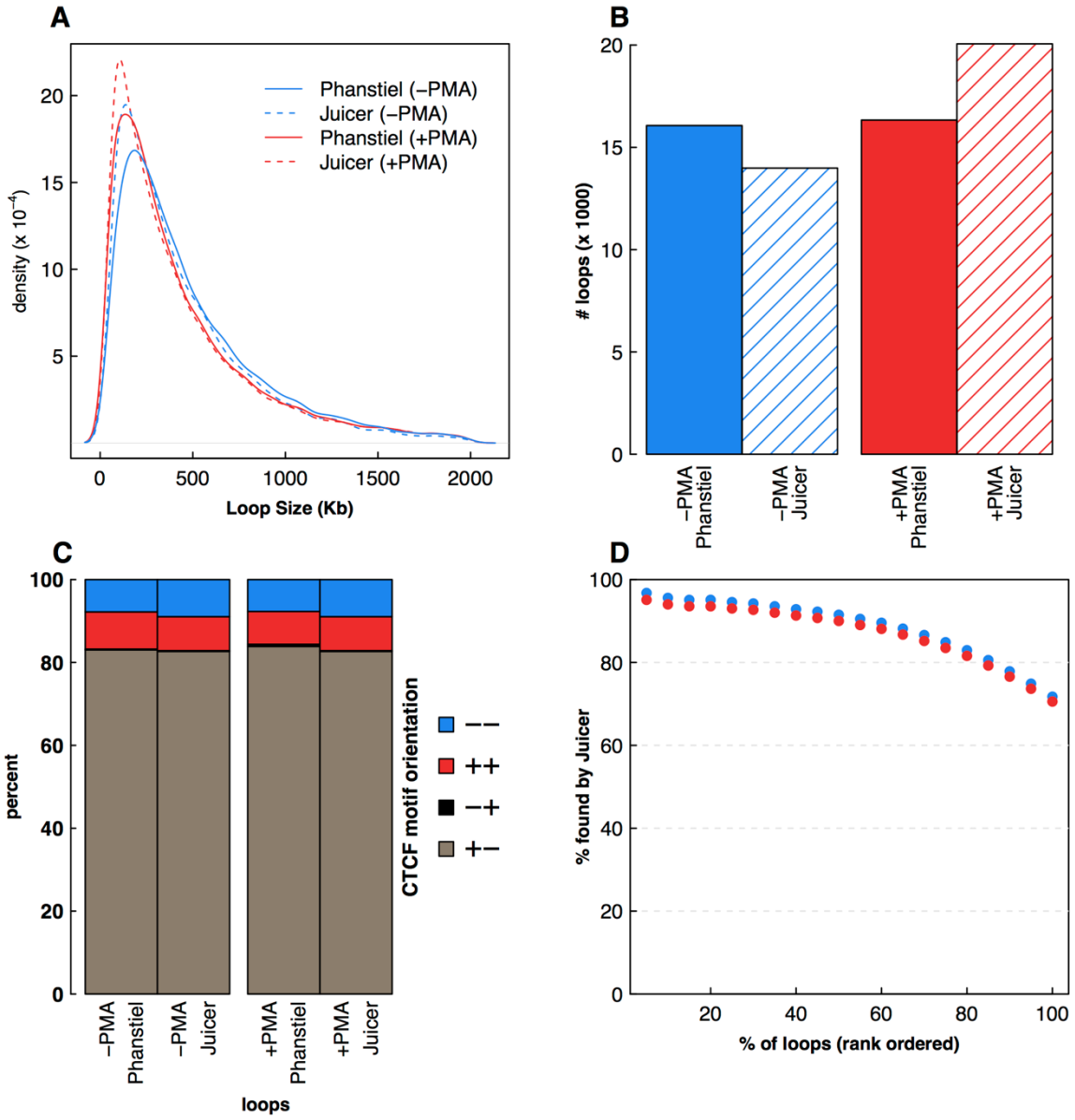

Figure S1: Comparison to loops detected by Juicer, Related to Figure 1. **(A)** A density plot depicts size distribution of loops detected by our method vs Juicer. **(B)** Bar plots depict the number of loops detected by our method vs Juicer for each data set. **(C)** Stacked bar plot depicting CTCF motif orientations at loop anchors as a percentage of all loops that contain a single CTCF bound peak at each anchor. **(D)** A scatter plot depicts the percent of loops that were also detected by Juicer as a function of rank order.

