Supplemental Figure Legends

Figure S1. Virus-dependent recruitment of transcription factors and general transcriptional machinery to several type I IFN genes, related to Figure 1

(A, C, E, G, I, K, & M) Namalwa B Cells were infected with Sendai virus or mock infected for the indicated times and analyzed by ChIP (IRF3, p65/RELA, MED1, Pol II (All), Pol II (S5P), and Pol II (S2P)). The genes investigated are displayed below the plot. Data are representative of at least three independent experiments.

(B, D, F, H, J, L, & N) The *Ifnb1* gene is analyzed (IRF3, p65/RELA, MED1, Pol II (All), Pol II (S5), and Pol II (S2P)) at the regions corresponding to the diagram. Data are representative of at least three independent experiments.

(O & P) The *Ifnb1* (O) and *Gapdh* (P) genes were analyzed by ChIP-qPCR for the indicated factors used in ChIP-seq analysis.

Figure S2. Genome-wide virus-dependent transcription factor binding sites, related to Figure 1

(A & B) Venn diagram showing the overlap between IRF3 (A) or p65/RELA (B) binding sites at basal state and four hours after Sendai virus infection

(C & D) Analysis of changes in IRF3 (C) and p65/RELA (D) sequence reads (tags) between basal state and Sendai virus infected cells. Scatter plot displays the number of IRF3 or p65/RELA sequence tags across all IRF3 or p65/RELA bound loci, respectively. Distributions of sequence tags near the TSS (within 5 kb) are indicated in black, and sequence tags within peaks distal to the TSS (> 5 kb) are shown in grey. Numbers represent the Pearson correlation coefficient (R) and the shaded blue line represents the linear regression, including the 95% confidence region.

(E) Analysis of sequence read (tag) density at factor occupied sites (peaks) between two virus-infected biological replicates. Scatter plot displays the number of IRF3, p65/RELA, MED1, NELFA, Pol II (All), or Pol II (S2P) sequence tags from two biological replicates across all factor bound loci called from the paired-end libraries. Distributions of sequenced tags are indicated in black. Numbers represent the Pearson correlation coefficient, and the line represents the linear regression line, which includes the 95% confidence interval)

Figure S3. Enriched sequence motifs at IRF3 bound loci suggest multiple antiviral regulatory partners, related to Figure 2

(A & B) Sequence motifs similar to the canonical IRF3 (A) or p65/RELA (B) binding elements identified by *de novo* motif analysis of the IRF3 or p65/RELA bound sites described in Figure 2A, respectively.

(C) Graphical representations of two additional DNA sequence motifs, CRE and Ets, identified within the IRF3 regions described in Figure 2A. Data are displayed as in Figure 2A.

(D) Pie charts representing the genomic DNA sequences of the IRF3 regions defined in (A). Data are displayed as in Figure 2B.

(E) Plot of the mean motif density at IRF3 regions defined in (A).

(F) Heatmap representation of IRF3 (black) and p65/RELA (blue) occupancy levels at differentially occupied loci defined in (A) that encompass the identified motif. Data are displayed as in Figure 2D.

Figure S4. Activated IRF3 and p65/RELA occupancy, related to Figure 5

(A) Plot is displayed as in Figure 5A. Data shows a 50 kb window surrounding the TSSs and TTSs of all annotated genes.

(B) Analysis of IRF3 (left) and p65/RELA (right) target gene pause ratio (PR) for high confidence target genes described in (A) before (red) and after (black) infection. Lower PR values signify more efficient elongation.

Figure S5. Virus-activated transcription at unannotated genomic locations, related to Figure 7

Additional examples of virus-dependent occupancy of IRF3+p65/RELA or IRF3 targets at unannotated loci. The IRF3, p65/RELA, MED1, NELFA, Pol II (All), and Pol II (S2P) occupancy at basal state and 4 h.p.i. are illustrated in genome browser views of virus-induced regions in chromosome 7 and 13.

Table S1. SOLiD tag sequencing data, related to Figures 1 - 7

Table S2. Inducibly bound peaks, related to Figures 1 – 7

Table S3. Target genes

Table S4. Bound sites' annotation and distance to TSS, related to Figures 4 and 5 and Figure S4

Table S5. GO terms, related to Figure 6

Table S6. Pause ratio, related to Figure 5 and Figure S4

Table S7. Primers List, related to Figure 7, 8 and Figure S1

Extended Experimental Procedures

Chromatin immunoprecipitation (ChIP) assays

In summary, cells were cross-linked for 20 min at room temperature by the addition of an 11% formaldehyde solution (50 mM HEPES-KOH pH 7.5, 100 mM NaCl, 1 mM EDTA pH 8.0, 0.5 mM EGTA pH 8.0, and 11% formaldehyde) to the growth media to achieve a final 1% formaldehyde solution concentration. Cells were washed three times with PBS, pelleted, and used immediately or frozen in liquid nitrogen for future analysis. 100 µl of Dynal magnetic beads (Invitrogen) were blocked with 0.5% BSA (w/v) in PBS, then washed and bound to 10 µg of the antibody (Pol II [8WG16]: Abcam ab817; Ser5P Pol II: Abcam ab5131; Ser2P Pol II: Abcam ab5095; IRF3: Abcam ab76367; NFκB p65: Abcam ab7970; MED1: Bethyl Labs A300-793A; NELFA: Santa Cruz (A-20) sc-23599). Cross-linked cells were lysed at 4°C with lysis buffer 1 (50 mM HEPES-KOH pH 7.5, 140 mM NaCl, 1 mM EDTA, 10% glycerol, 0.5% NP-40, 0.25% Triton X-100, and 1× protease inhibitors (Calbiochem)), nuclei was purified by centrifugation, and washed with lysis buffer 2 (10 mM Tris-HCl pH 8.0, 200 mM NaCl, 1 mM EDTA, 0.5 mM EGTA, and 1× protease inhibitors).

