 216 healthy donors was measured using qPCR. The average expression level of HLA-A was normalized to β 2M mRNA using the $2^{-\Delta\Delta C_t}$ method. The relative expression value is plotted twice for each donor (i.e. once for each HLA-A lineage present). Expression levels correlate significantly with HLA-A lineage and are continuously distributed ($R = 0.6$, $P = 5 \times 10^{-25}$, ANOVA). Allelic lineages with ≥ 5 individuals are shown. The horizontal line indicates the raw average expression for the specific lineage. HLA-A homozygous individuals are marked in green dots. Red dots represent linear regression estimates of average expression levels for each HLA-A allelic lineage (estimated as a diploid homozygote).

Ramsuram et al. Human Molecular Genetics, 2015, 24 (15).

Relationship between eQTLs and HLA alleles



Expression of alleles from different genes on the same vs on different haplotypes



Conclusions

- ▶ A pipeline which accounts for the HLA variation provides better expression estimates, especially for HLA-DQA1 and HLA-DRB1;
- ▶ HLA alleles are associated with disease phenotypes, and the pipeline allows quantification of allele-level expression;
- ▶ Do the eQTLs explain variation in HLA allele expression?
- ▶ Much of the HLA literature is focused on the association of disease phenotypes with HLA haplotypes, but we see no correlation of expression attributed to haplotype membership.