**Supporting Figures and Tables**

**Fig. S1-S11**

**Table S7**

**Separate Excel files**

**Table S1.** Differential splicing analysis comparing uninfected and IAV-infected conditions.

**Table S2.** Gene set enrichment of differentially spliced genes using Enrichr and the MSigDB hallmark gene set.

**Table S3.** Significant sQTL (FDR < 0.05) for uninfected and IAV-infected conditions.

**Table S4.** Gene set enrichment of sGenes using Enrichr and the MSigDB hallmark gene set.

**Table S5.** Colocalization analysis of PARP2 sQTL and anti-HSV-1 IgG.

**Table S6.** iCPAGdb analysis of causal sQTLs shared with other human traits/diseases in the NHGRI-EBI GWAS Catalog.

**Fig. S1**. Intron junctions identified by Leafcutter classified into 6 types. On the left (blue), all junctions are counted, while the right barplots (red) count junctions that are significantly differentially spliced between IAV-infected and uninfected conditions at qvalue<0.05. SE: skipped exon; AFE, Alternative first exon; A5SS, alternative 5' splice site; A3SS, alternative 3' splice site; MXE, mutually exclusive exon; ALE, alternative last exon.

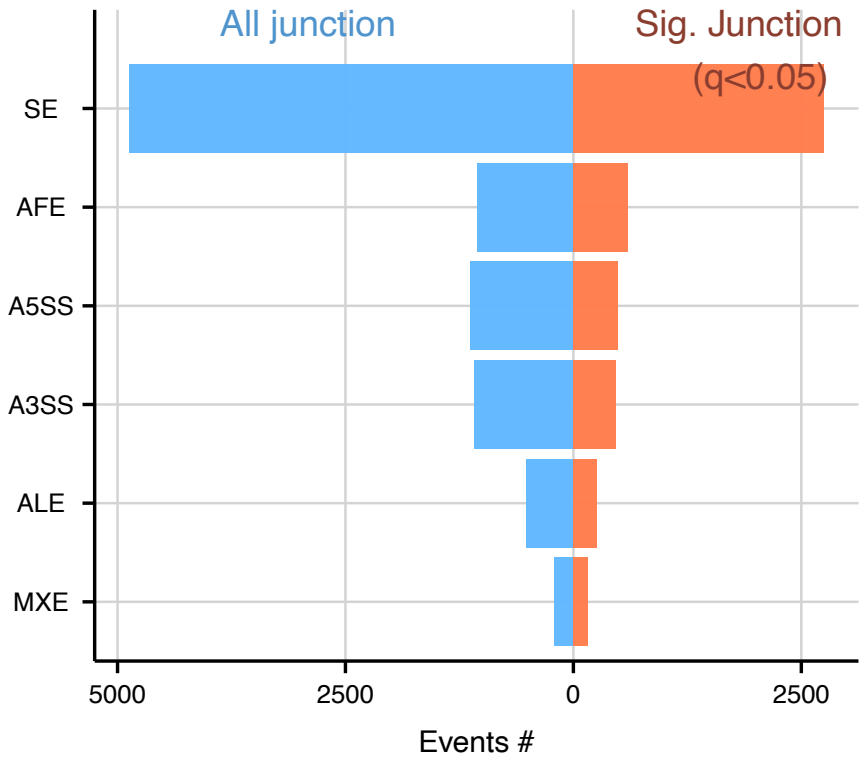


**Fig. S2.** Barplot of gene set enrichment analysis of genes carrying significant differential junctions between IAV and uninfected from Leafcutter. Enrichment was performed using Enrichr based on MSigDB database. Vertical dashed line indicates FDR of 0.05.