Nuclei were resuspended and sonicated in lysis buffer 3 (10 mM Tris-HCl pH 8.0, 100 mM NaCl, 1 mM EDTA, 0.5 mM EGTA, 0.1% Na-Deoxycholate, 0.5% N-lauroylsarcosine, and 1× protease inhibitors) for 60 cycles in 15 s increments in an ice water bath and rested in an ice water bath between cycles for 45 s. Triton X-100 was added to a final concentration of 1% to the sonicated lysates. Clarified, sonicated lysates were incubated overnight at 4°C with magnetic beads bound with antibody, beads were washed five times with RIPA (50 mM HEPES pH 7.5, 500 mM

LiCl. 1 mM EDTA, 1% NP-40, and 0.7% Na-Deoxycholate), and once with TE & 50 mM NaCl. Bound immune complexes were eluted in elution buffer (50 mM Tris-HCl pH 8.0, 10 mM EDTA, 1% SDS) at 65°C for 30 min with occasional vortexing, and crosslinks reversed at 65°C for 12-15 hr. RNA and protein were digested using RNase A and Proteinase K, respectively, and DNA was purified with a phenol/chloroform extraction followed by ethanol precipitation.

SOLiD sequencing

SOLiD (ABI) ChIP-seq analysis (sample preparation, emulsion-PCR (e-PCR), sequencing, and SOLiD data analysis) was carried out according to the manufacturer's protocols. A summary of the protocol used is described below.

Sample preparation

Purified immunoprecipitated DNA was prepared for sequencing according to the 5500xl Series SOLiD Systems Fragment Library Preparation protocol. Fragmented DNA was prepared by blunt-ending the DNA, size selecting DNA between 100-250 bp using Agencourt AMPure XP Reagent beads, and adding a dA-tail to allow for directional ligation. Following the addition of a single adenine nucleotide overhang, a 1:20 dilution of the appropriate adaptor pair was used in the ligation step. After ligation, the DNA library was size selected to a narrow range of fragment sizes by using Agencourt AMPure XP Reagent (~200-300 bp, which represents shear fragments between 100 and 200 nt in length and ~100 bp of primer sequence). A subsequent PCR with limited amplification (14-17 cycles) was conducted and a final

size selection was carried out prior to e-PCR and paired-end sequencing on the ABI SOLiD series 5500xl DNA sequencing platform.

SOLiD ChIP-seq data analysis

All sequence data were aligned to the human hg19 assembly using BioScope v1.3.1. The reference genome was converted to colorspace for appropriate alignment with colorspace reads, initially locating perfect, full-length 50 bp matches for each read. If a perfect match could not be found, then 25 bases were aligned with 2 colorspace mismatches allowed, starting at position 0 (i.e. the first sequenced base). The alignment was then extended base-by-base toward the 3' end. If the alignment failed within the first 25 bp of the read, then 25 bases of the read were aligned, with 2 allowed colorspace mismatches, starting at position 15 of the read (i.e. the 16th sequenced base), and extended toward the 5' end, and forward toward the 3' end until the best alignment is obtained. If this failed, then the read was considered unmapped. For genome-wide analysis only uniquely mapped reads were retained. Operating under the default parameters and using the sequenced input DNA as the control, MACS software was used to identify binding sites (or peaks) in each sample. We further filtered peaks that are contained in signal artifact regions, as specified by the set of blacklists used for Grch37/hg19: (ftp://encodeftp.cse.ucsc.edu/users/akundaje/rawdata/blacklists/hg19/).

Data analysis was performed using HOMER, a software suite for ChIP-Seq analysis. Each ChIP-Seq experiment was normalized to a total of 10^7 uniquely mapped tags by

adjusting the number of tags at each position in the genome to the correct fractional amount given the total tags mapped. This normalization was used for all downstream analysis. All metagene data (Figure 5A, B, & C and Figure S4C) used a customized set of 24,723 RefSeq genes, from which all genes with TSSs within 1,000 bps of each other have been excluded.

Genome Browser and Pause Ratio (PR) Analysis

ChIP-Seq experiments were visualized by preparing custom tracks for the UCSC Genome browser in a manner similar to that previously described (Figure 5D, Figure 7C & D, and Figure S5) (Robertson et al., 2007). A "pausing ratio" (PR) was used to quantify the degree of promoter proximal RNA Polymerase II (Figure 5D and Figure S4D). The PR is calculated as the ratio of Pol II (All) sequenced tag density from -300 to +300 around the nearest TSS relative to the tag density +300 bp from the TSS to +3,000 bp after the gene end. Tag densities at each promoter were determined by first adjusting the position of each tag by half of the estimated length of the isolated ChIP fragments. Tags were then summed for each promoter for gene-specific levels (e.g., Figure 5D) or at each position in the promoter to create a profile (e.g., Figure 5A). Pol II density within gene bodies was determined by adding the number of tags within the gene body defined by RefSeq and normalizing by the length of the gene. Total exon and intron tag densities were calculated by adding the number of tags found within exons and introns defined by RefSeq and dividing these totals by the lengths of these features. PR values were calculated for all Pol II bound genes and

are included in Table S6 The implemented methods are freely available at http://biowhat.ucsd.edu/homer/.

Heatmap Analysis

ChIP-seq enrichment for indicated factors was determined in 25 bp bins and centered on each peak (Fig. 3C) or motif center (Fig. 2D and 6D) within a 6 kb window. Generally, the genomic site list for each representation was rank ordered based on the amount of signal for the indicated factor, from most to least, and then clustered by k-means. K-means clustering was performed with Cluster 3.0 and visualization with Java Treeview (Eisen et al., 1998).

Factor Co-incidence Analysis

We find that IRF3, p65, MED1, NELFA, Pol II (All) and Pol II (S2P) enrichment all spatially overlap with one another in a variety of genomic contexts. To determine the spatial relationships between all the factors, we mapped the location of genomic sites that are differentially bound in the infected sample (2, 3, 4, and 10-fold enrichment) relative to enriched sequenced tag density for the other factors (Fig. 3A & B). This algorithm is designed to operate on top of traditional bound region enrichment models—such as MACS—to precisely map high confidence binding sites from ChIP-seq data at higher resolution.

Motif Analysis

The novel motif discovery algorithm within the software suite HOMER was used to identify candidate protein–DNA interaction motifs in an unbiased manner. Input to the program consisted of 100 bp (for IRF3 and p65/RELA) or 200 bp (for MED1, NELFA, and Pol II) sequences centered at the peak positions displaying a > 2-fold increase in occupancy after infection (p-value < 1×10^{-5}). We only reported enriched motifs of very significant p-values (< 1×10^{-50}). The logo plots were generated using the seqLogo package in R (http://www.bioconductor.org/packages/2.12/bioc/html/seqLogo.html).

The top-scoring motifs from HOMER were queried against the JASPAR, Transfac, and HOMER databases to identify the best matching known motifs.

