Supplemental Data:

Genetic control of splicing of *SIRPG* modulates risk of type 1 diabetes

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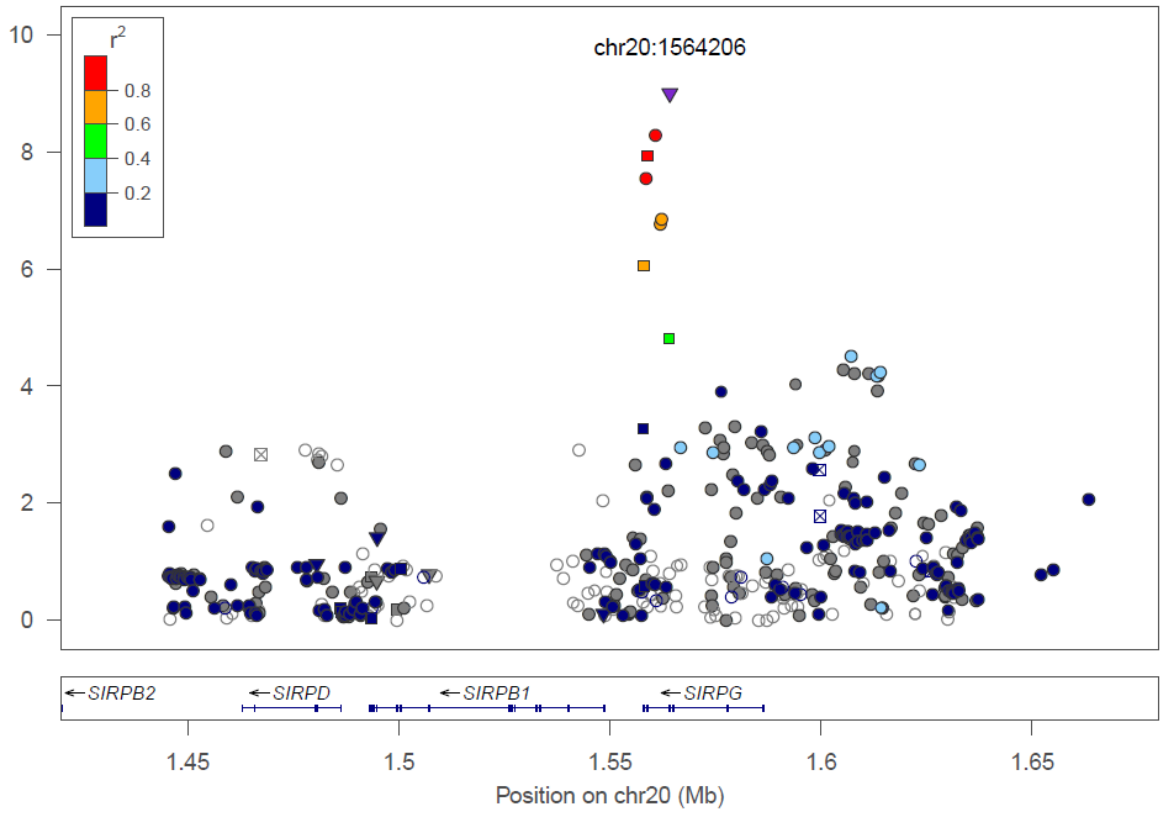
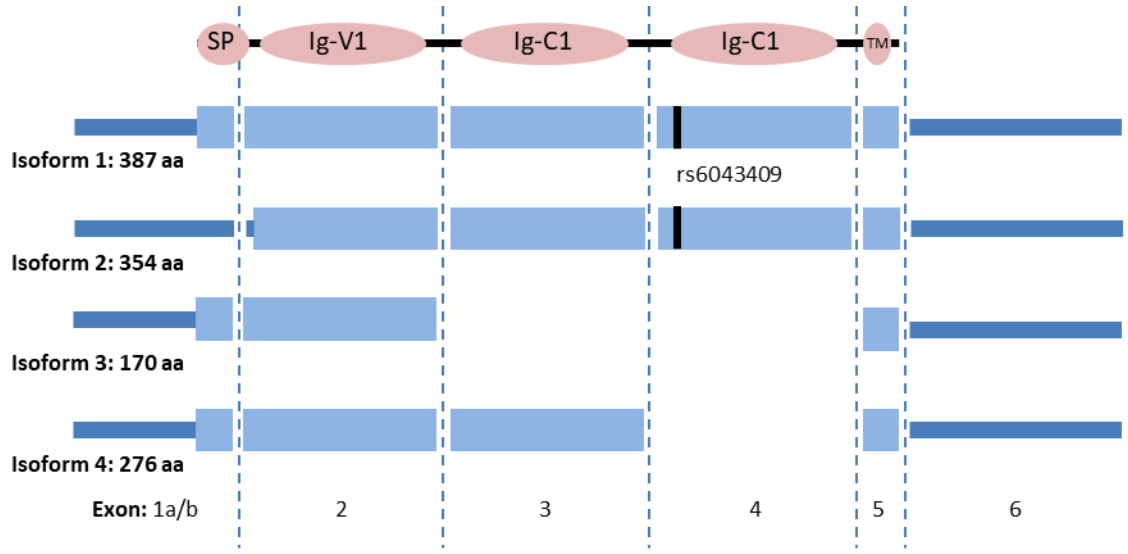
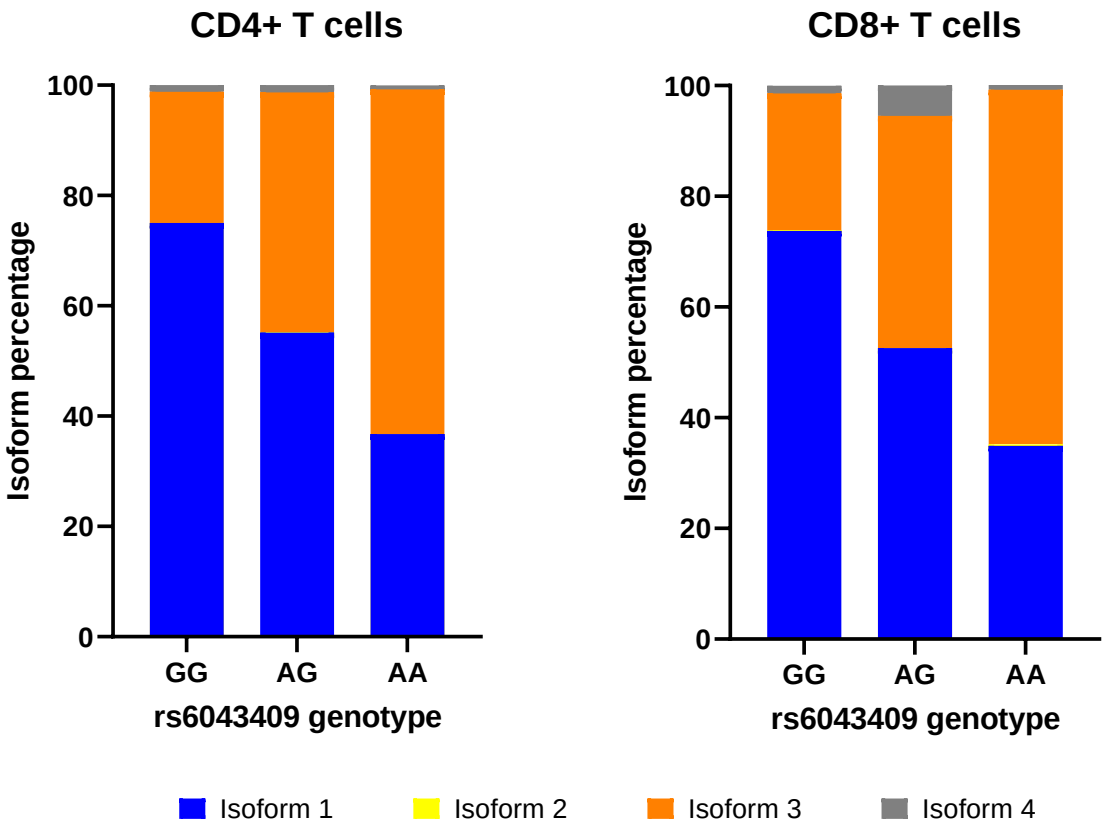