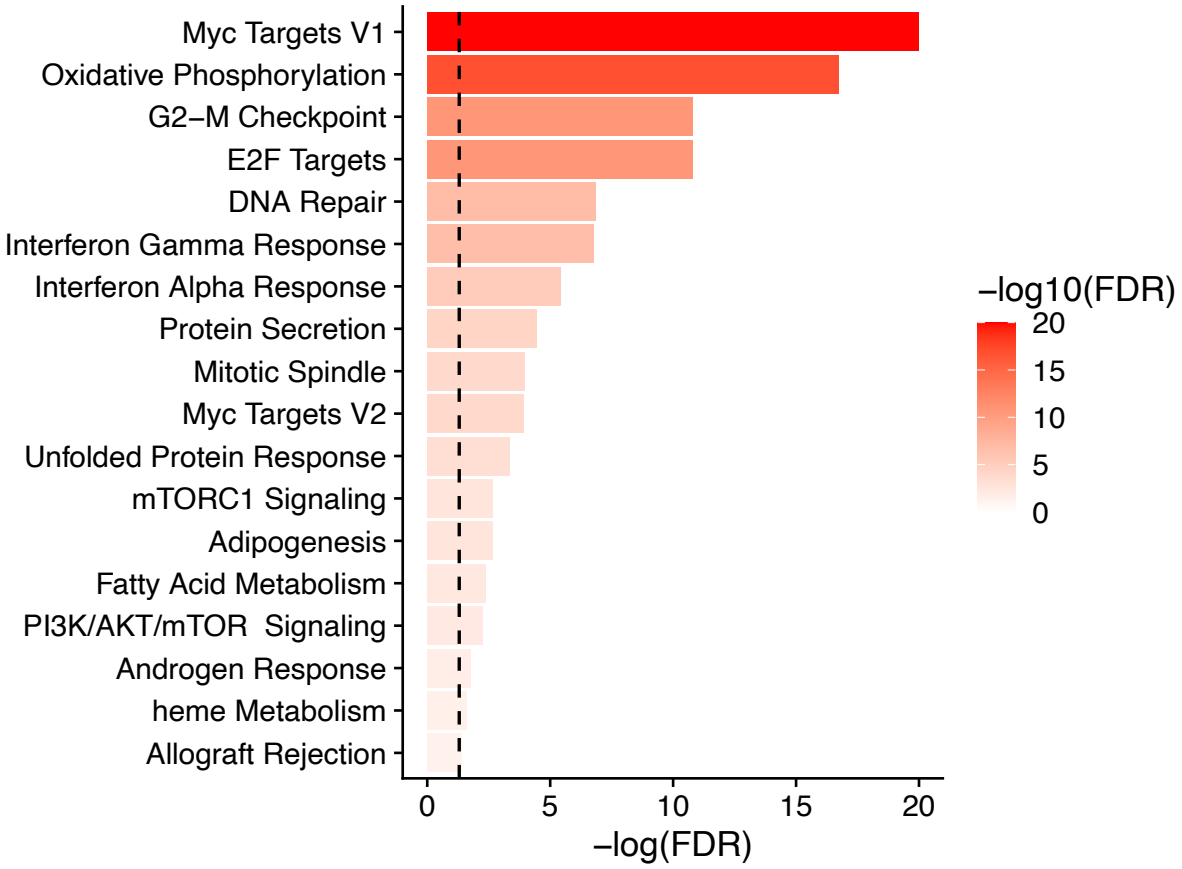


**Fig. S3.** Single cell visualization of viral burden, interferon genes and pathways. **A)** UMAP of IAV (CA09)-infected and uninfected revealed a total of 12 clusters. **B)** UMAP visualization of percent of viral reads per cell. **C)** UMAP visualization of *IFITM1* gene expression. **D)** Violin plot of *IFITM1* gene expression, and Interferon Alpha and Gamma pathways scores. The Interferon Alpha and Gamma pathways scores were calculated using R Seurat “AddModuleScore”.

