Figure S1

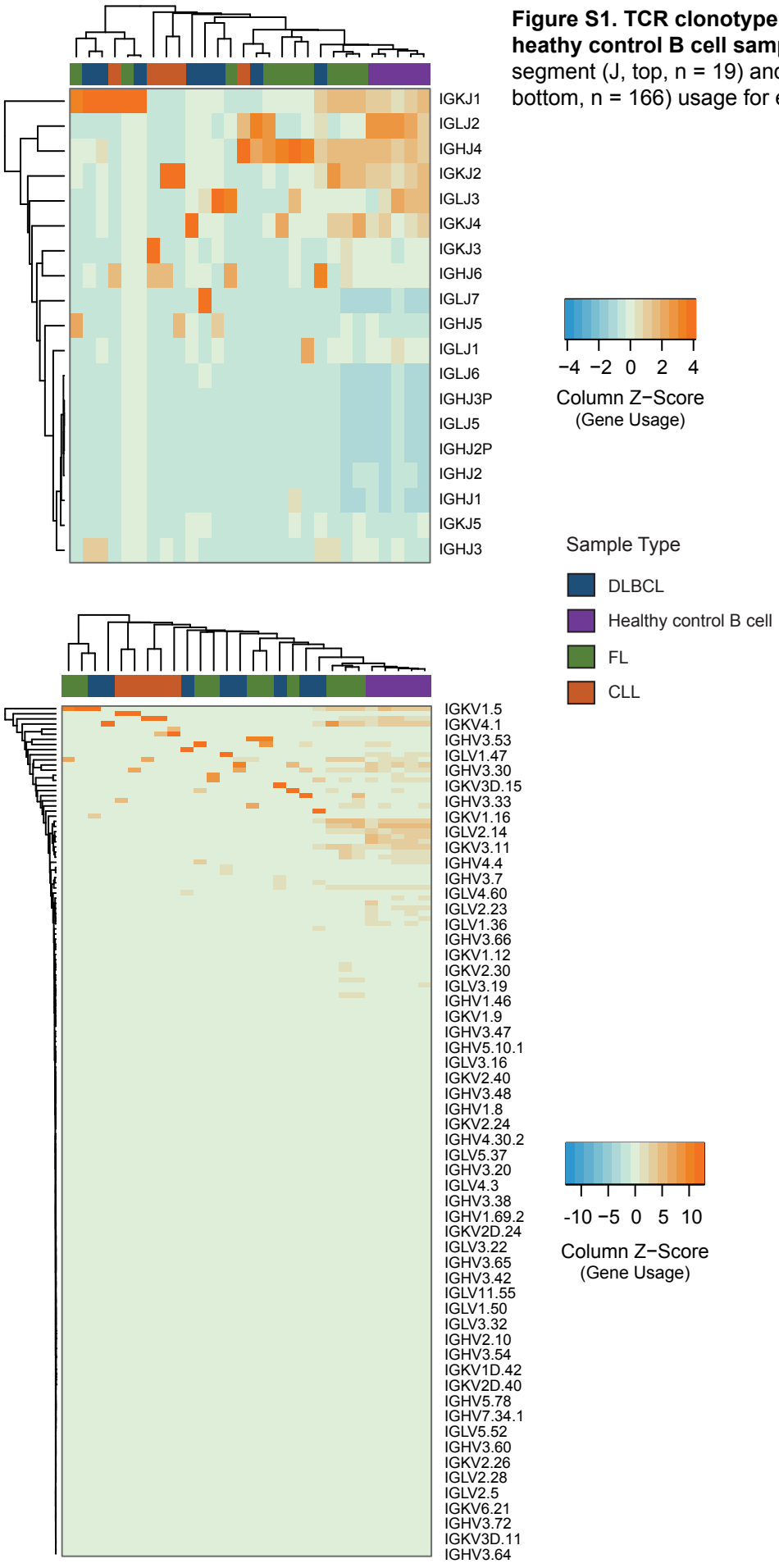

Figure S1. TCR clonotype analyses for each BCL and heathy control B cell sample. Heatmaps show Joining segment (J, top, n = 19) and Variable segment (V, bottom, n = 166) usage for each sample.