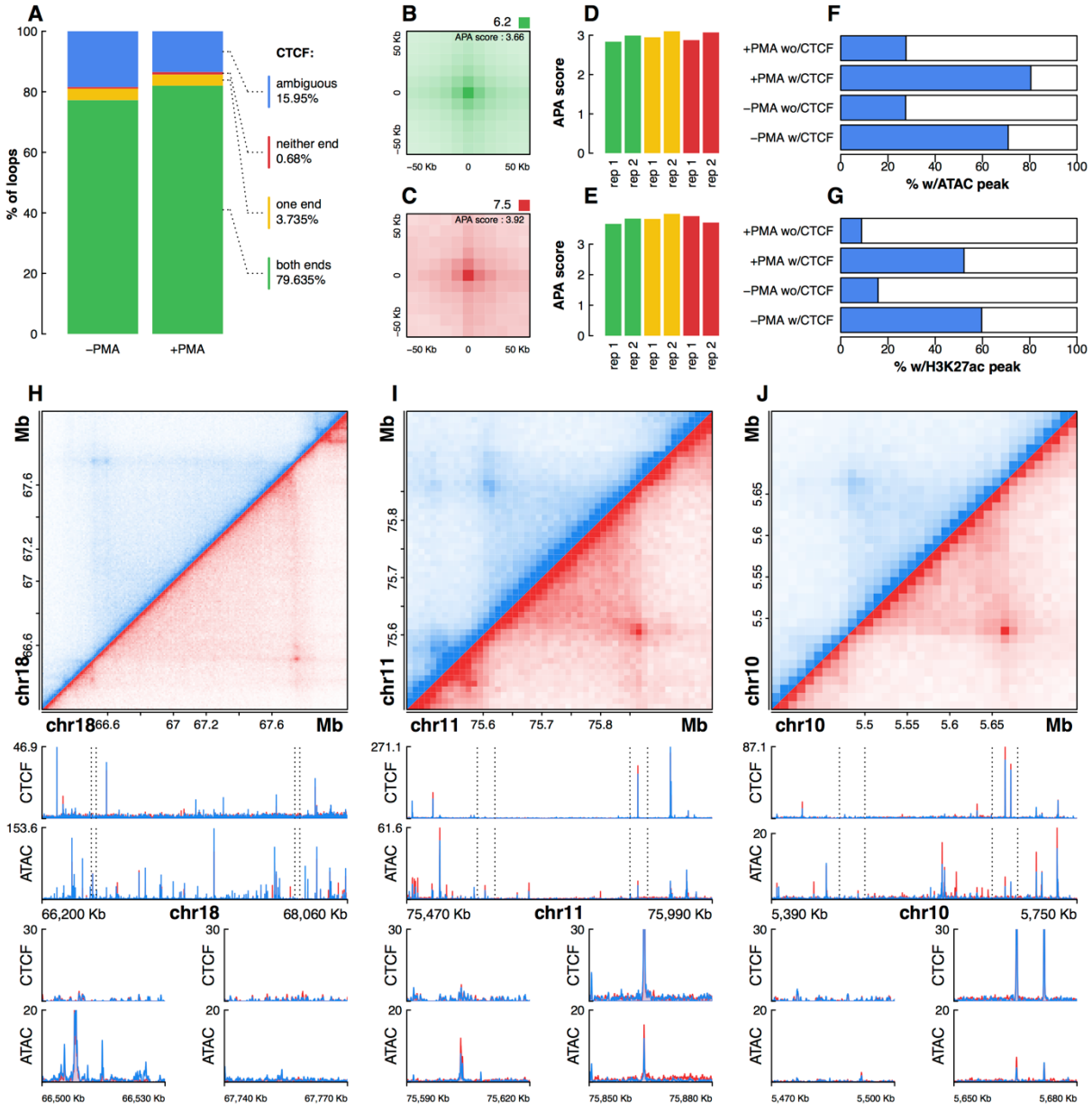

Figure S2: Non-CTCF-bound loops in untreated and PMA-treated THP-1 cells, Related to Figure 1. **(A)** A stacked bar plot depicts the percent of loops in each data sets that had a CTCF binding site, determined by ChIP-seq, at zero, one, or two ends. Loop anchors which lacked a CTCF binding site but were within 10 Kb of a CTCF binding site were categorized as 'ambiguous'. APA plots for loops with CTCF at both **(B)** or neither **(C)** end. Bar plots depicting APA scores for subsets of DNA loops that were bound at one (yellow), two (green), or neither (red) end for both untreated **(D)** and PMA-treated **(E)** THP-1 cells. **(F)** The percent of loop anchors that overlap an ATAC-seq peak was determined for anchors that did and did not overlap a CTCF binding site. **(G)** The percent of loop anchors that overlap an H3K27 acetylation peak was determined for anchors that did and did not overlap a CTCF binding site. **(H-J)** Hi-C contact matrices, ChIP-seq signal tracks, and ATAC-seq signal tracks for three regions harboring loops that lack CTCF binding sites at one or both anchors.