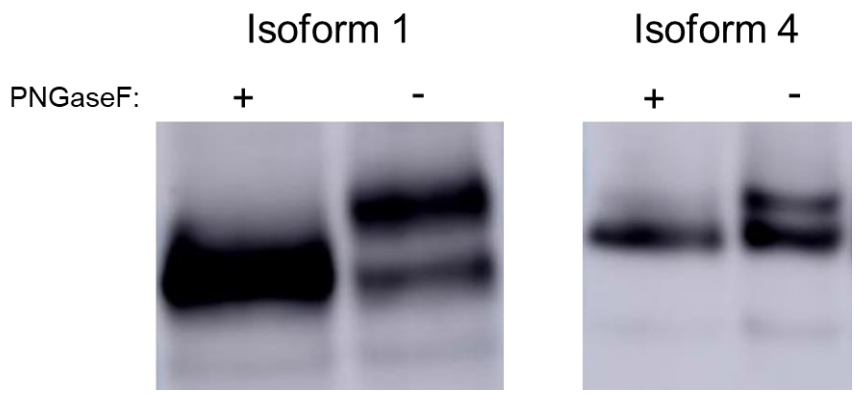
Supplemental Figure 1: Prior evidence for association with type 1 diabetes in the chromosome 20p13 region. Locus zoom plot depicting the evidence for allelic association with type 1 diabetes for loci at chromosome 20p13 derived from ImmunoChip genotyping. Vertical axis shows the evidence for association plotted as the $-\log_{10}$(p-value). Horizontal axis shows physical distance in Mb with the positions of genes indicated. The index marker, rs6043409, with the most significant disease association in the region is depicted in purple. The correlations (r^2) of alleles at other variants in the region to rs6043409 are indicated by their fill color. Shape of the symbol indicates the type of variant (inverted triangle = coding, non-synonymous, filled square = coding or 3'untranslated region, square with diagonal lines = placental expression).



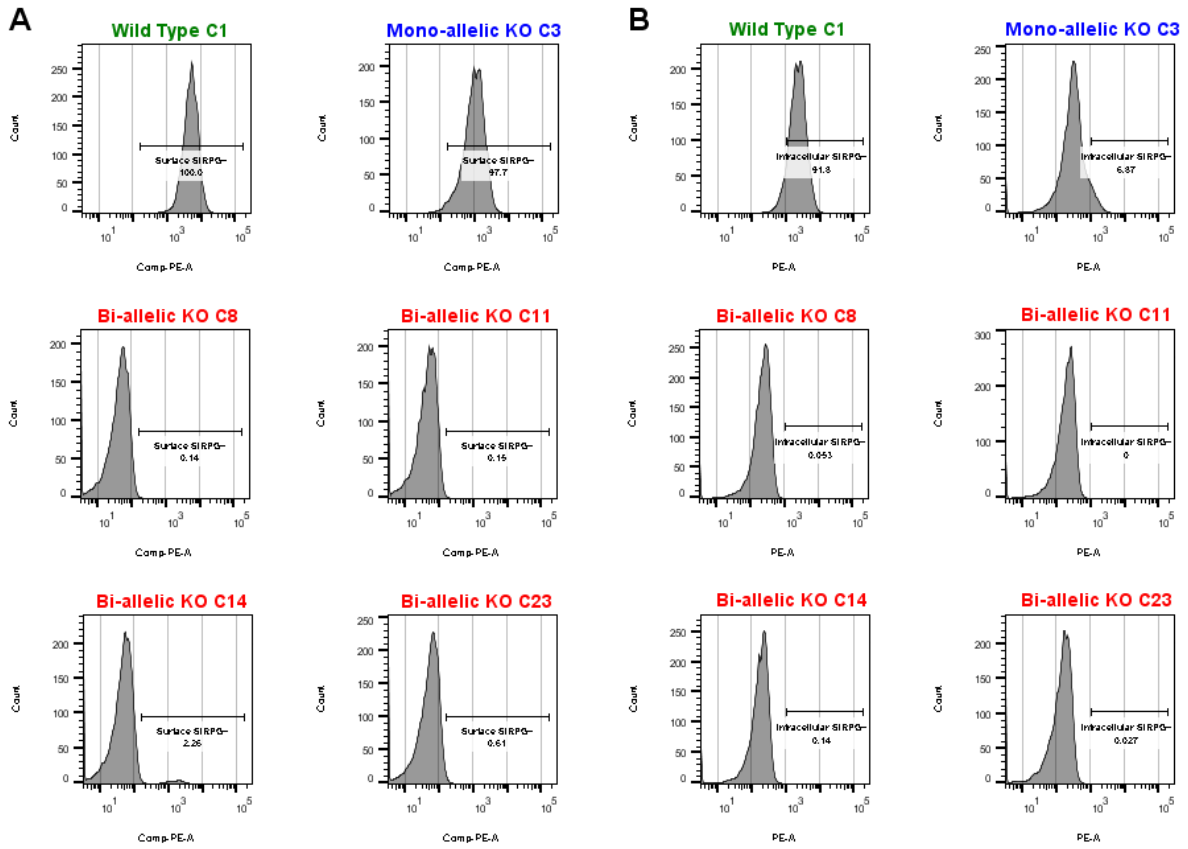
Supplemental Figure 2: *SIRPG* transcript isoforms and their expression in T cells. The top line indicates the protein structure of SIRPγ. SP indicates the signal peptide. Ig indicates and immunoglobulin homology domain of either the variable (V1) or constant (C1) type. TM indicates the transmembrane region. Subsequent lines depict the 4 most prominent transcript isoforms of *SIRPG* and the numbering system used in the manuscript. Narrow blue bars indicate noncoding regions while wider bars indicate coding. Vertical dashed lines indicated exon-exon boundaries and the exon numbering system is provided in the last line. In isoforms 1 and 2, the vertical black bar in exon 4 indicates the position of the genetic variant rs6043409.