Functional Classification Analysis

Statistical analysis of the overrepresented gene ontology (GO) categories for genes associated with inducibly bound IRF3, p65/RELA, MED1, NELFA, and Pol II (All) regions (4-fold increase; p-value < 1×10^{-5}) was performed using the functional enrichment algorithm within HOMER's software suite. Enrichment scores of example categories in Figure 6E were log transformed and plotted using the ggplot2 package in R (http://cran.r-project.org/web/packages/ggplot2/index.html).

Sequence Analysis

The vertebrate phastCons conservation scores of IRF3 or p65/RELA bound regions

demonstrating a greater than 2-fold increase in occupancy following virus infection (p-value < 1 x 10^{-5}) were obtained from the UCSC Genome Browser database (Karolchik et al., 2008). The conservation scores are in 10bp bins and centered on each peak (+/- 2.5 kb; Figure 1B).

Co-Association Analysis

The binding peaks from all the ChIP-seq datasets were assigned a z-score, derived as a measure of significance of the observed base overlap ratio (Dunham et al., 2012). A matrix of z-scores representing all pairwise comparisons were used to generate heatmaps using the pheatmap package in R (http://cran.r-project.org/web/packages/pheatmap/index.html) (Figure 4C).

Three iterations of this procedure were performed to compare: bound genomic sites in (1) the whole genome, (2) promoter regions within 2 kb of the nearest RefSeq TSS, and (3) distal regions > 10 kb from the nearest RefSeq TSS.

Boxplot Analysis

We quantified the difference in ChIP-Seq occupancy for the indicated factors at IRF3 and p65/RELA binding sites between cells at basal state and after Sendai virus infection (Figure 1D & H, 2E & F, and 7A & B). For each bound loci, we calculated the mean sequence tag density of the indicated factor in the ±1 kb window centered on the peak summit. The binding sites were partitioned according to their genomic

location as indicated. The difference between the mean sequence tag densities was calculated using a statistical test (Welch's two tailed t test).

Scatterplot Analysis

We quantified the ChIP-Seq occupancy of IRF3 and p65/RELA before and after infection at IRF3 and p65/RELA binding sites, respectively (Figure S2C-E). For each bound loci, we calculated the mean sequence tag density of the indicated factor in the ±1 kb window centered on the peak summit. The correlation between the mean sequence tag densities was calculated using a statistical test (Pearson correlation coefficient, R).

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Robertson, G., Hirst, M., Bainbridge, M., Bilenky, M., Zhao, Y., Zeng, T., Euskirchen, G., Bernier, B., Varhol, R., Delaney, A.*, et al.* (2007). Genome-wide profiles of STAT1 DNA association using chromatin immunoprecipitation and massively parallel sequencing. Nat Methods *4*, 651-657.

Table S1. Summary of SOLiD tag sequencing data and MACS scoring results

		Paired-End sequence tags mapped to genome	Peaks identified (P value cutoff = 1e-5)
IRF3	Mock	16,978,044	1,648
	SeV	24,965,834	6,141
p65	Mock	17,194,554	692
	SeV	22,890,812	1,107
MED1	Mock	32,172,140	3,863
	SeV	21,754,990	3,752
NELFA	Mock	4,492,264	10,870
	SeV	11,127,564	12,769
Pol II (8WG16)	Mock	7,512,714	27,376
	SeV	13,481,438	28,182
Pol II (S2P)	Mock	13,434,320	58,862
	SeV	27,195,040	55,493
Input	---	14,852,624	---

Table S2. Inducibly Bound Peaks

	IRF3	p65	MED1	NELFA	Pol II (8WG16)	Pol II (S2P)
Total Peaks (In SeV infected B Cells)	6,141	1,107	3,752	12,769	28,182	55,493
Differentially Bound Peaks (2-fold more tags)*	4,316	596	1,377	1,247	4,335	6,396
Differentially Bound Peaks (3-fold more tags)*	3,935	572	1,049	1,066	3,946	4,994
Differentially Bound Peaks (4-fold more tags)*	3,392	471	819	912	3,449	3,461
Differentially Bound Peaks (10-fold more tags)*	1,476	139	173	457	900	167

*Looked for peaks that have xxx-fold more tags (sequencing-depth independent) and a cumulative Poisson p-value less than 0.0001 (sequencing-depth dependent), ensuring that the analysis focused on genomic regions of high confidence.

Table S7. Primer List

RT-PCR Primers

	Forward Primer	Reverse Primer
Chr1 (36,000,000)	5'- GAGTATGGGACATGCGAGGG -3'	5'- TTCTCTGCACTGCCTCTGTG -3'
Chr 3 (23,000,000)	5'- AGGGGTCTAGAAGAGCGGTT -3'	5'- AAGAACCCAGGCCAACAGAG -3'
Chr 12 (97,114,000)	5'- CCTTCTGTCCGAGGTGGAAC -3'	5'- CCTCCACCACAATCTCCAGC -3'
Chr 12 (97,110,000)	5'- TGTCTTCCCACCCAAGAACA -3'	5'- GGGCCTGTTTGTGAACTCCA -3'
Chr 14 (75,000,000)	5'- AAACCACAAATGTGCCTGCC -3'	5'- CCGCAAAGGAGAGTCAAGGT -3'
IFNB1	5'- CATTACCTGAAGGCCAAGGA -3'	5'- CAATTGTCCAGTCCCAGAGG -3'
GAPDH	5'- ACAGTCAGCCGCATCTTCTT -3'	5'- ACGACCAAATCCGTTGACTC -3'