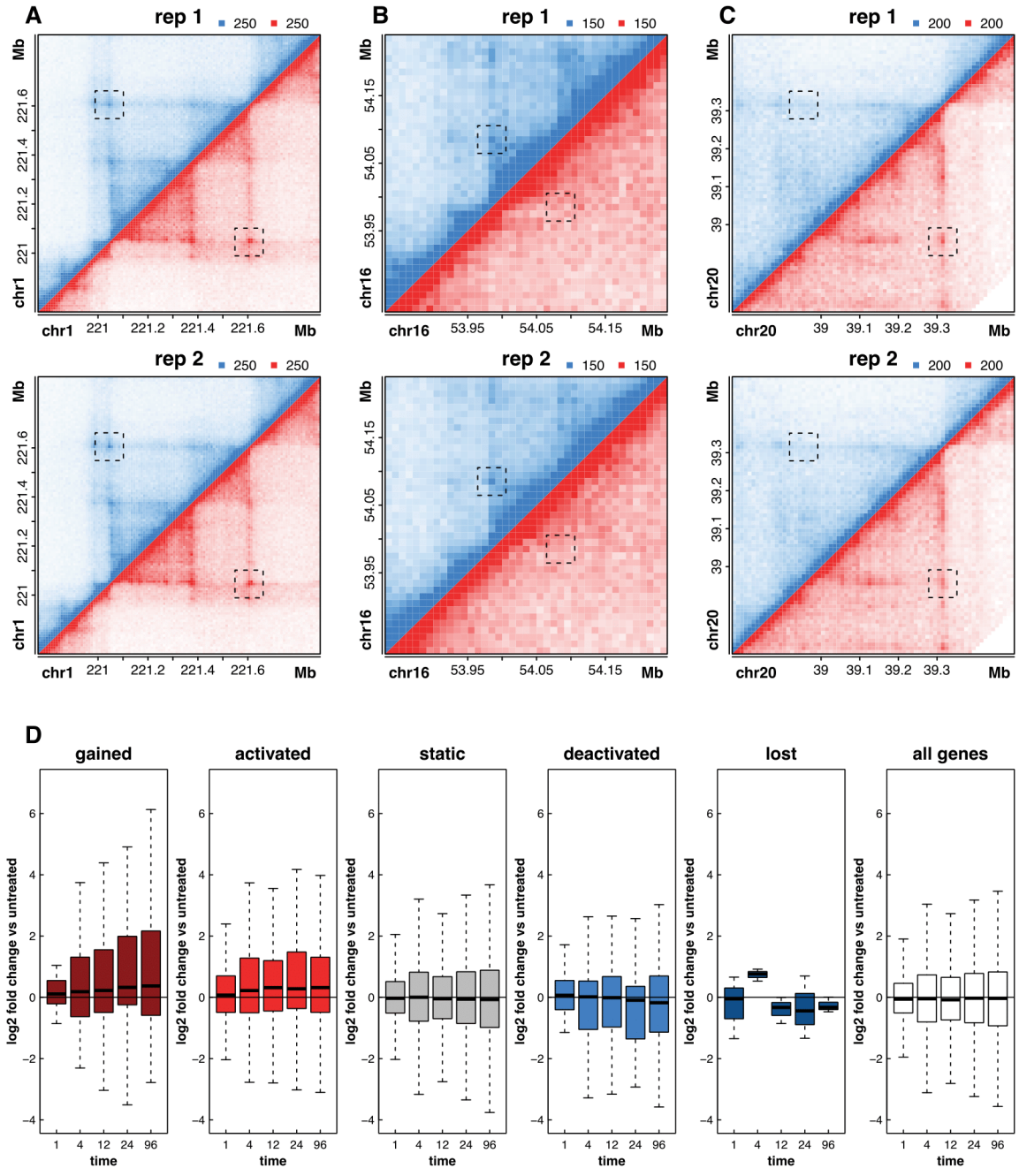

Figure S3: Differential loops and TSS usage, Related to Figure 2. Hi-C contact matrices for biological replicates are shown for examples of **(A)** static, **(B)** lost, and **(C)** gained loops. Contact matrices for untreated THP-1 cells are shown in blue and 72 hour PMA-treated THP-1 cells in red. Data from biological replicate 1 are shown in the first row. Data from biological replicate 2 are shown in the second row. Boxes highlight the pixel representing each loop. **(D)** Boxplots depict CAGE fold-change for TSS at the anchors of various loop subsets at multiple time points following PMA treatment as compared to untreated THP-1 cells.