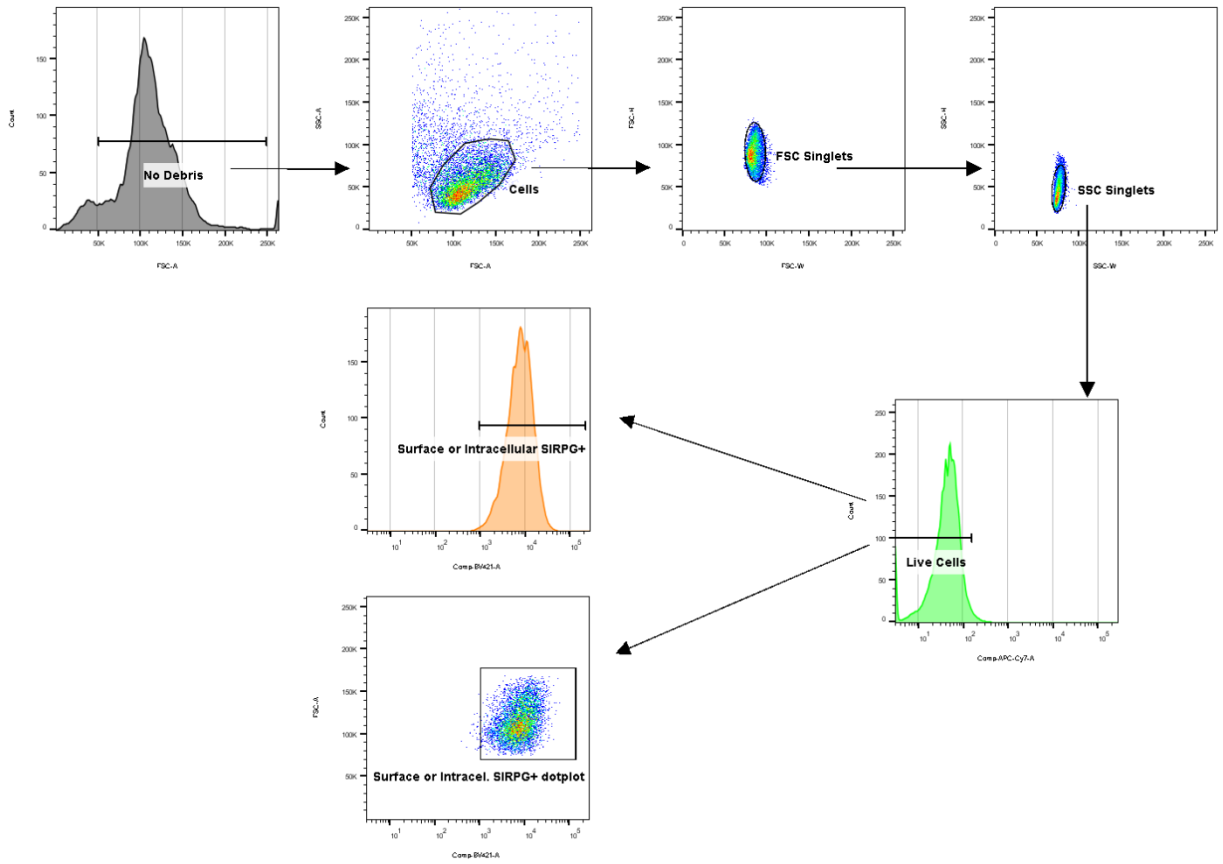
Supplemental Figure 3: Percentage of total *SIRPG* transcripts contributed by each alternatively spliced isoform in subjects with type 1 diabetes clustered by their genotypes at *rs6043409*. The contributions of individual isoforms determined from RNA-seq data are indicated by the stacked bars. All columns show the percentages of all four isoforms in the order 1-4 from bottom to top.



