**Distinct genetic architectures and environmental factors associate with host response to the γ2-herpesvirus infections.**

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**Supplementary Tables**

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**Supplementary Tables**

Supplementary Table 1. Seroprevalence of co-infection with EBV or KSHV

| Infection | EBV (N=3956) | KSHV (N=3988) |
|-----------|--------------|---------------|
| EBV | - | 3800 (95%) |
| KSHV | 3800 (96%) | - |
| HIV | 267 (6.7%) | 179 (4.5%) |
| HBV | 118 (2.9%) | 101 (2.5%) |
| HCV | 151 (3.8%) | 124 (3.1%) |

N represents the number of seropositive individuals

Supplementary Table 2. Associations with previously identified candidate variants

| Gene | Variant | $P_1$ (OR) | $P_{UG.ORF73}$ (b) | $P_{UG.K10.5}$ (b) | $P_{UG.K8.1}$ (b) |
|------|---------|------------|---------------------|---------------------|--------------------|
| *IL12A* | rs568408 | 0.02 (2.4) | 0.006 (-0.08) | 0.81 (-0.006) | 0.18 (-0.04) |
| *IL6* | rs1800795 | 0.04 (N.R) | 0.42 (-0.08) | 0.91 (0.01) | 0.58 (-0.05) |
| *IL4* | rs2243248 | 0.05 (2.8) | 0.77 (0.01) | 0.96 (0.001) | 0.64 (0.01) |
| *IL13* | rs20541 | 0.01 (1.88) | 0.87 (-0.004) | 0.56 (-0.01) | 0.62 (-0.01) |
| *IL8RB* | rs1126579 | 0.003(0.49) | 0.87(0.01) | 0.36 (0.03) | 0.27(0.04) |
| *IL6* | rs1800795 | 0.05 (3.7) | 0.42 (-0.07) | 0.91 (0.01) | 0.58 (0.05) |
| *FCgRIIIA* | rs396991 | 0.00028 (N.R) | 0.31 (-0.03) | 0.93 (-0.003) | 0.67 (-0.01) |
| *IRAK1* | rs1059702 | N.R | 0.37 (0.05) | 0.90 (0.05) | 0.77 (0.02) |
| *HLA-A* | *A*6801* | 0.02 (2.6) | 0.38(-0.09) | 0.37(-0.09) | 0.08(-0.19) |
| *HLA-A* | *A*30* | 0.019 (0.48) | 0.22(-0.03) | 0.21(-0.03) | 0.62(-0.01) |
| *HLA-B* | *B*14* | 0.033 (4.27)* | 0.76(0.01) | 0.85(-0.01) | 0.83(-0.01) |
| *HLA-B* | *B*58* | 0.00001 (0.03) | 0.88(0.0005) | 0.40(0.03) | 0.49(-0.02) |
| *HLA-C* | *C*0701* | 0.002 (1.6) | 0.39(0.03) | 0.16(0.04) | 0.42(0.03) |
| *HLA-C* | *C*05* | 0.0006 (0.32) | 0.19(0.14) | 0.15(0.16) | 0.62(0.06) |
| *HLA-C* | *C*07* | 0.01 (2.4) | 0.92(-0.003) | 0.68(0.01) | 0.91(0.003) |
| *HLA-DQB1* | *DQB1*0502* | 0.0465 (0.519) | 0.29(0.14) | 0.83(-0.03) | 0.56(0.08) |
| *HLA-DQB1* | *DQB1*0604* | 0.0017 (7.74) | 0.90(-0.005) | 0.73(0.01) | 0.95(-0.002) |
| *HLA-DRB1* | *DRB1*04* | 0.02 (3.4) | 0.78(-0.02) | 0.24(0.09) | 0.90(0.0008) |
| *HLA-DRB1* | *DRB1*1104* | 0.0473 (2.1) | 0.19(0.17) | 0.94(-0.009) | 0.49(0.09) |
| *HLA-DRB1* | *DRB1*1302* | 0.0037 (5.82) | 0.82(0.008) | 0.59(-0.02) | 0.65(0.01) |

$P_1$ – P-value from original study

$P_{UG.ORF73}$– P-value from Uganda GPC anti-ORF73 IgG GWAS

$P_{UG.K8.1}$ – P-value from Uganda GPC anti-K8.1 IgG GWAS

$P_{UG.K10.5}$ – P-value from Uganda GPC anti-K10.5 IgG GWAS

N.R – Not reported

*FDR (False Discovery Rate)