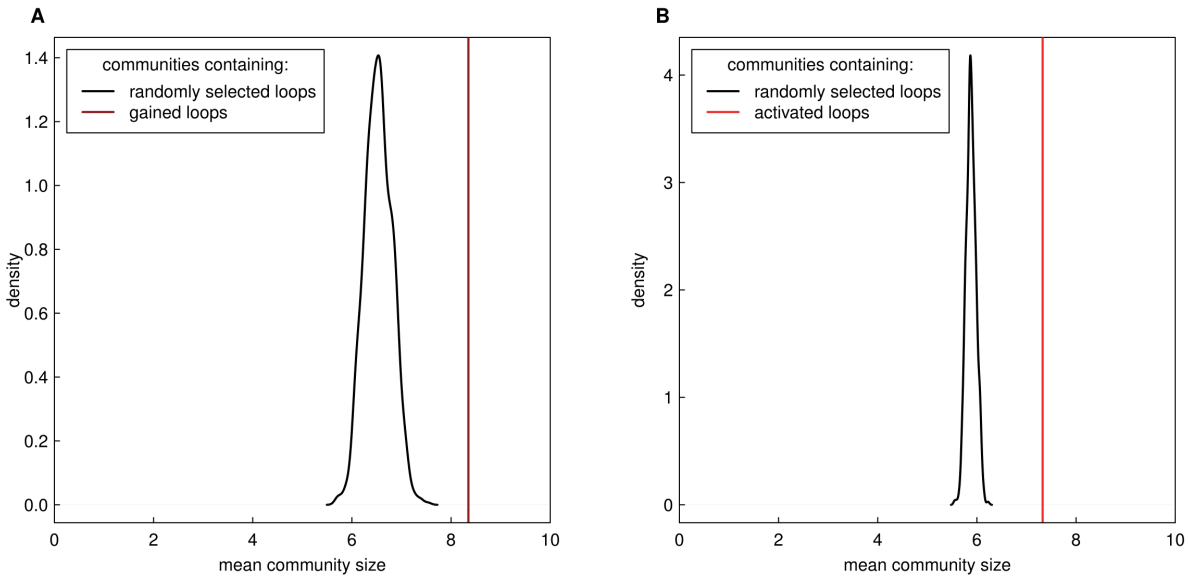

Figure S4: Community sizes of gained and activated loops compared to randomly chosen loops, Related to Figure 4. (A) 1000 random sets of loops, equal in number to gained loops, were selected. For each set, we determined the mean size of communities that contained at least one selected loop. The distributions are shown in panel A. The mean community size for the observed gained loops is shown as a dark red line. **(B)** The same analysis was performed for activated loops.