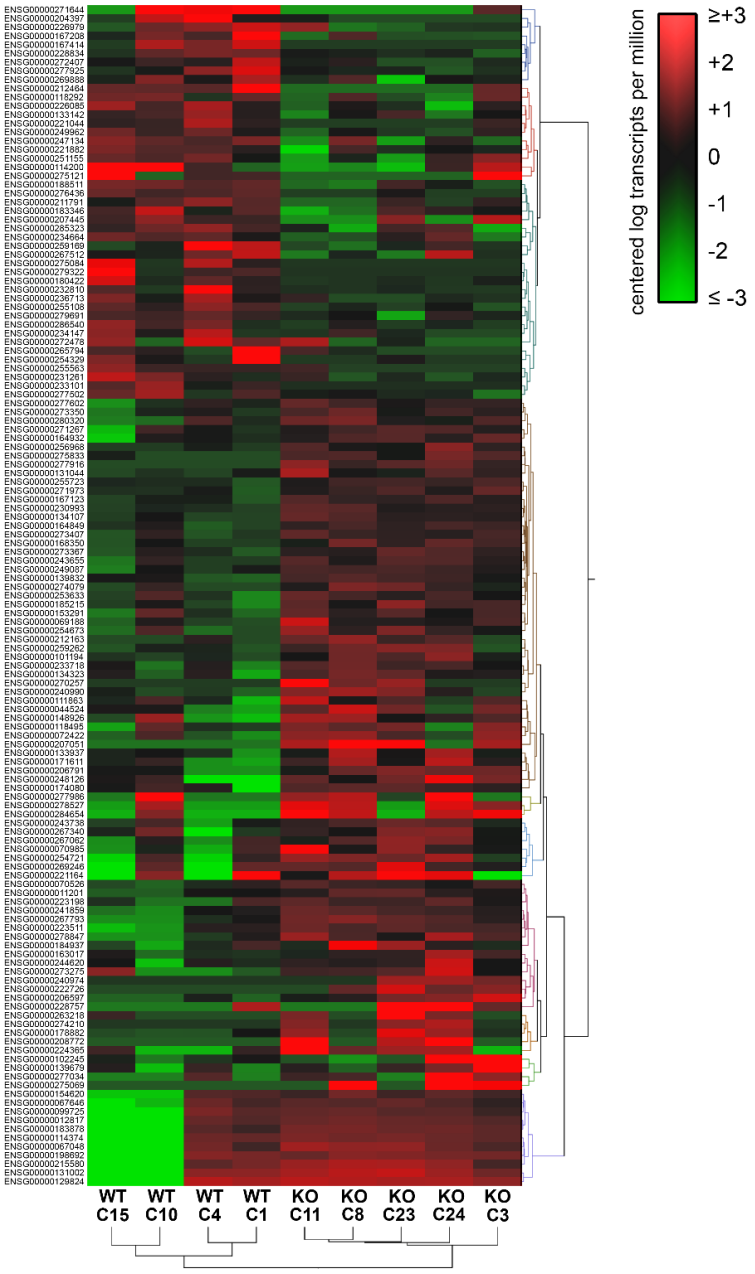
Supplemental Figure 4: PNGaseF treatment reduces the molecular weight of immunoblotted bands corresponding to SIRPγ isoforms 1 and 4. HEK293 cells were transiently transfected with plasmids encoding V5 epitope tagged version of the indicated SIRPG isoforms. Cells were lysed with EBC buffer (0.05 M Tris HCl pH 8.0, 0.12 M NaCl, 0.5% NP40, 1 mM EDTA, 0.05 M NaF, 1mM Na_3VO_4, 1 mM β-mercaptoethanol, cOmplete ULTRA protease inhibitor (Roche), and PhosSTOP phosphatase inhibitor (Roche)). Whole cell lysates from HEK293T cells containing transfected *SIRPG* isoforms were treated with PNGase F (Sigma P7367) or H_2O (mock-treated). Lysates were treated with 0.02% SDS and 8.6 mM β-mercaptoethanol with 15.5 mM NH_4HCO_3 for a final concentration of 1 mg/mL denatured isoform 4. The solution was incubated at 100℃ for 10 minutes before 5 uL of 15% Triton X-100 was added. 2.5 Units of PNGase F or 5 uL of H_2O (mock-treated) was introduced prior to a 1 hour incubation at 37℃. The reaction was stopped by heating at 100℃ for 5 minutes. Lysates were separated on poly-acrylamide gels and immunoblotted with an antibody directed at the V5 epitope tag. The double bands corresponding to isoforms 1 and 4 were reduced to a single band upon treatment with PNGaseF suggesting that the doublets reflected the effects of glycosylation.