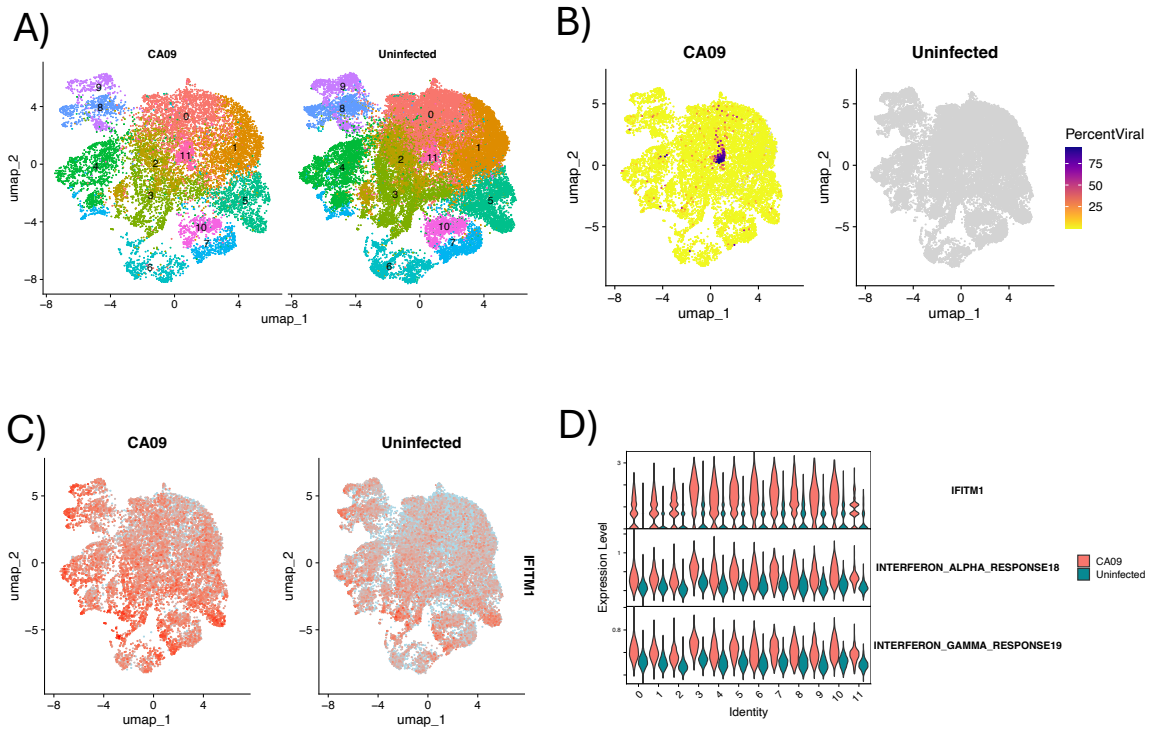


**Fig. S4.** A summary of sJunctions and their effects on splicing. An sJunction is defined as a splicing junction from Leafcutter that is associated to at least 1 sQTL. A) The sJunction counts for uninfected and IAV-infected LCLs from scHi-HOST. B) The number of sJunctions that have each category of effect for uninfected and IAV-infected LCLs.

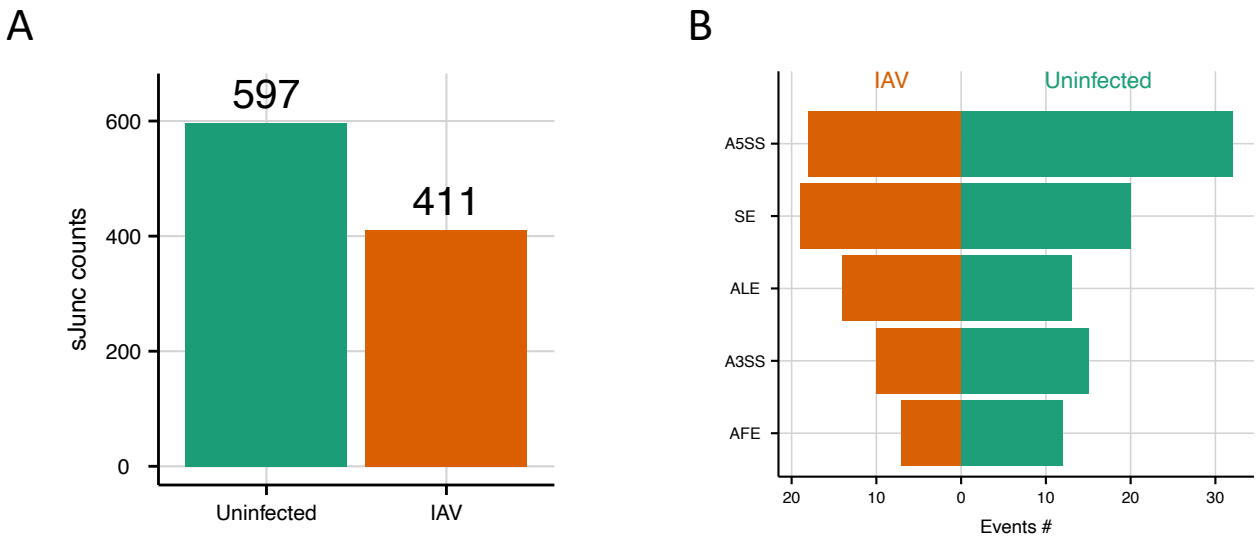
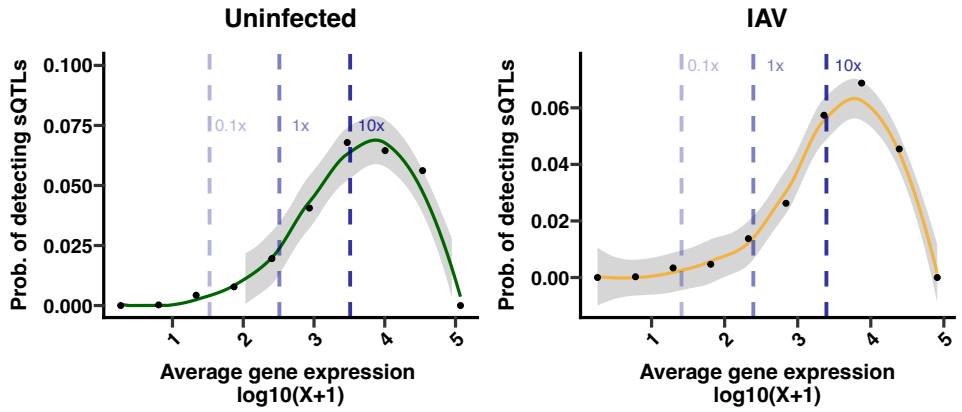