Figure S2

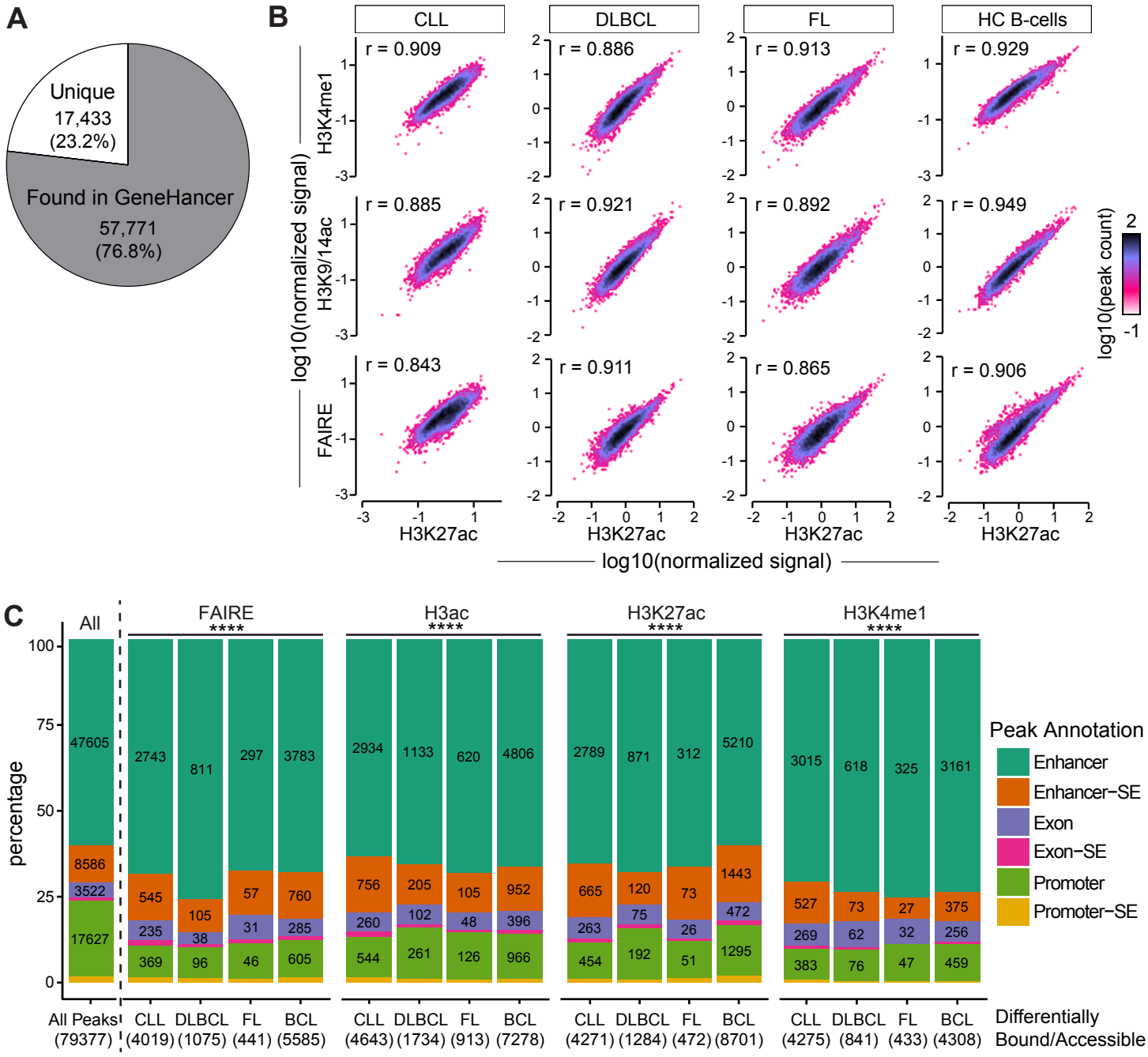

Figure S2. Histone modifications and chromatin accessibility in active regulatory elements are highly correlated and a greater proportion of enhancers are differentially bound than promoters. **A)** Overlap of putative enhancers and promoters identified in the WUSM BCL cohort and the GeneHancer data base of regulatory elements. **B)** Scatter plots show ChIP/FAIRE-seq signal at peaks with significant changes in H3K27ac (n = 7772; absolute log2 fold change > 2, FDR < 0.01) between any of the BCL subtypes and controls in each group. Pearson correlation coefficient shown (r). **C)** Stacked bar graph shows the relative proportions and counts for differentially bound/accessible elements absolute log2 fold change > 2, FDR < 0.01) compared to healthy control B cells grouped by BCL subtype and peak annotation. Total counts are shown below each group label. Chi-squared test was used to compare observed versus expected proportions of peak annotations in each group to those for all peaks (**** $p < 0.0001$).