ChIP-qPCR Primers

	Forward Primer	Reverse Primer
IFNB1 (1)	5'- AGCAGGCCCCAGTGACCAGA -3'	5'- AGCCAATGCAAGGAGCTTCAGAGG -3'
IFNB1 (2)	5'- CCACCCTGGTTGGGCCTTCTCTA -3'	5'- TCAAACCAACCAGTCACAGCCCTT -3'
IFNB1 (3)	5'- GGGAGAAGTGAAAGTGGGAAA -3'	5'- CAGGAGAGCAATTTGGAGGA -3'
IFNB1 (4)	5'- TGGCACAACAGGTAGTAGGCGACA -3'	5'- TGGAGAAGCACAACAGGAGAGCA -3'
IFNB1 (5)	5'- TCAGTGTCAGAAGCTCCTGTGGC -3'	5'- ATGCGGCGTCCTCCTTCTGGA -3'
IFNB1 (6)	5'- TCCCTGAGGAGATTAAGCAGCTGCA -3'	5'- AGCATCTCATAGATGGTCAATGCGG -3'
IFNB1 (7)	5'- TCTAGCACTGGCTGGAATGAGACT -3'	5'- TGCAGACTGCTCATGAGTTTTCCCC -3'
IFNB1 (8)	5'- GGGGAAAACTCATGAGCAGTCTGCA -3'	5'- CCACTCTGACTATGGTCCAGGCACA -3'
IFNB1 (9)	5'- ACTGAAGATCTCCTAGCCTGTGCC -3'	5'- ACAGCATCTGCTGGTTGAAGAATGC -3'
IFNB1 (10)	5'- TCTGGCCCCTGCCTTTAAGGAATTT -3'	5'- ATTCCCCCATAAGGTTCAGGTCCC -3'
IFNB1 (11)	5'- GATTTGGTCCCAGGGGAGCCCT -3'	5'- TTGGCCAAGAGGGCTGGTGAAC -3'
IFNA2	5'- GGTGAGAAAAACAGCTGAAAACCCA -3'	5'- GACCTTGCTTTGTGCCTAGCCTT -3'
IFNW1	5'- CCCAGACGTTTTTCATTTGAT -3'	5'- GGATGCTCCTGGCTTTACT -3'
GAPDH	5'- GCGTGTAAGGGTCCCCGTCCT -3'	5'- GTTCAACTGGGCACGCACCGA -3'

ChIP-qPCR & RT-PCR Primers

	Forward Primer	Reverse Primer
Chr1 (213,000,000)	5'- CCACGGGTCCCACTACTCTA -3'	5'- AAACCTGGGGCCATACACTC -3'
Chr2 (61,000,000)	5'- CCAAGGCAGACCCTTTGCTA -3'	5'- CGAGTGCTGGAAGCTCAAGA -3'
Chr 5	5'- TCCCAGATCCTGCCTGAAGA -3'	5'- CTAAATTCGCACTCCCCCGT -3'
Chr 7	5'- TCGTGTGCCTTGTGTTTCAG -3'	5'- CTGGAGCAAGAAGAGAACCTCA -3'
Chr 9	5'- AGGTGTCAACAGAGTCCCAAA -3'	5'- CTTGACTCTCCTGCCCTGTG -3'
Chr 10	5'- TTCCCAAGAGGTCTGTCCGT -3'	5'- CACGTCACTGGGAGACATCAA -3'
Chr 12	5'- GGCCTGTCACTTGAAAGATTGG -3'	5'- TGGTCACCTAGTTGGTAATGTGA -3'
Chr 13	5'- CTCATTGCTGAGTTTGCCCTG -3'	5'- TTCTTATTGGTGGGGGTAGGG -3'
Chr 16 (109)	5'- TGAGTTCTCTGTGCAACCCTC -3'	5'- TTGGAAGAAAGCACCCTCCC -3'
Chr 16 (574)	5'- ATTCCCCAAAAGGGTGAGGC -3'	5'- CTTCCGGGCACCTGTTATTCA -3'