Supplementary Table 3. Loci with significant evidence of association with anti-EBV IgG levels (N=3,289)

| Trait | Chr:Pos(b37) | Variant | Nearest Gene[a] | Consequence[a] | EA | EAF (%) | P | b (95% C.I) |
|-------|--------------|---------|-----------------|----------------|-----|---------|---|-------------|
| EBNA-1 | 6:32604654 | rs9272371 | HLA-DQA1 | Intron | C | 26.9 | $5.24 \times 10^{-33}$ | -0.37 (-0.43 – -0.31) |
| EBNA-1 | 6:32404220 | rs3129867 | HLA-DRA | Upstream | G | 49.2 | $1.63 \times 10^{-22*}$ | -0.25(-0.30 - -0.20) |
| VCA | 6: 32615738 | rs28394498 | HLA-DQA1 | Intron | T | 17.9 | $9.15 \times 10^{-11}$ | -0.23 (-.29 - -0.16) |

EA – Effect Allele, EAF – Effect Allele Frequency

[a]Annotated using Ensembl VEP

*P.conditional on lead SNP, b (95%C.I)=$6.01 \times 10^{-11}$, -0.17(-0.22 - -0.12)

Supplementary Table 4. Credible set showing strong evidence of association with anti-EBNA-1 IgG levels after meta-analysis

| Lead SNP | Chr:Pos(b37) | Locus | Alleles Effect/ Other | Ugandan (N=4365) | | | | European Ancestry (N=2162) | | | | MANTRA EUR + UG (N=6527) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | EAF | Beta | SE | P | EAF | Beta | SE | P | $\log_{10}BF$ | $P_Q{}^*$ |
| rs6927022[a] | 6:32612397 | HLA-DRB1 | A/G | 0.73 | 0.26 | 0.02 | $1.36 \times 10^{-21}$ | 0.59 | 0.16 | 0.015 | $7.35 \times 10^{-26}$ | 44.3 | 0.06 |
| rs9272371[b] | 6:32604654 | HLA-DQA1 | C/T | 0.3 | -0.36 | 0.02 | $3.63 \times 10^{-44}$ | 0.37 | -0.02 | 0.015 | 0.14 | 42.6 | $3.56 \times 10^{-8}$ |
| rs9274247 | 6:32631295 | HLA-DQB1 | A/G | 0.22 | -0.32 | 0.02 | $2.63 \times 10^{-29}$ | 0.35 | -0.13 | 0.015 | $4.51 \times 10^{-16}$ | 42.2 | 0.63 |

EAF - Effect Allele Frequency

SE – Standard Error
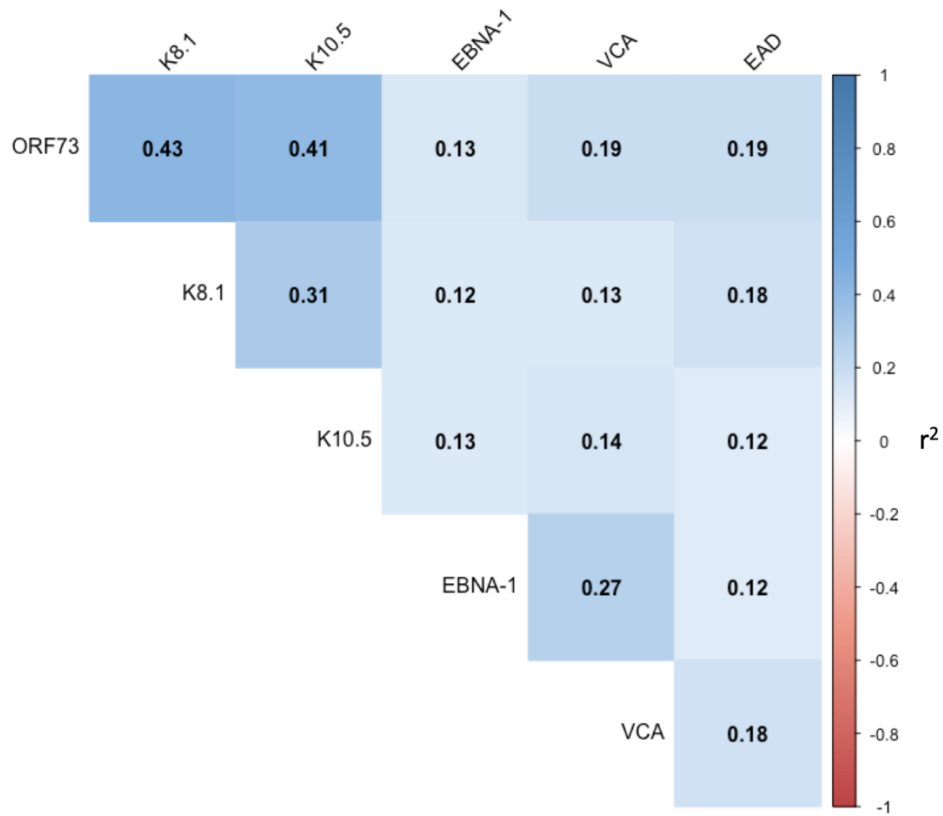
[a]European (EUR) lead SNP