**Fig. S5**. Evaluation of power in the scHi-HOST sQTL pipeline. A) Mean expression of genes across LCLs vs. the probability of detecting a sQTL in both uninfected (top left) and IAV-infected conditions (top right). The probability of detecting sQTL was defined as fraction of genes in each bin associated with at least 1 sQTL (FDR < 0.05), 31,228 genes were tested for uninfected and 30,769 for IAV. B) The aggregated counts of sQTLs against average gene expression per bin for both uninfected (bottom left) and IAV-infected conditions (bottom right). Gene expression was transformed using log10(x+1).

**A)**




**B)**

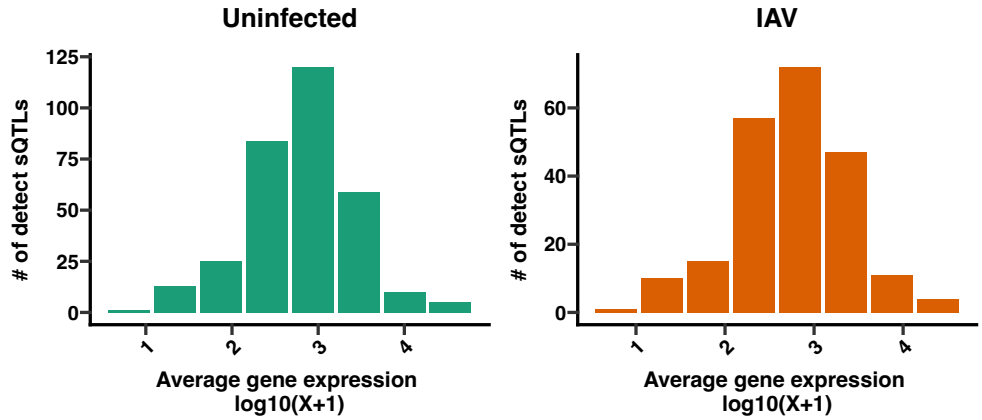