Supplemental Figure S1

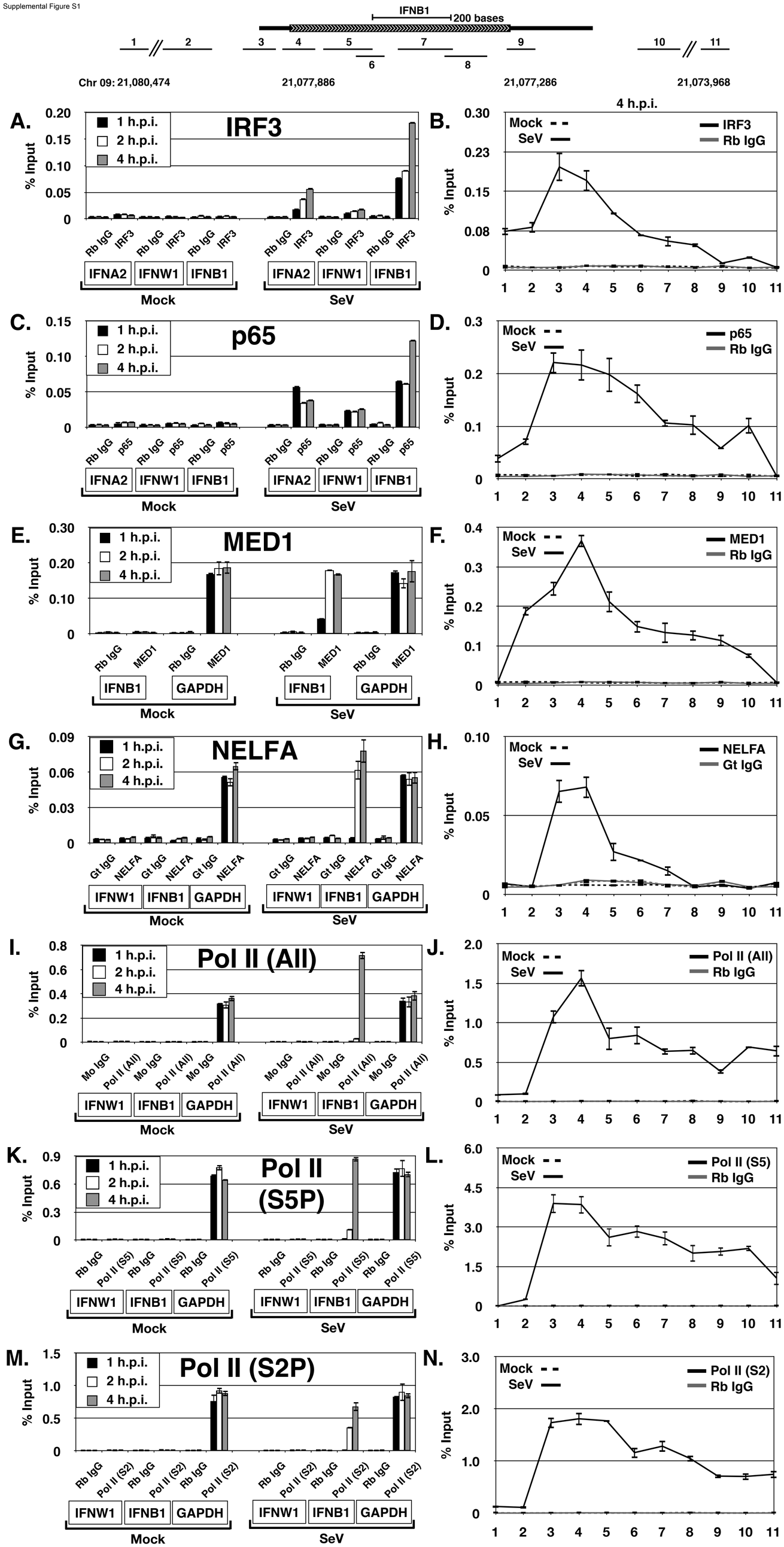
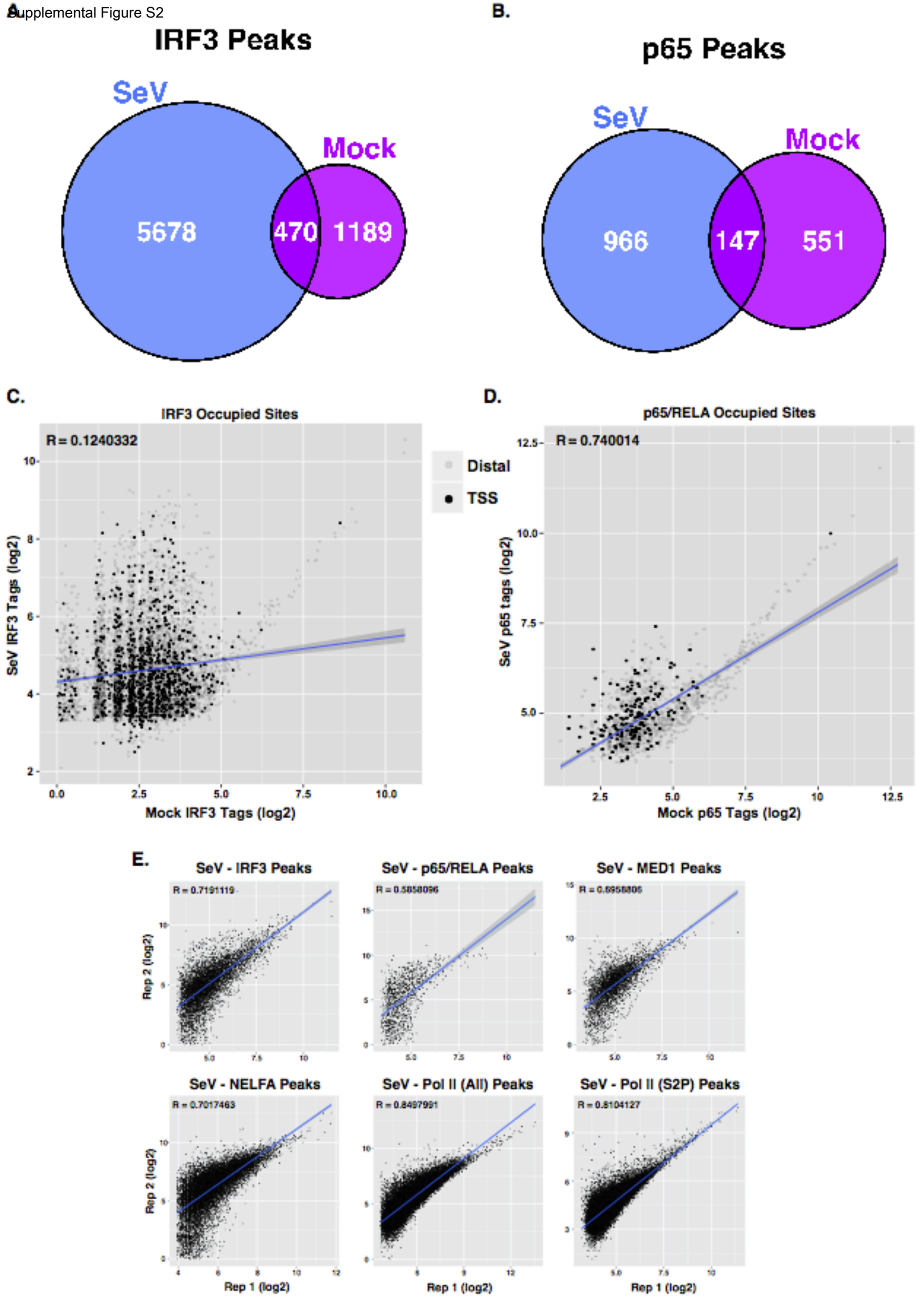


Figure S1

Supplemental Figure S2



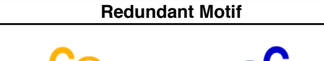
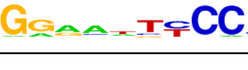
A.

Similar IRF3 consensus motifs found

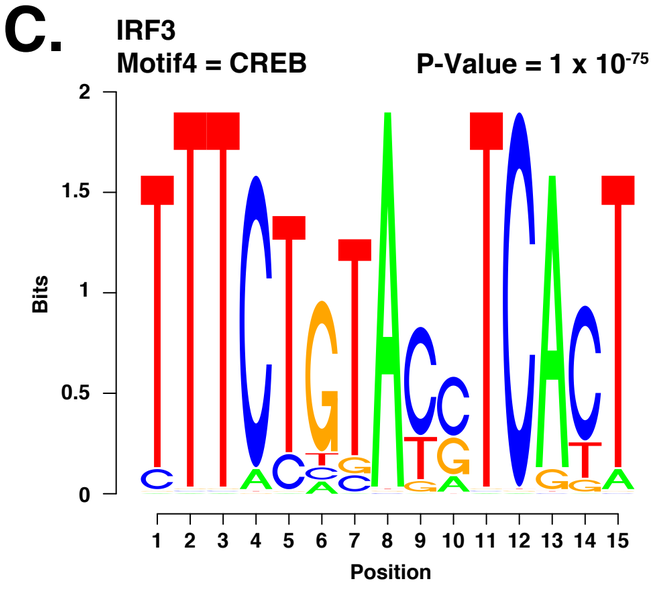
Rank	Match Score	Redundant Motif	P-value	% of Targets	% of Background
1	0.821		1 X 10^{-286}	17.24%	3.40%
2	0.919		1 X 10^{-266}	11.68%	1.53%
3	0.775		1 X 10^{-249}	4.82%	0.12%
4	0.855		1 X 10^{-236}	17.42%	4.20%
5	0.793		1 X 10^{-228}	11.84%	1.93%
6	0.889		1 X 10^{-165}	22.38%	8.60%
7	0.732		1 X 10^{-139}	3.54%	0.18%
8	0.794		1 X 10^{-97}	12.74%	4.64%
9	0.779		1 X 10^{-80}	2.50%	0.19%
10	0.773		1 X 10^{-56}	3.29%	0.60%
11	0.713		1 X 10^{-48}	14.37%	7.76%
12	0.641		1 X 10^{-44}	8.34%	3.68%
13	0.715		1 X 10^{-39}	1.83%	0.25%
14	0.638		1 X 10^{-33}	0.83%	0.04%
15	0.601		1 X 10^{-23}	0.79%	0.07%