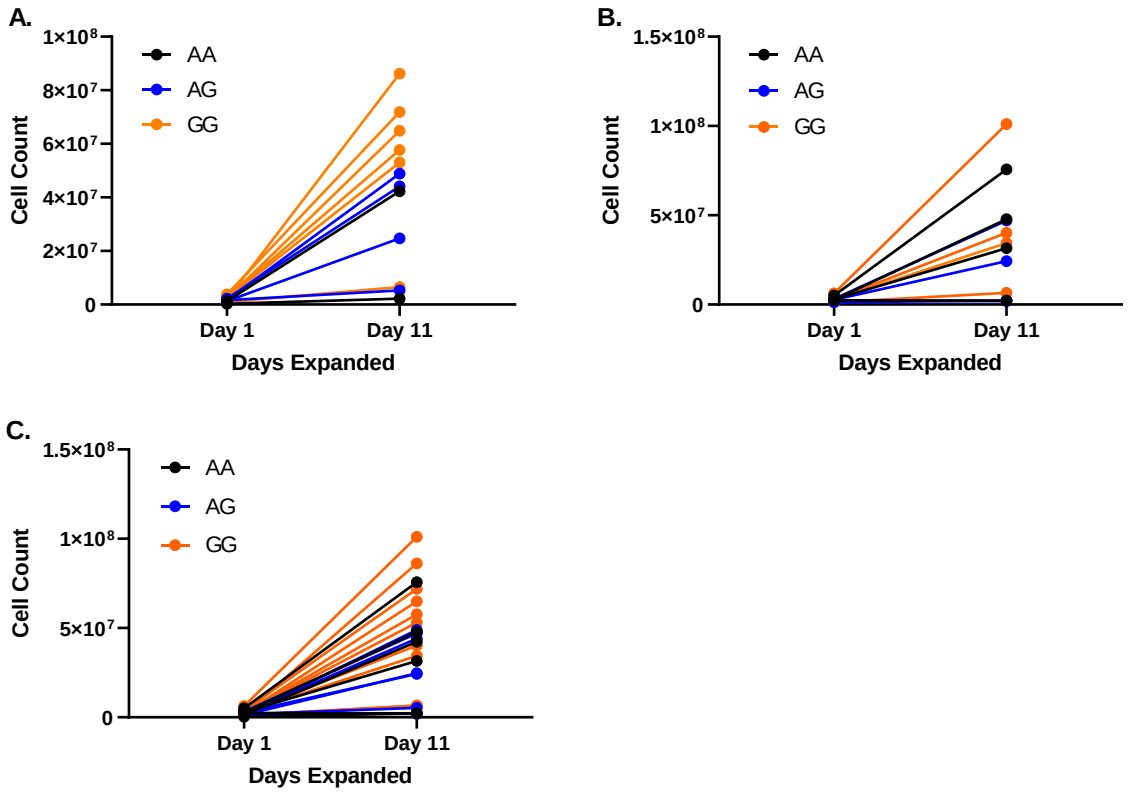
Supplemental Figure 5: Cell surface and intracellular expression of SIRPγ in Jurkat cells with CRISPR-targeted mutations in exon 4 of *SIRPG*. Jurkat cell clones were acquired on a BD LSR Fortessa and selected for no debris, morphology, singlets and viability according to the gating strategy described in Supplemental Figure 5. SIRPγ surface (A) and intracellular (B) expression levels were quantified in Wild Type Jurkat p2 and clones carrying a SIRPγ mono or bi-allelic truncating mutation (KO) in exon 4 by using PE anti-human CD172g (SIRPγ) antibody.