Figure S3

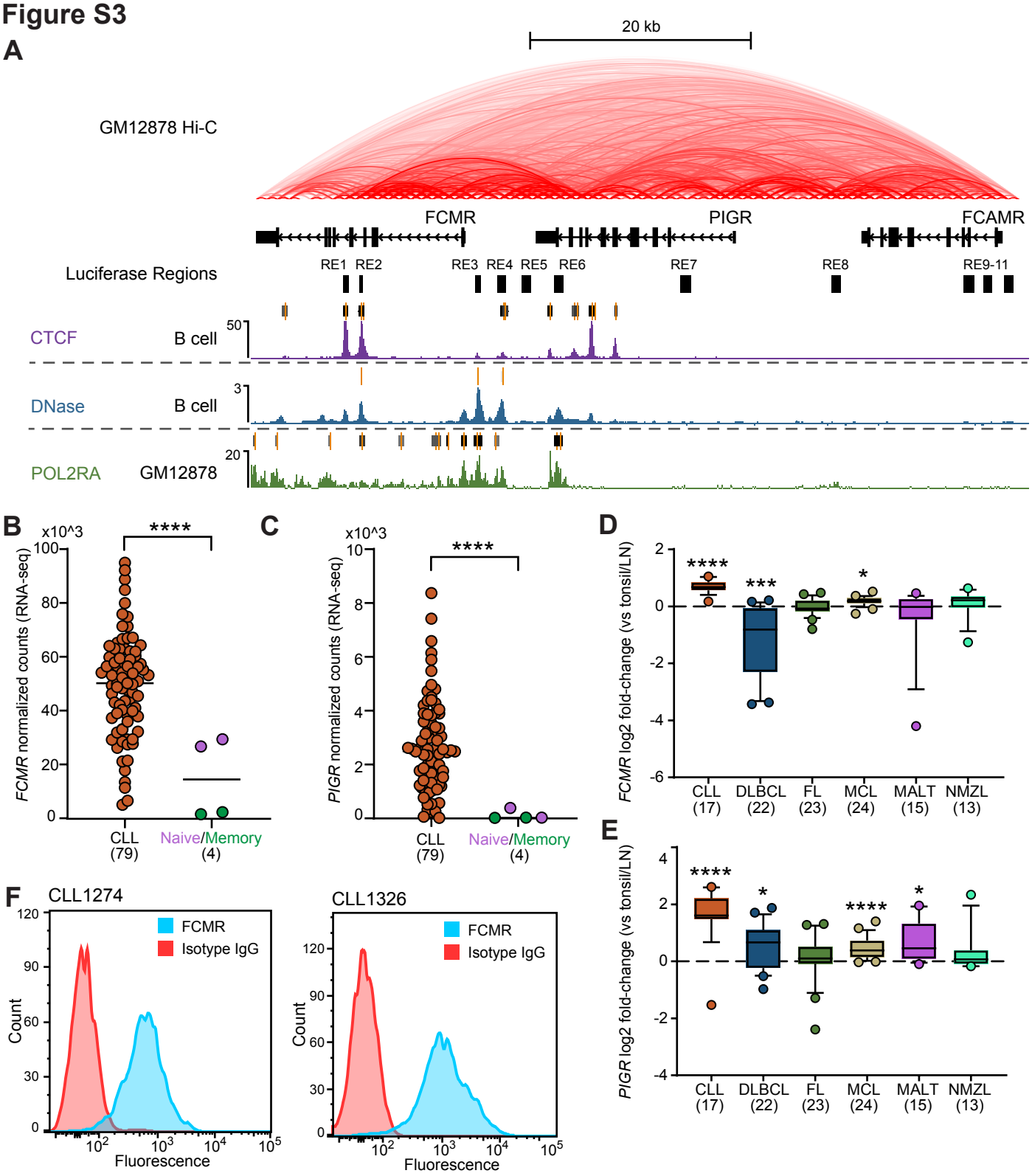

Figure S3. High expression of PIGR and FCMR is validated in external BCL datasets. **A)** WU Epigenome browser screenshots show differences between B cells (CD20+ and GM12878 B lymphoblastoid) and transverse colon in Hi-C interactions, CTCF ChIPseq, DNA accessibility (DNase-seq), and POL2RA ChIP-seq data (ENCODE) for the genomic region surrounding FCMR and PIGR. CTCF and POL2RA are shown as fold change over input controls. DNase-seq is shown as read-depth-normalized signal. **B-C)** DESeq2-normalized RNA-seq counts of (B) FCMR and (C) PIGR in a CLL dataset from Pastore et al. (GSE119103)(5) (**** adjusted P < 0.0001). **D-E)** Box plots for log2 fold changes of BCL subtypes to controls (6 tonsils and 7 lymph nodes) for RNA microarray expression of **(D)** FCMR and **(E)** PIGR in a BCL dataset from Gómez-Abad et al. (GSE32018)(6). Mann-Whitney Tests performed for each BCL subtype to controls using raw ratios of each sample to microarray reference RNA (* P < 0.05, *** P < 0.001, **** P < 0.0001). Whiskers extend from 10th-90th percentiles. Sample numbers are shown below the group labels. **F)** Flow cytometry for surface FCMR staining on CD19+ B cells from primary CLL peripheral blood samples from the WUSM cohort.