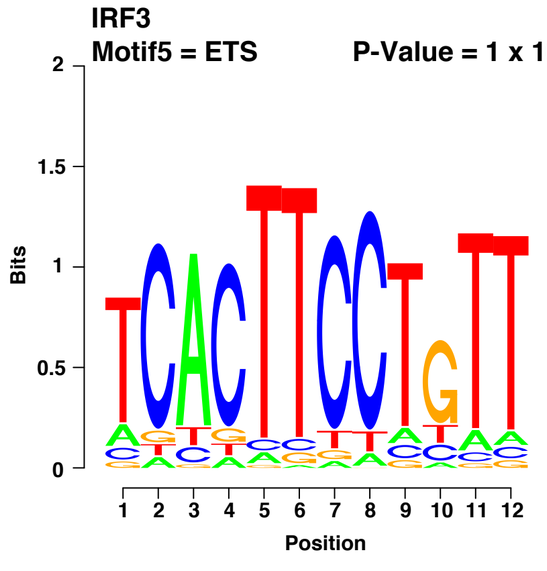
B.

Similar p65/RELA consensus motifs found

Rank	Match Score	Redundant Motif	P-value	% of Targets	% of Background
1	0.962		1 X 10^{-89}	23.99%	2.63%
2	0.945		1 X 10^{-89}	22.99%	2.37%
3	0.815		1 X 10^{-35}	12.08%	1.84%
4	0.810		1 X 10^{-32}	6.71%	0.45%
5	0.708		1 X 10^{-32}	36.07%	15.99%
6	0.671		1 X 10^{-31}	29.19%	11.27%

C.





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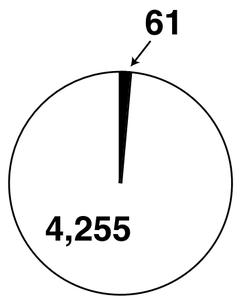
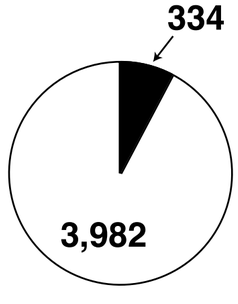
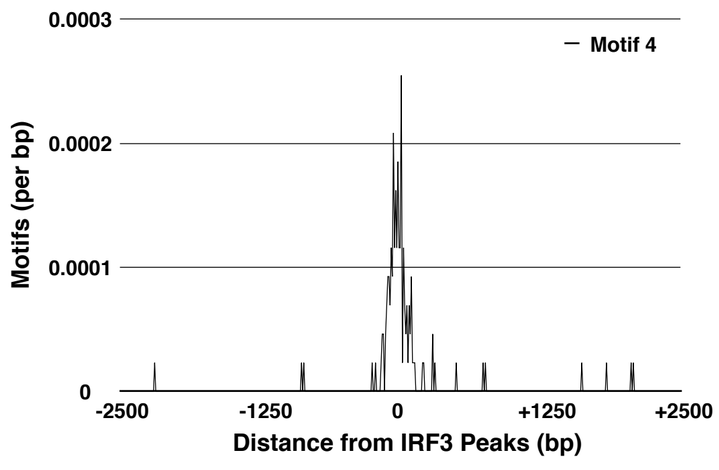
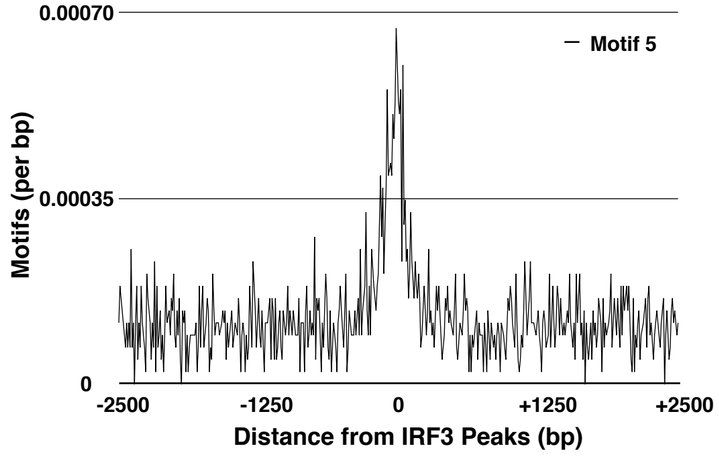


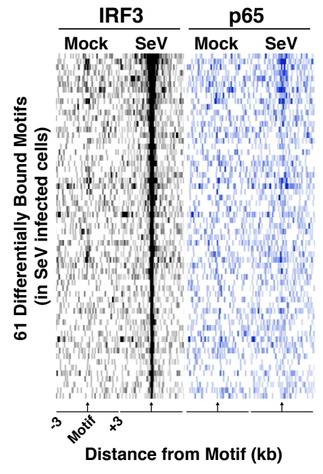


E.





F.