Supplemental Figure 6: Gating strategy for SIRPγ cell expression. Jurkat cell clones were acquired on a BD LSR Fortessa and gated according to i) No Debris, ii) FSC and SSC (morphology), iii-iv) FSC/SSC area and height (singlets selection), and v) living cells (by viability staining). Then, SIRPG+ cells were defined by surface or intracellular SIRPγ expression.



Supplemental Figure 7: RNA-seq analysis of *SIRPG*-targeted clones. RNA-seq was performed on the indicated wild-type and *SIRPG*-targeted Jurkat clones. Heatmap depicts mean-centered log-TPM values, where each gene's expression is centered such that the mean is 0, for 135 genes with log fold change in expression >1 or <-1 when comparing *SIRPG*-targeted clones to wild-type clones.



Supplemental Figure 8: Expansion of purified CD4$^+$ T cells by genotype at rs6043409.

Purified T cells were expanded with anti-CD3/CD28 beads and IL-2 for 11 days. Day 1 and day 11 cell counts are connected by lines and colored by genotype. Three datasets were analyzed: (A) samples previously used for RNA (Figure 1A) and protein (Figure 2C) extraction, (B) an independent replication set of PBMCs selected using the same criteria as in (A), and (C) combined data from (A) and (B). Overall P = 0.088 for genotype differences.

Clone	Allele	Sequence	Frameshift
C1 (Jurkat)	1	TATCTGACCAAAGGG	0
	2	TATCTGACCAAAGGG	0
C3	1	TATCTGACCAAAGGG	0
	2	TATCTGACC AAGGG	-1
C8	1	TATCTGACC*GC*AAAGGG	+2
	2	TATCTGACC*GC*AAAGGG	+2
C11	1	TATCTGA CAAAGGG	-1
	2	TATCTGA CAAAGGG	-1
C14	1	TATCTGA CAAAGGG	-1
	2	TATC*GCG* CAAAGGG	-1
C23	1	TATCTG*GGGGT*AAAGGG	+2
	2	TATCTG*GGGGT*AAAGGG	+2

Supplemental Table 1: SIRPG exon 4 targeted CRISPR clones. The unmodified sequence in exon 4 of *SIRPG* in Jurkat cells (clone C1) at the targeted site is indicated. Variation from this sequence in modified clones is shown. Gaps indicate deletion of the corresponding nucleotides while italicized and underlined nucleotides represent insertions relative to the wild-type C1 sequence.