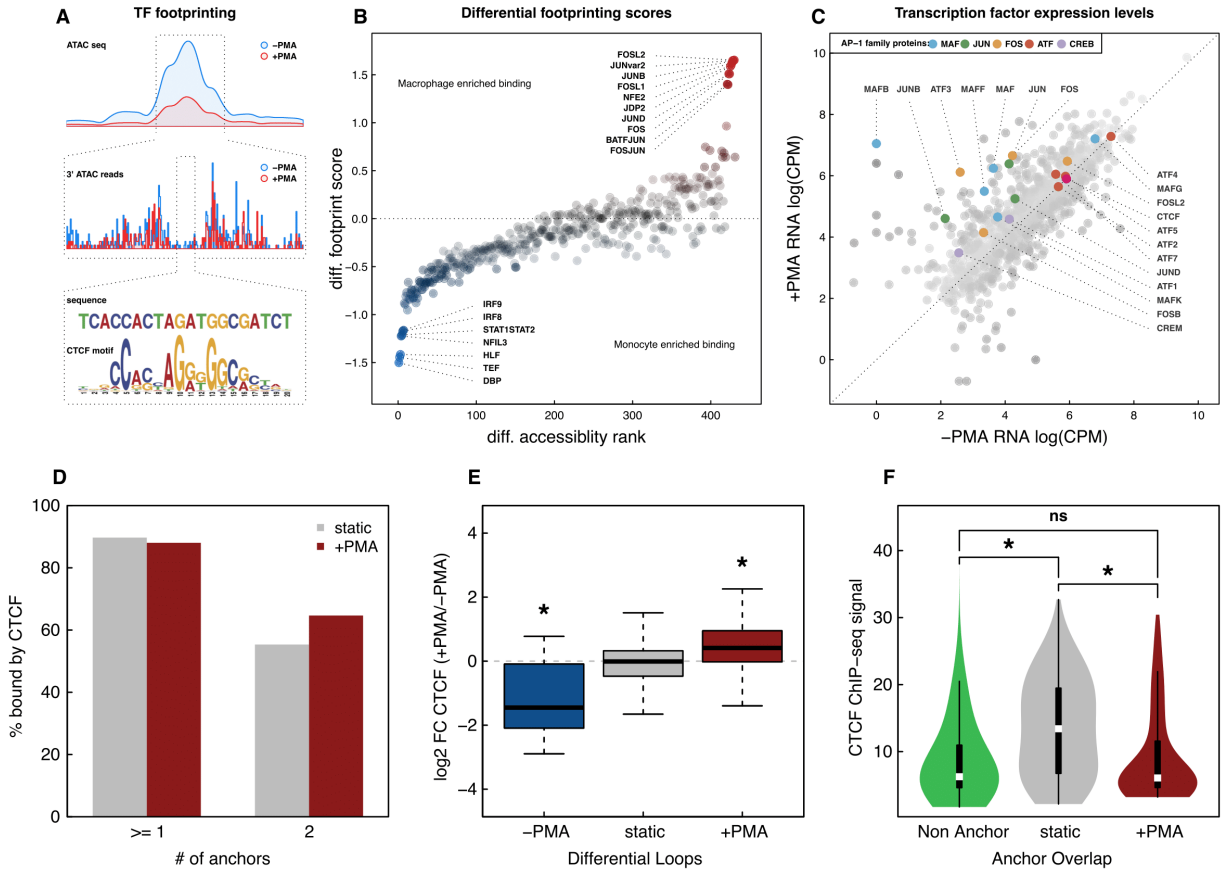

Figure S5: TF footprinting and CTCF binding at loop anchors, Related to Figure 5. (A) Depiction of footprinting method. ATAC-seq signal track identifies accessible region (Top). Signal track depicting 3' of ATAC seq reads reveals TF footprint (Middle). Sequence analysis within the footprint reveals CTCF motif (Bottom) **(B)** TF footprints plotted by differential median accessibility rank on the x-axis and median differential footprinting score on the y-axis. Both scores were determined by Wellington. **(C)** Scatter plot depicting gene level FPKM values in untreated and PMA-treated macrophages for all transcription factors. AP-1 family proteins and CTCF are colored. **(D)** Bar plot depicting the percent of static (grey) or gained (red) loops with CTCF peaks at the anchors. No significant difference is detected between static and +PMA loops ($p > 0.01$ based on Fisher's Exact Test). **(E)** Box plot showing the fold changes of CTCF acetylation peaks at lost, static, and gained loop anchors. Asterisks indicate $p < 10^{-3}$ based on Wilcox Rank Sum Test. **(F)** Violin plot representing distributions of CTCF ChIP-seq signal at static, gained, and non- loop anchors. Asterisk indicate $p < 10^{-9}$ based on Wilcox Rank Sum Test.