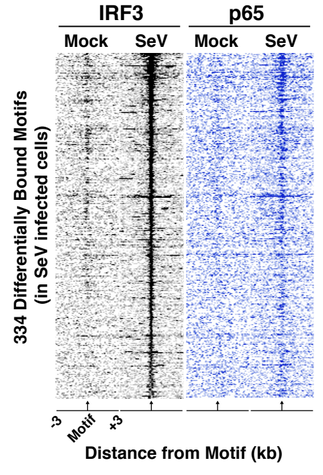
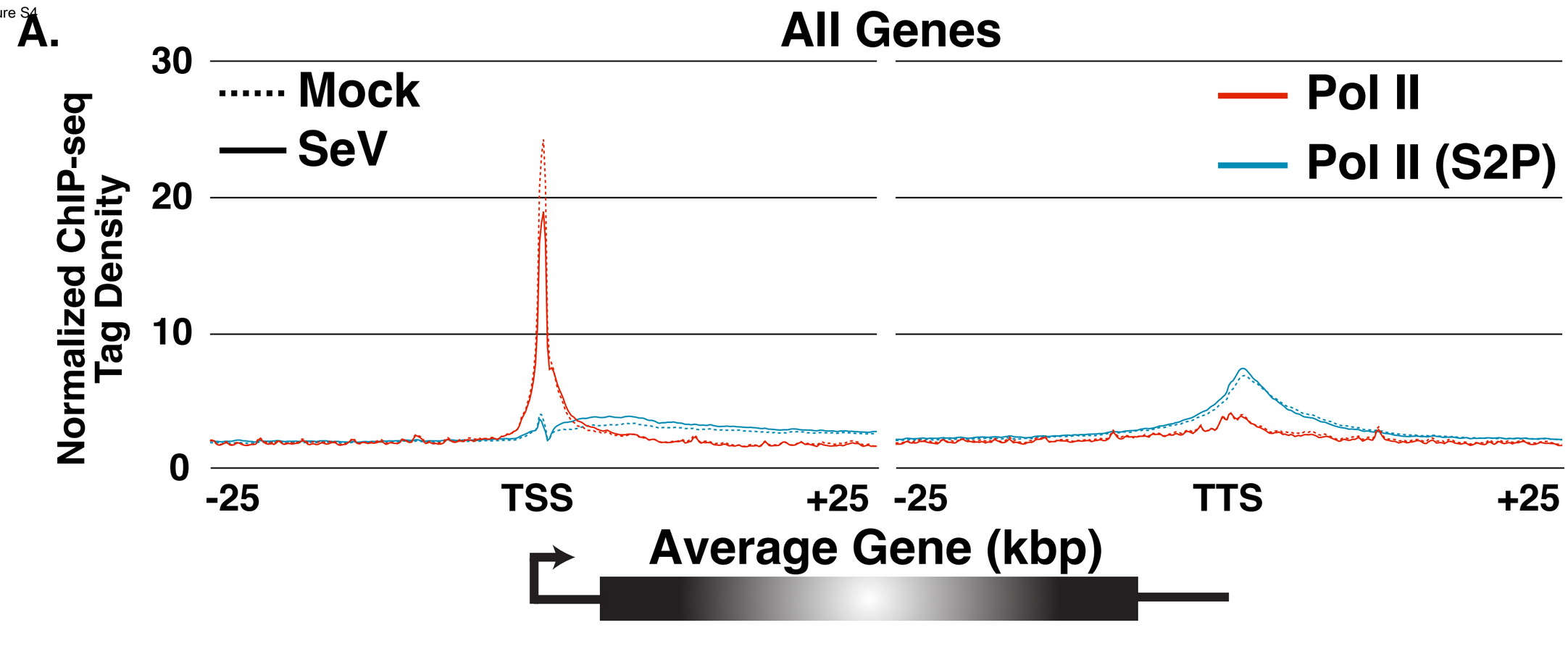


Figure S3

Supplemental Figure S4



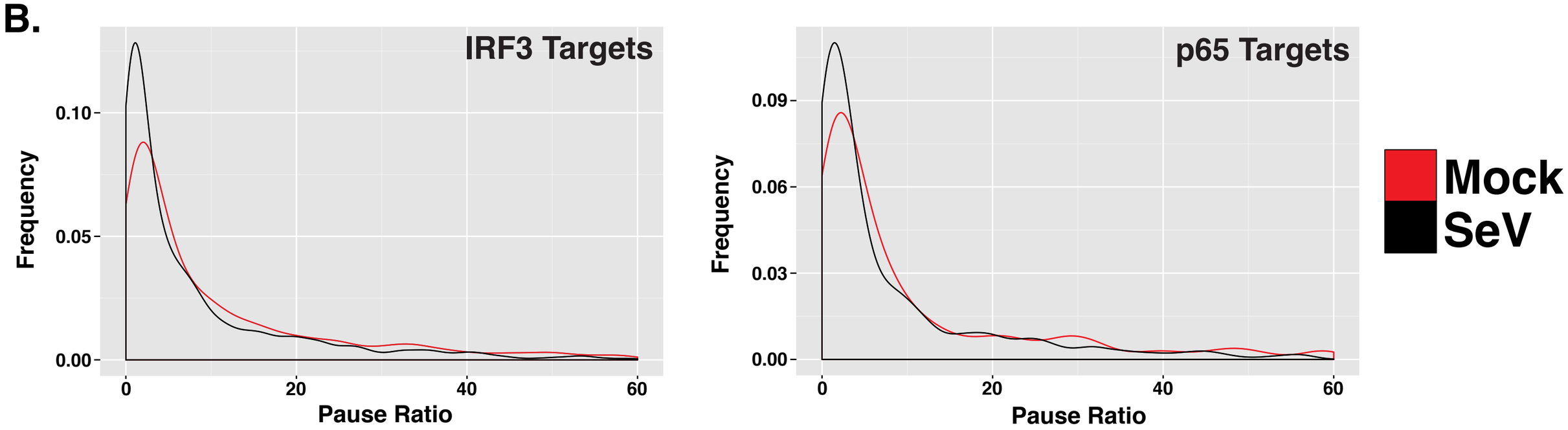
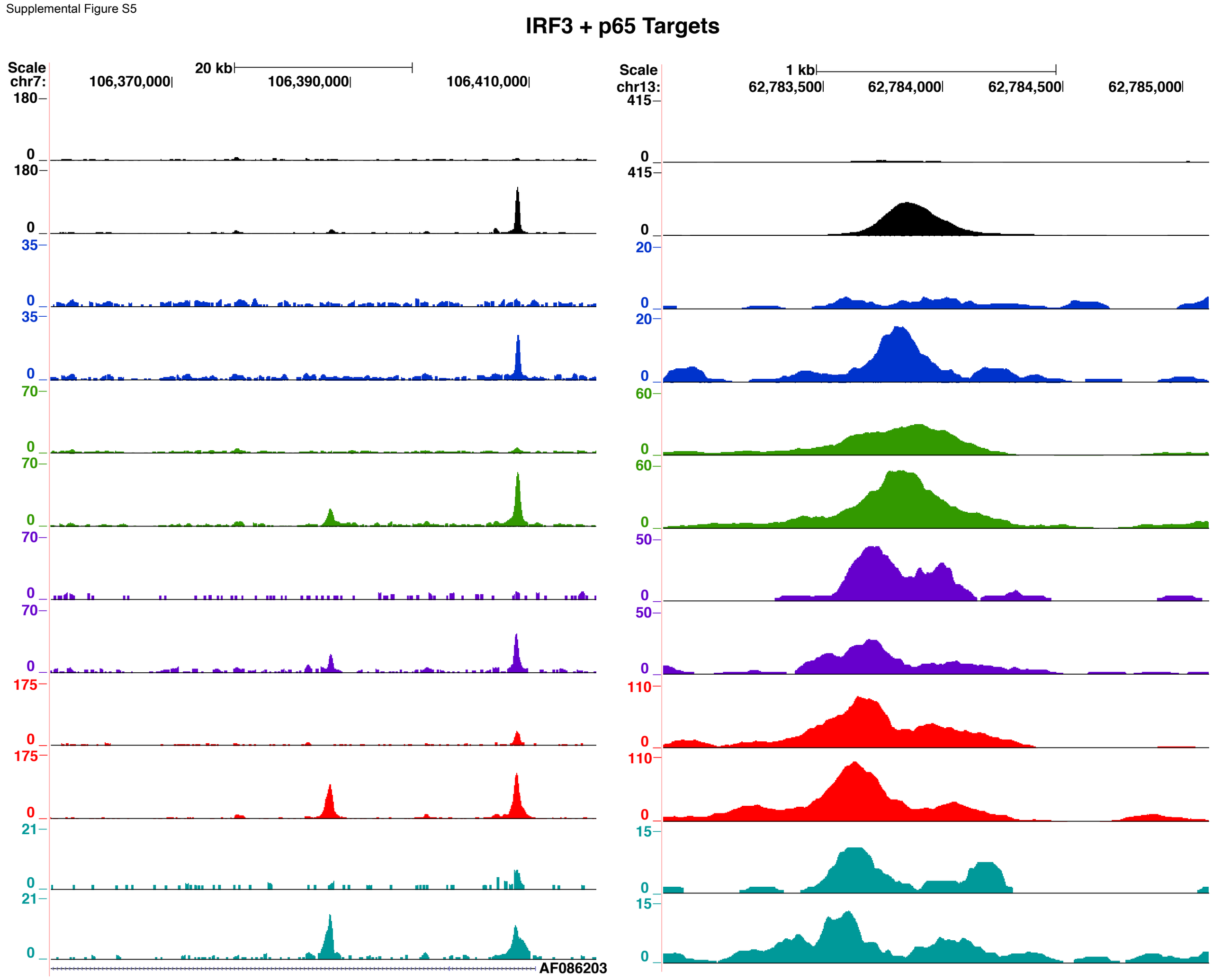