Figure S4

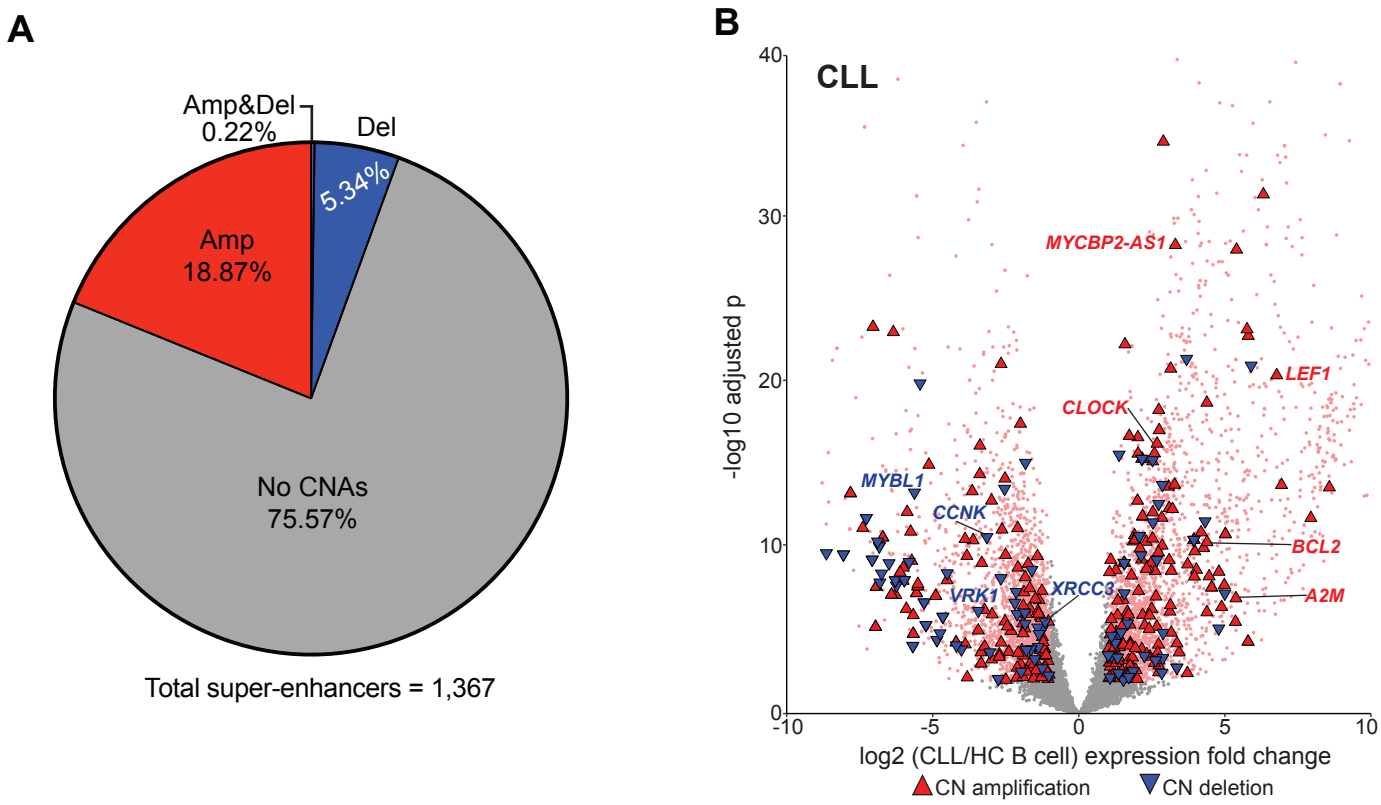

Figure S4. Genome copy number alterations in BCL have corresponding epigenetic and expression changes. **A)** Pie chart shows the percentage of SE containing genome copy number alterations (CNA) in at least 10% of BCL samples. Amp - amplification, Del - deletion, Amp&Del - amplification or deletion detected in the same region in different samples**. B)** Volcano plot shows log2 fold change and -log10 adjusted p value for expression (RNAseq) in CLL versus healthy control (HC) B-cells. Differentially expressed genes (absolute log2 fold change >1 and adjusted $p < 0.01$) are pink. Genes