**Fig. S6.** Characterization of sQTLs based on their locations in a gene.

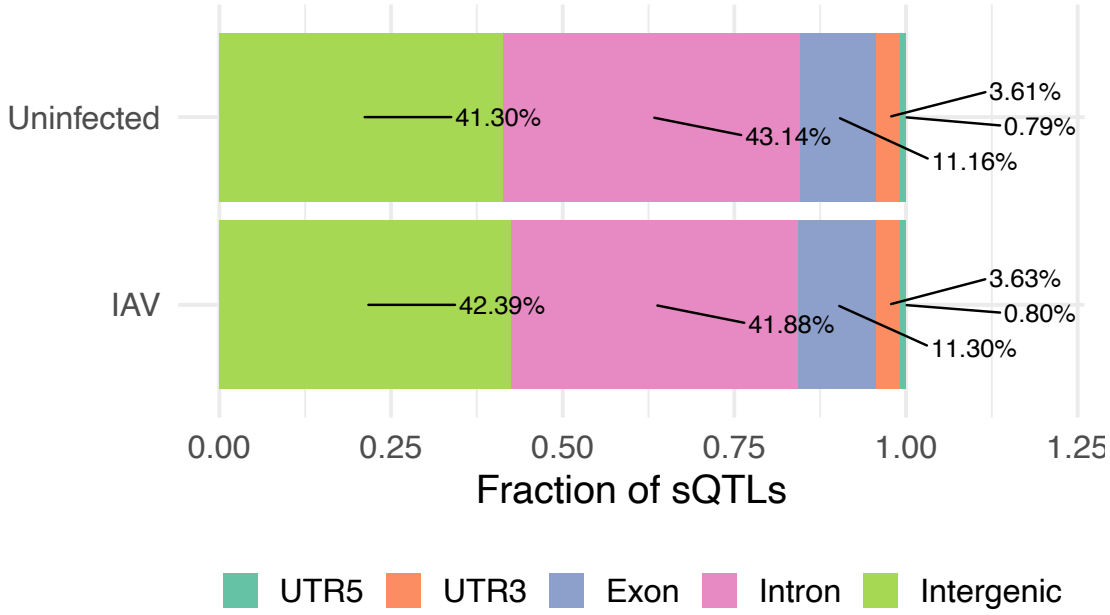


**Fig. S7.** Relative distance of sQTL from AI-predicted variants (either SpliceAI or Pangolin >= 0.2)

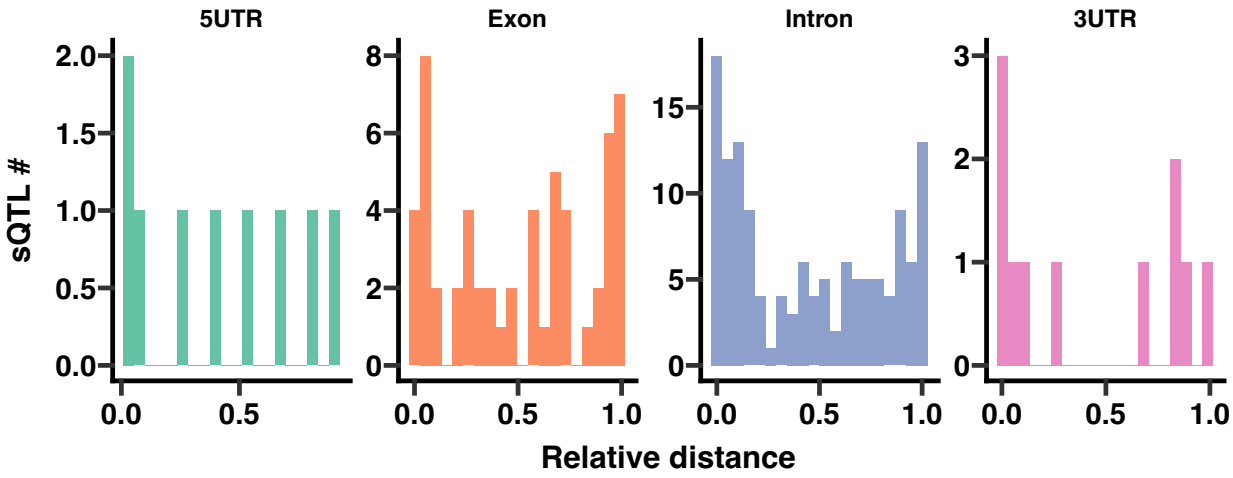


**Fig. S8.** Sashimi plot of U2AF1L4 rs17638853 with splice prediction from AlphaGenome.

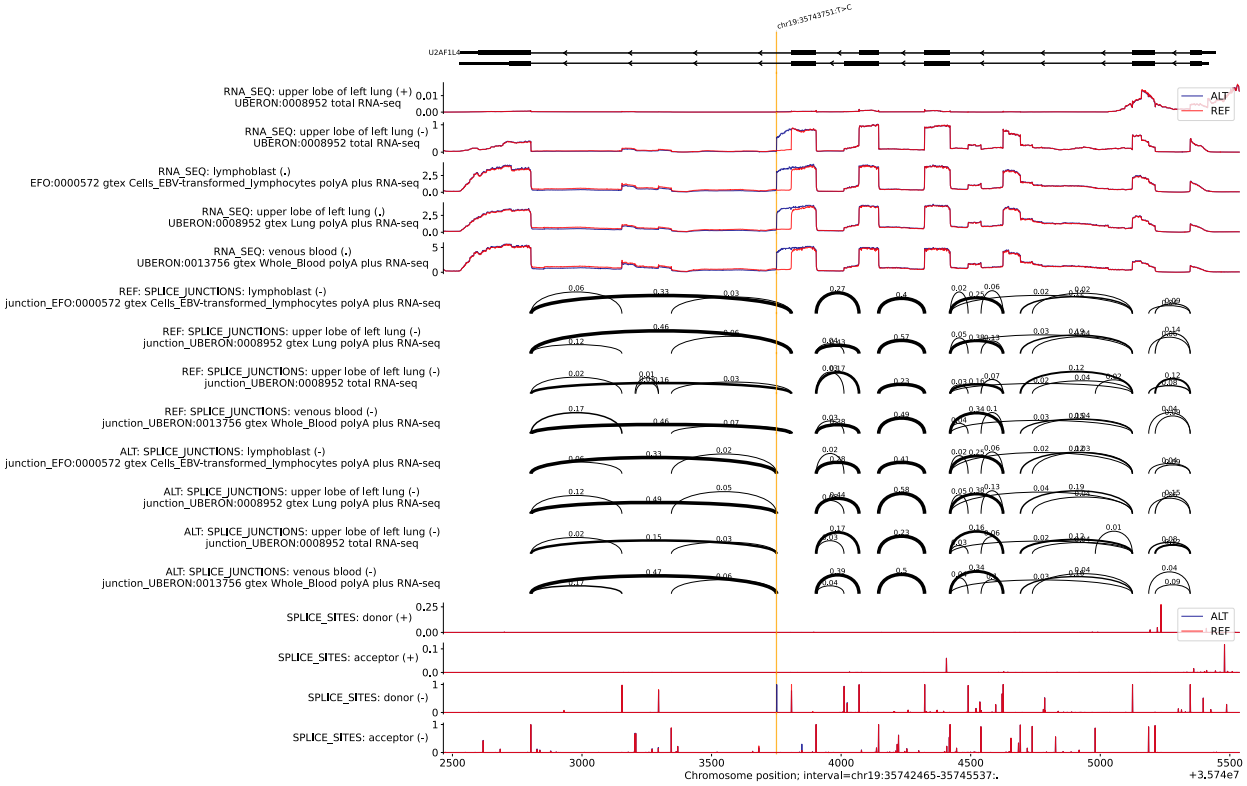


**Fig. S9.** Top causal variant rs10774671 is associated with alternative splicing of two *OAS1* transcripts. A) Sashimi plot showing RNA-seq read coverage and junction usage at OAS1 stratified by rs10774671 genotype. (B, C) Genotype boxplots of normalized junction expression for two junctions highlighted from A).