Figure S4

Supplemental Figure S5



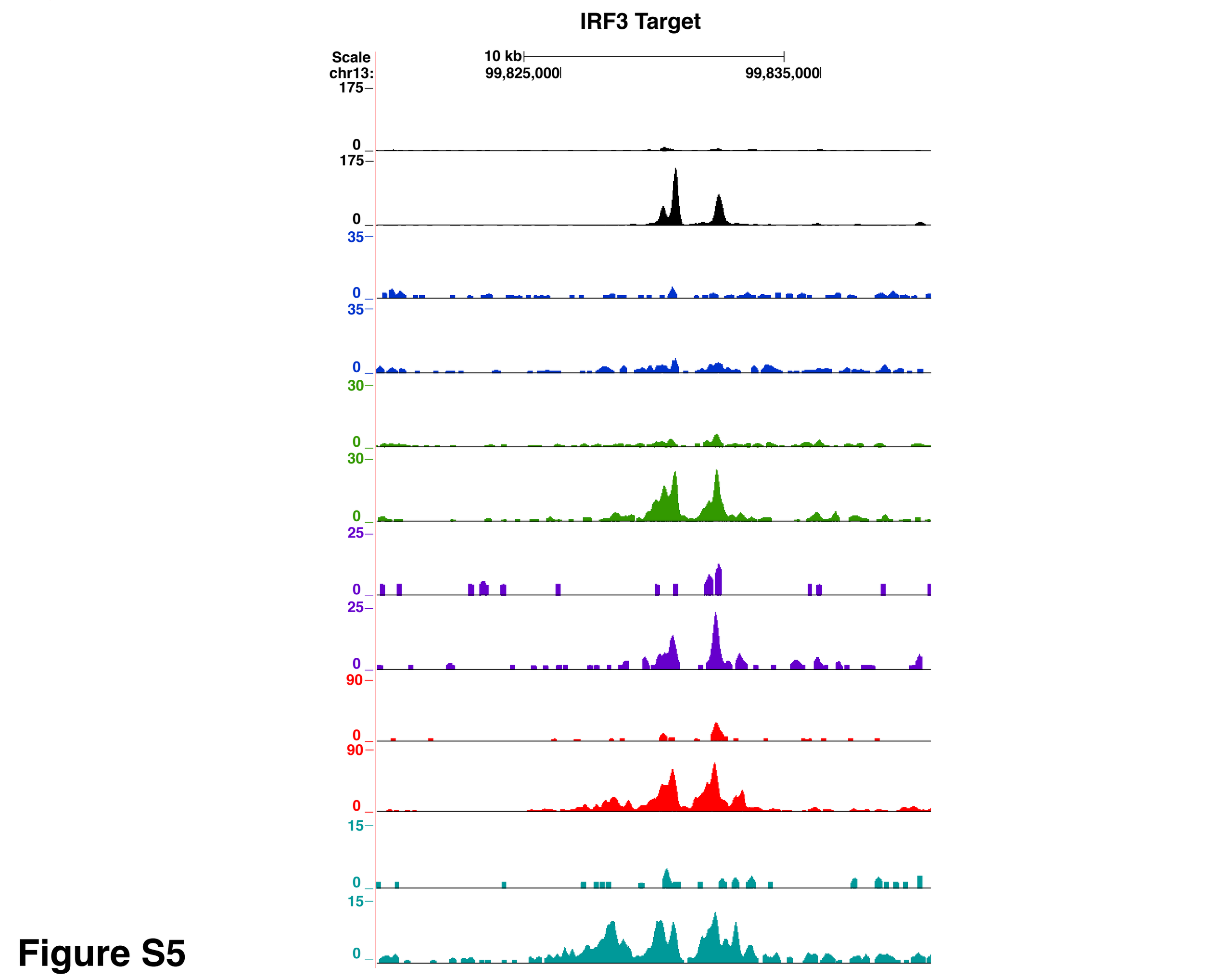


Figure S5