[b]Ugandan (UG) lead SNP

*$P_Q$ – Cochran's Q-test for heterogeneity

**Supplementary Figures**
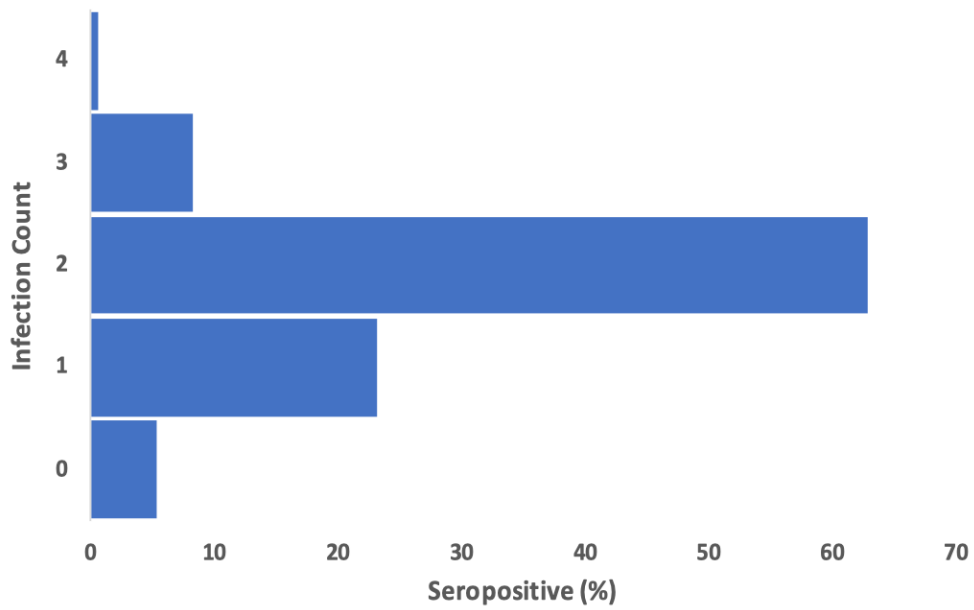


Supplementary Figure 1. Burden of viral infections tested in the GPC Round 22 (2011). The number of seropositive reactions to viruses for all participants, the infection count represents the minimum number of infections participants are seropositive for.