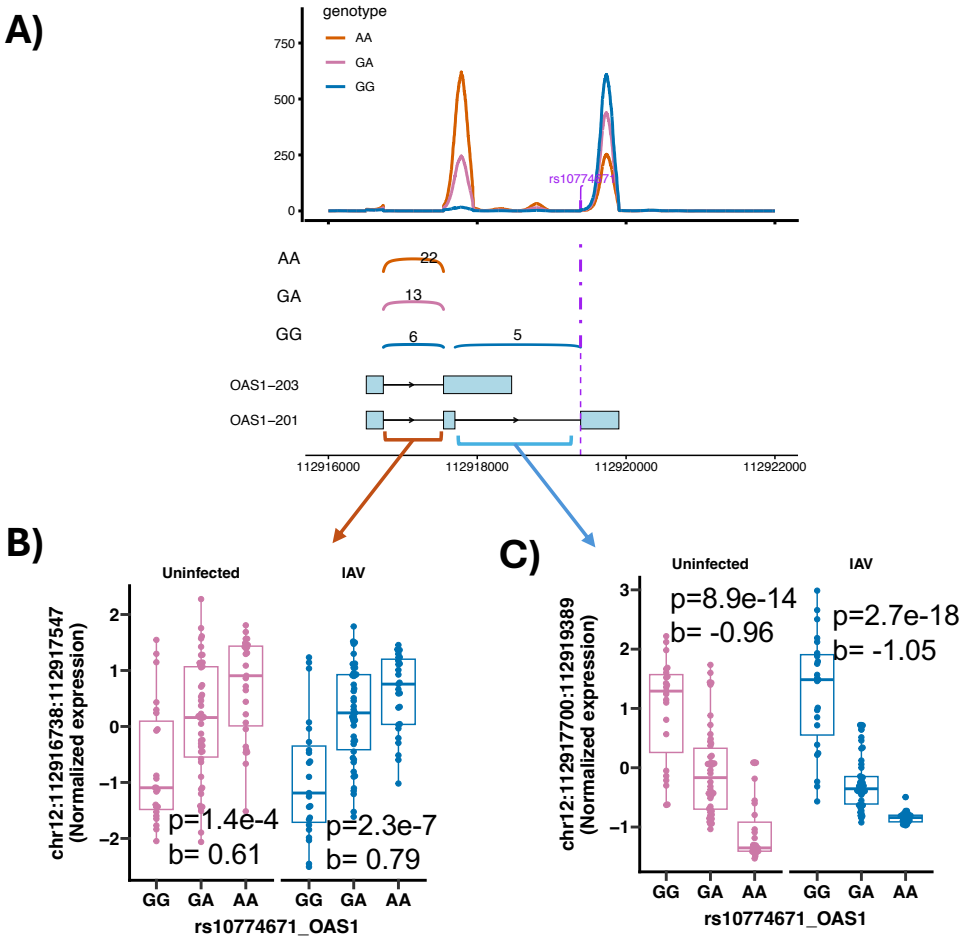


**Fig. S10.** Sashimiplot of PARP2 rs2297616 splice prediction from AlphaGenome.

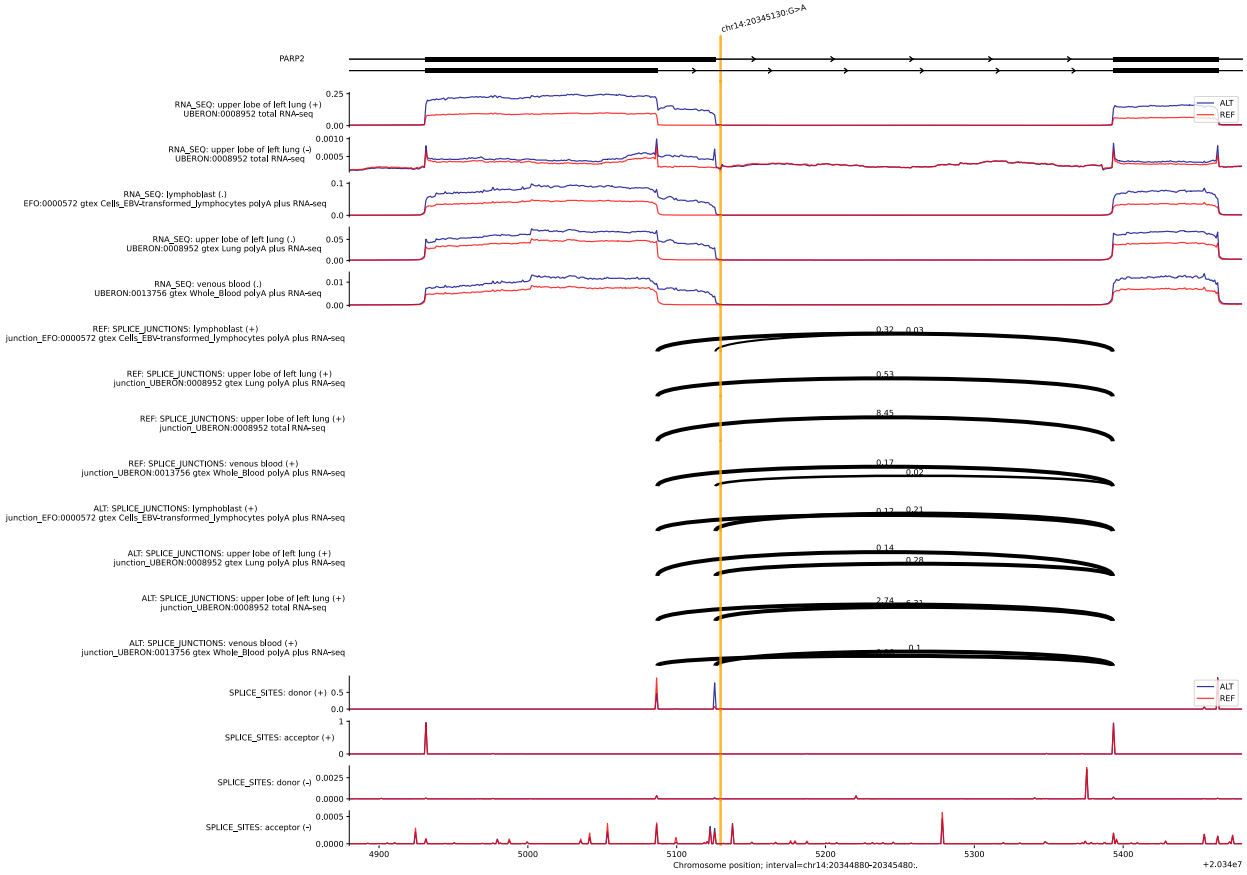


**Fig. S11.** Sanger sequencing validation of the PARP2 rs2297616 minigene splice reporter assay.

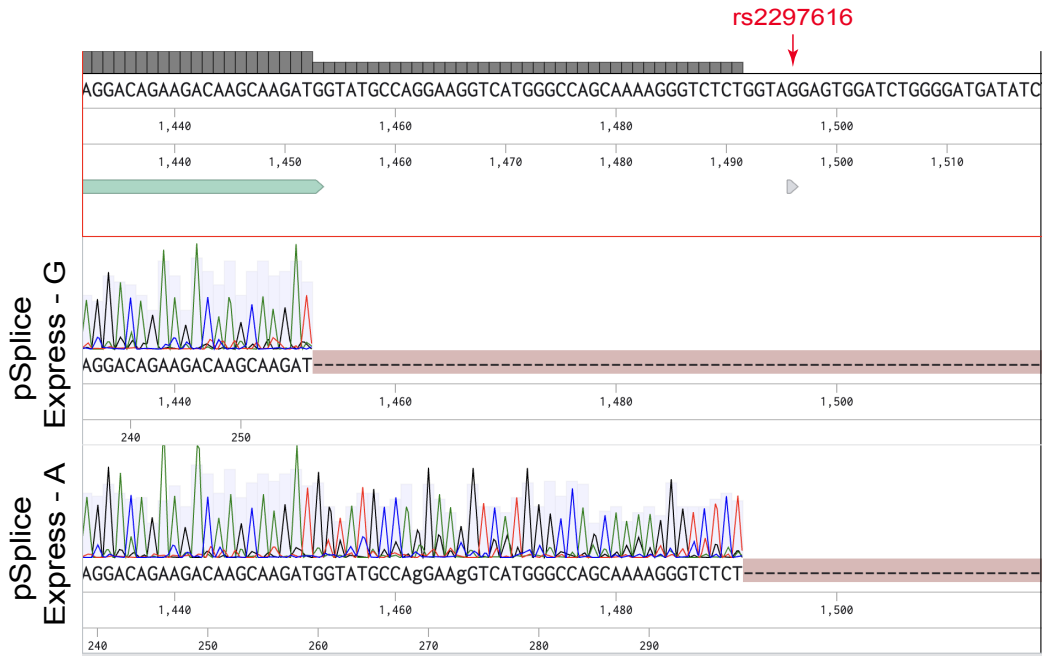