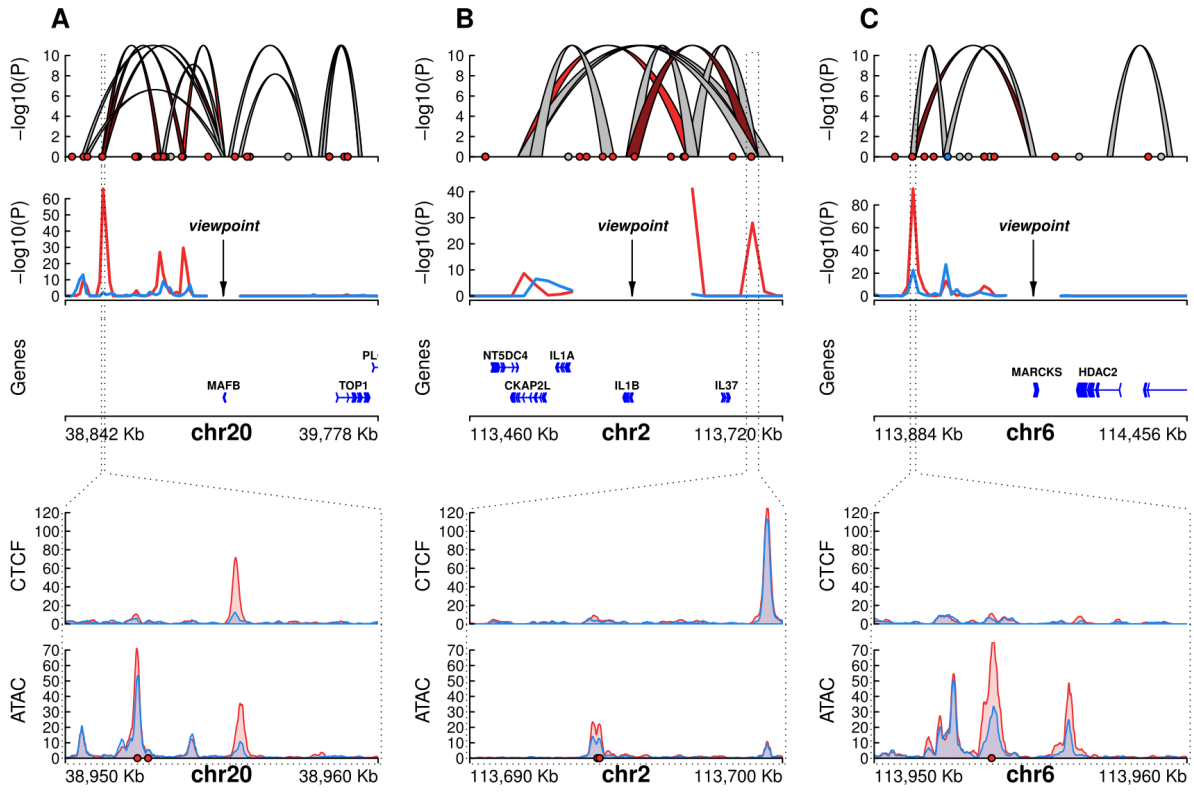

Figure S6: AP-1-bound activation hubs, Related to Figure 6. Three example regions harboring an AP-1-bound activation hub are shown **(A-C)**. From top to bottom: DNA loops determined by in situ Hi-C are colored according to loop subset; -log10(P) of loop pixel enrichment compared to local background of loops connecting to the viewpoint indicated by an arrow (untreated shown in blue; PMA-treated shown in red); Genes and orientations depicted as arrows; CTCF binding profile at +PMA-specific anchor region; ATAC-seq signal at +PMA-specific anchor region. Top and bottom plots including circles indicating presence of AP-1 footprint which are colored according to cell type specificity (red = increased in PMA-treated cells, blue = increased in non-treated cells, grey = no significant change).