Supplementary Figure 2. Correlation matrix of antibody responses (MFI) for KSHV and EBV. Positive correlations are in blue and intensity is proportional to the correlation coefficients ($r^2$) labelled in the squares and indicated on the right-hand side of the correlogram. All tests meet Pearson's significance threshold of $p < 0.05$.
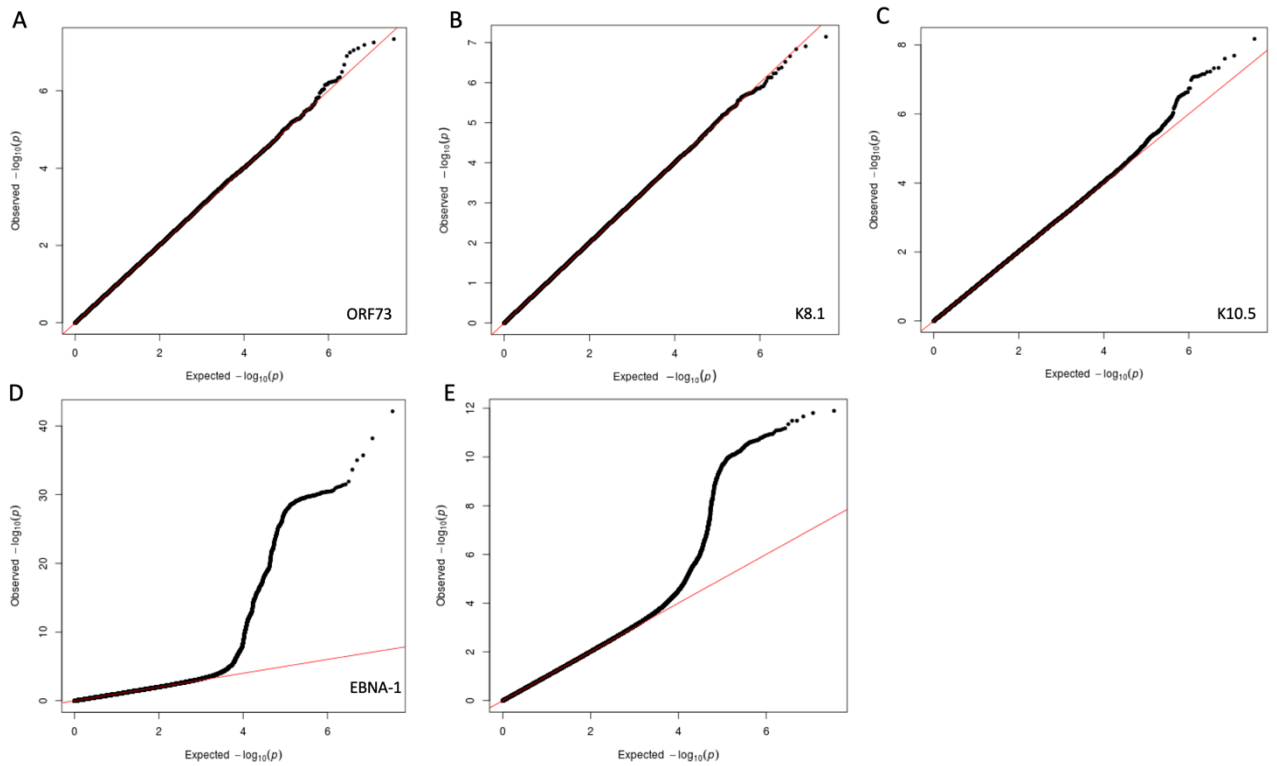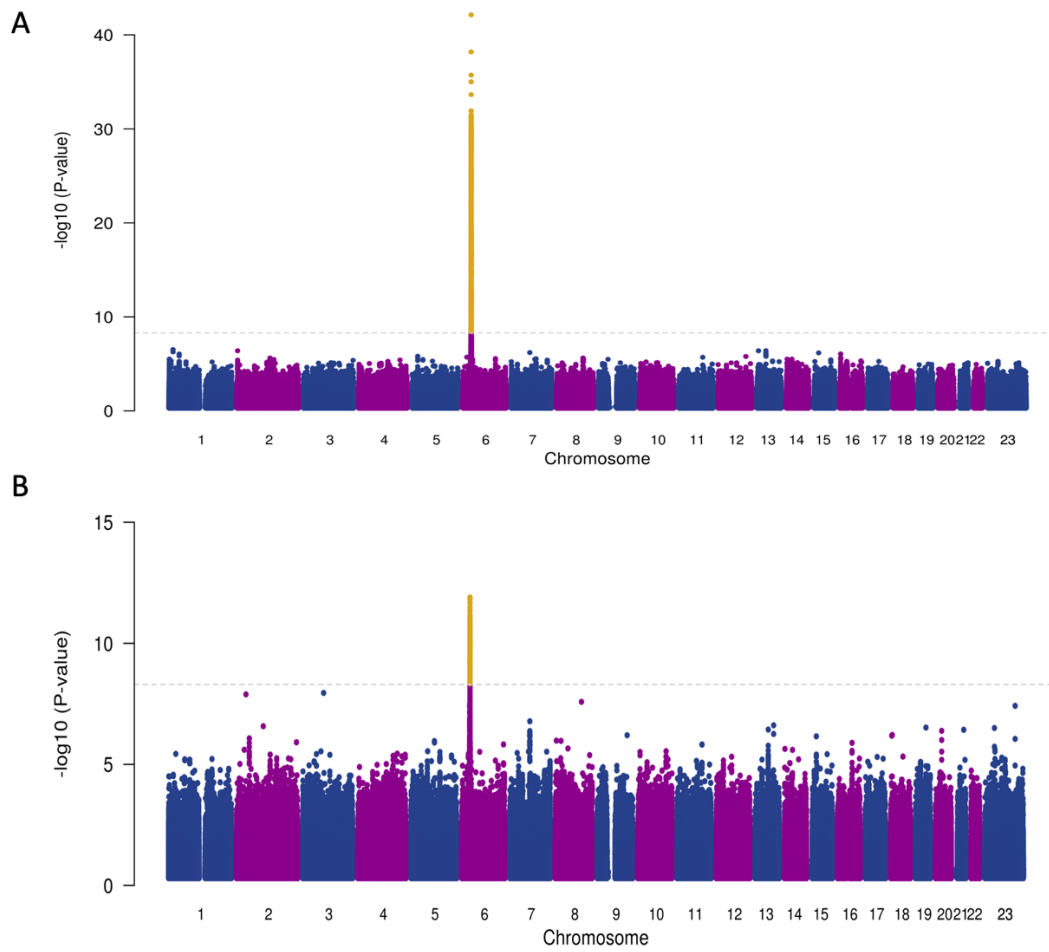
Supplementary Figure 3. Genome-wide association QQ-plots of all IgG response levels in 4,365 individuals. A. Anti-Orf73 IgG association. B. Anti-K8.1 IgG association. C. Anti-K10.5 IgG association. D. Anti-EBNA-1 IgG association. E. Anti-VCA IgG association.