**Fig. S12**. Correlation of PEER factors, sex, and genotypic PCs.

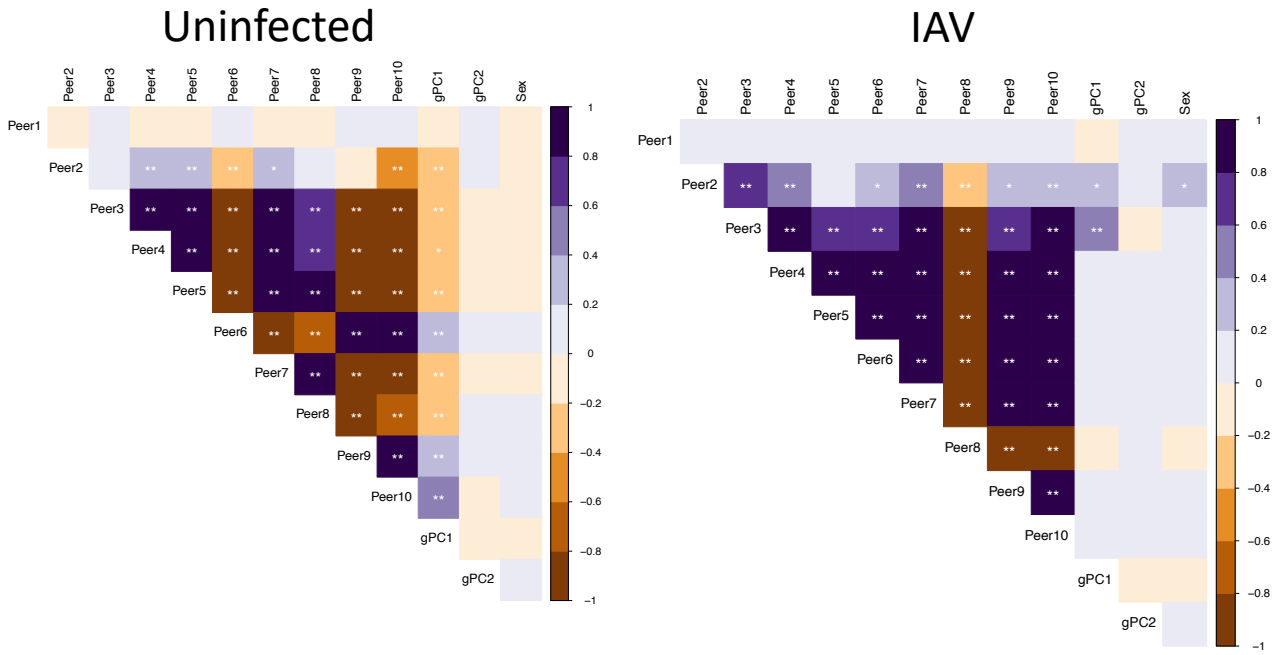


**Table S7**. Primers used for CRISPR-Cas9 editing of PARP2.

| | **SEQUENCE 5' --> 3'** |
|---|---|
| **GRNA1** | AAAAGGGUCUCUGGUAGGAG |
| **GRNA2** | CUCUGGUAGGAGUGGAUCUG |
| **GRNA3** | UCUCUGGUAGGAGUGGAUCU |
| **HDR_G** | AGGAAGGTCATGGGCCAGCAAAAGGGTCTCTGGTAGGAGTCGATCT GCCGATGATATCTTGTTATTTCAACTCCTATTT |
| **HDR_A** | AGGAAGGTCATGGGCCAGCAAAAGGGTCTCTGGTAAGAGTCGATCT GCCGATGATATCTTGTTATTTCAACTCCTATTT |
| **ATTB1F** | GGGGCAAGTTTGTACAAAAAAGCAGGCTAATGGCAACACGGCTCCAGAAGAC |
| **ATTB2R** | GGGGACCACTTTGTACAAGAAAGCTGGGTCTTCCCCACCTTGGCTGTACACTCT |
| **RS2297616_F** | AATGGCAACACGGCTCCAGAAGAC |
| **RS2297616_R** | CTTGTTGTTGTTGAACTGGAGATTGG |