with differential expression and CNA are highlighted by triangle shape and color: red/point up = amplification, blue/point down = deletion. Not differentially expressed and no CNA = grey.

Figure S5

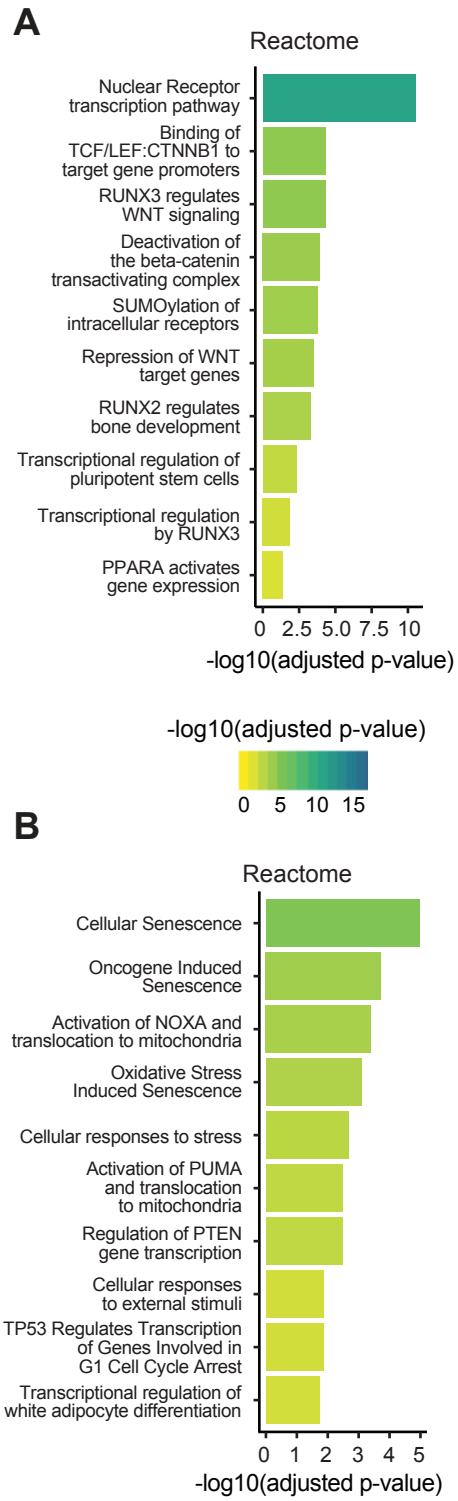

Figure S5. Distinct transcription factor expression profiles are enriched in lymphoma-relevant gene pathways. A) Barcharts show the top 10 most significant results from Reactome pathway enrichment analyses for Clusters 1-3 (upregulated in one or more BCL subtypes) or **B)** Clusters 4-6 (upregulated in healthy control B cell subsets compared to one or more BCL subtypes) (as in **Fig. 5**).