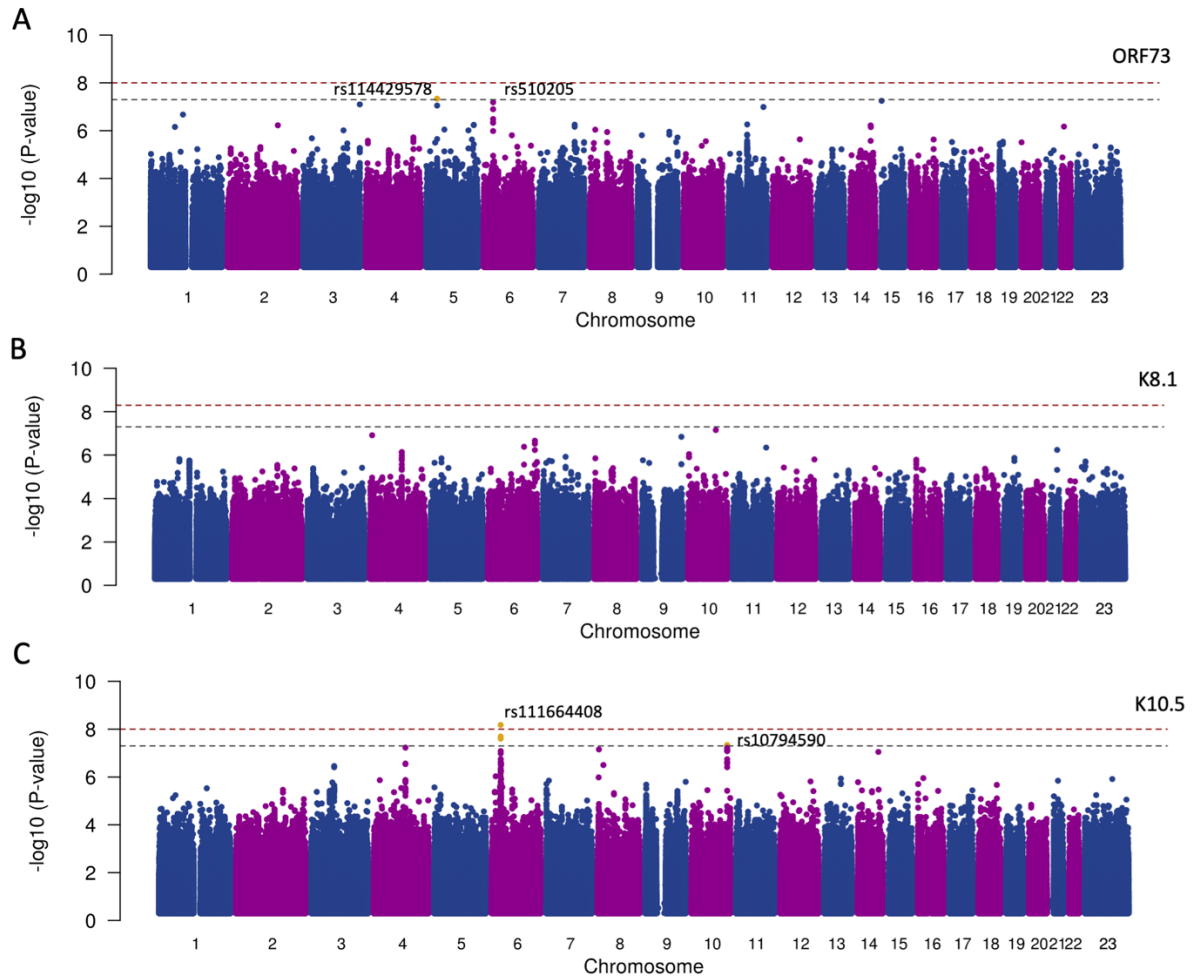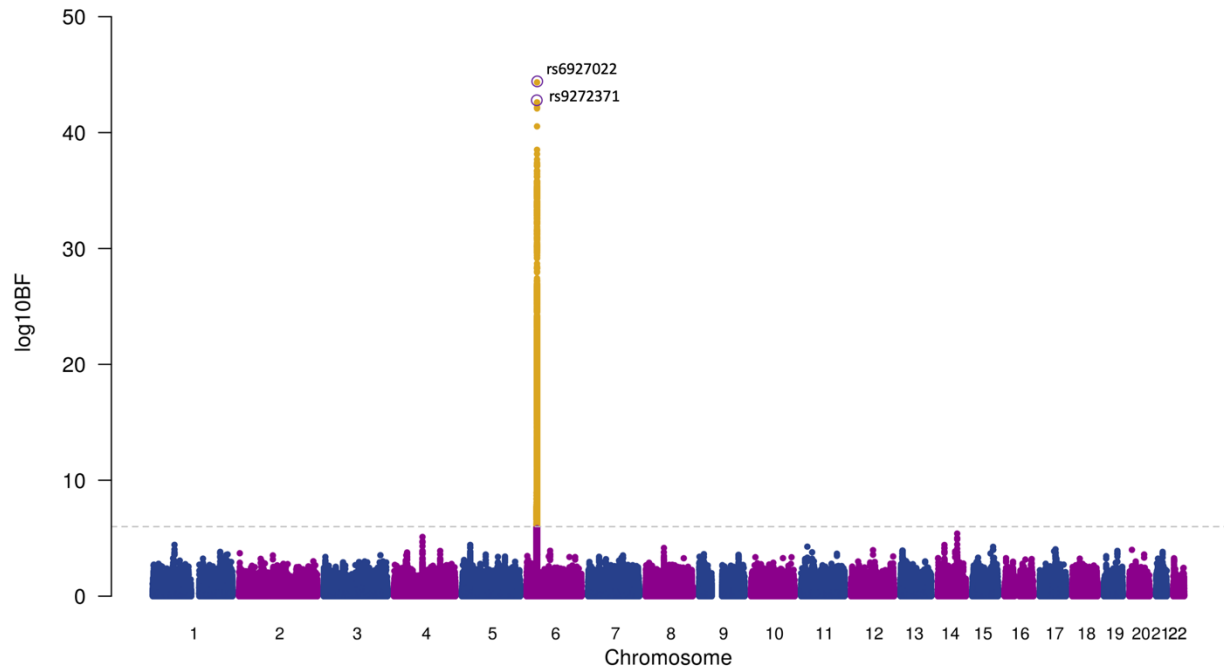
Supplementary Figure 4. Genome-wide association results of anti-KSHV IgG response levels in 4,365 individuals. A. Anti-ORF73 IgG association. B. Anti-K8.1 IgG association. C. Anti-K10.5 IgG association. GWAS performed using linear mixed model accounting for kinship in GEMMA. Red dashed line: Genome wide significance threshold ($p<1x10^{-8}$), grey dashed line: Standard genome-wide significance threshold ($p<5x10^{-8}$), 23=X Chromosome. Yellow: SNPs that meet the standard genome-wide significance threshold ($p<5x10^{-8}$).

Supplementary Figure 5. Genome-wide association results of anti-EBV IgG response levels in 4,365 individuals. A. Anti-EBNA-1 IgG association. B. Anti-VCA IgG association. Manhattan Plot: Grey dashed line: Genome wide significance threshold ($p < 1 \times 10^{-8}$), 23=X Chromosome. Yellow: SNPs that meet the genome-wide significance threshold.

Supplementary Figure 6. Trans-ethnic meta-analysis association plot for EBNA-1 IgG response levels in 6152 individuals of Ugandan and European Ancestry (EUR). The lead SNPs for EUR (rs6927022, log10BF= 44.3) and Uganda (rs9272371, log10BF= 42.6) GWASs on chromosome 6 within the *HLA* region are labelled and circled in purple. Grey dashed line: threshold= $\log_{10}BF > 6$. Yellow: SNPs that meet the statistical significance threshold.