Figure S6

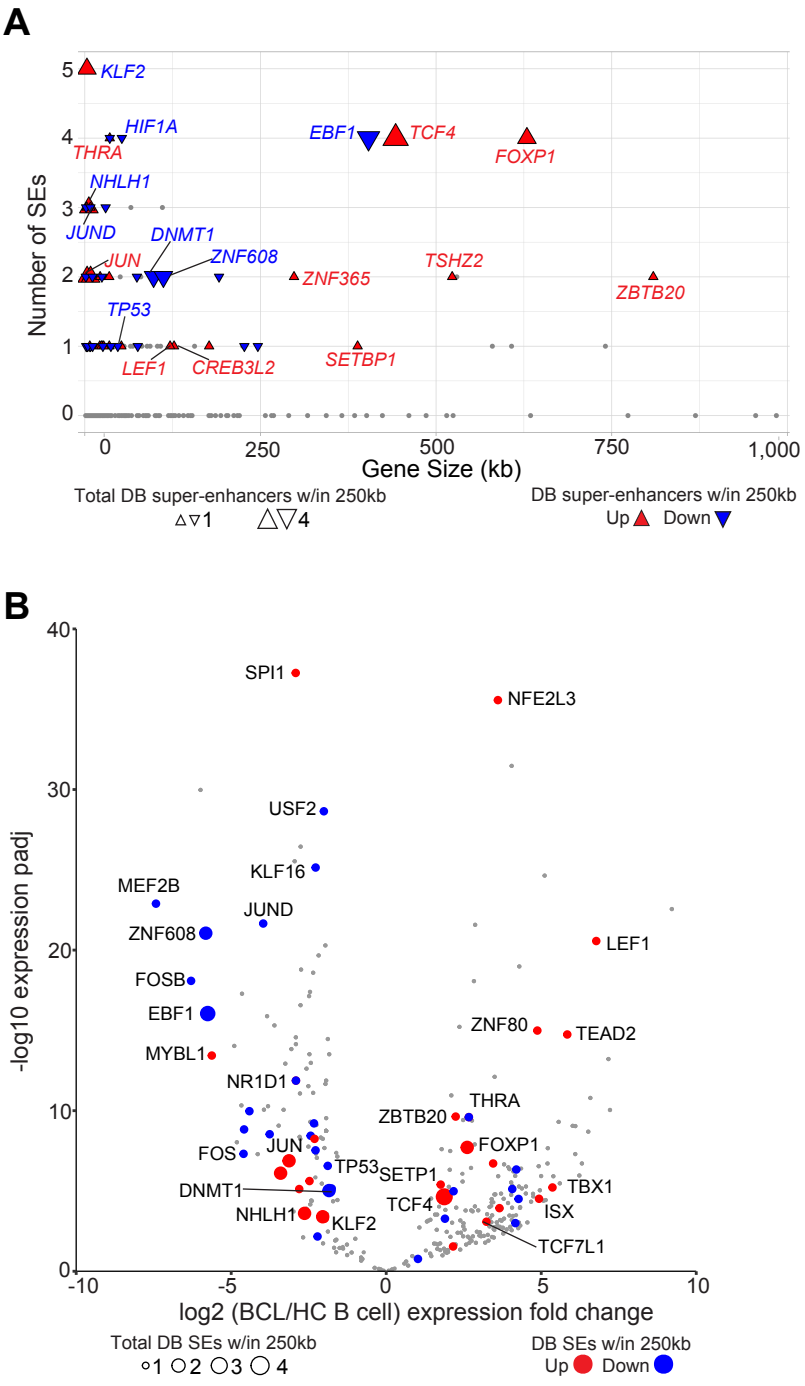

Figure S6. BCL-altered transcription factors have super-enhancer powered transcriptional feedback loops. A) XY plot shows the number of total SEs within 250kb of each TF (Y axis) by gene size in kb (X axis) (TFs as in Fig. 5). TF genes with differentially bound (DB) SEs within 250 kilobases (kb) are highlighted by color (red = increased, blue = decreased, grey = unchanged level of histone acetylation) and size (number of DB SEs). **B)** Volcano plot shows log2 fold change and -log10 adjusted p value for expression of TFs in BCL versus healthy control (hc) B-cells. Size and colors as in (A).