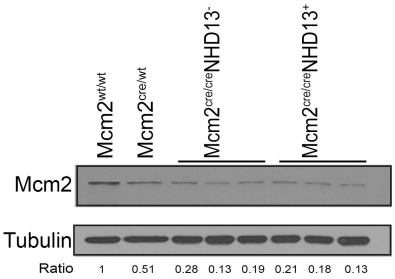
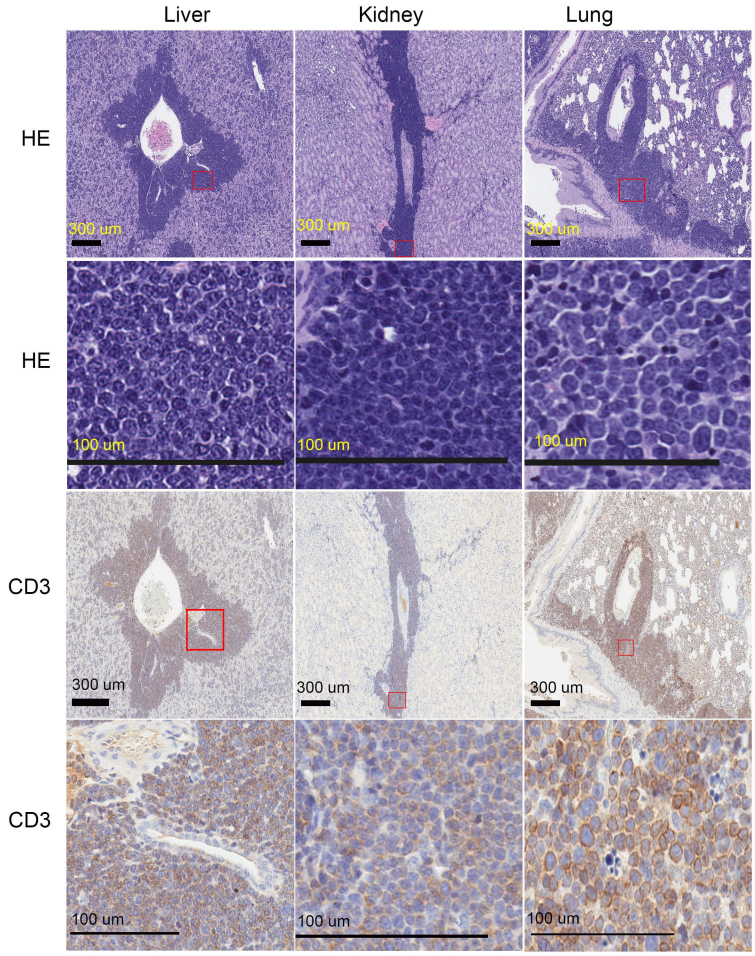
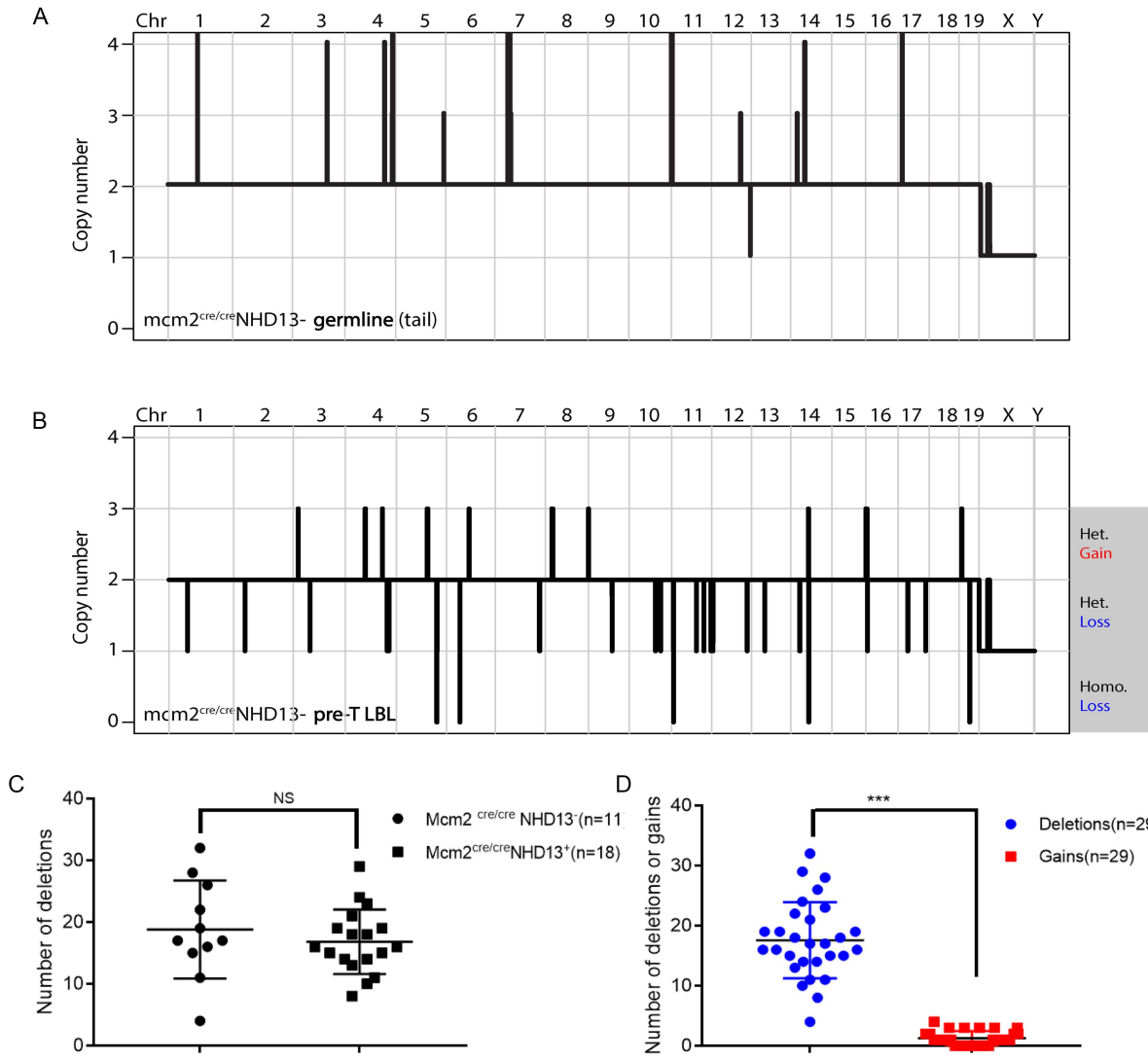


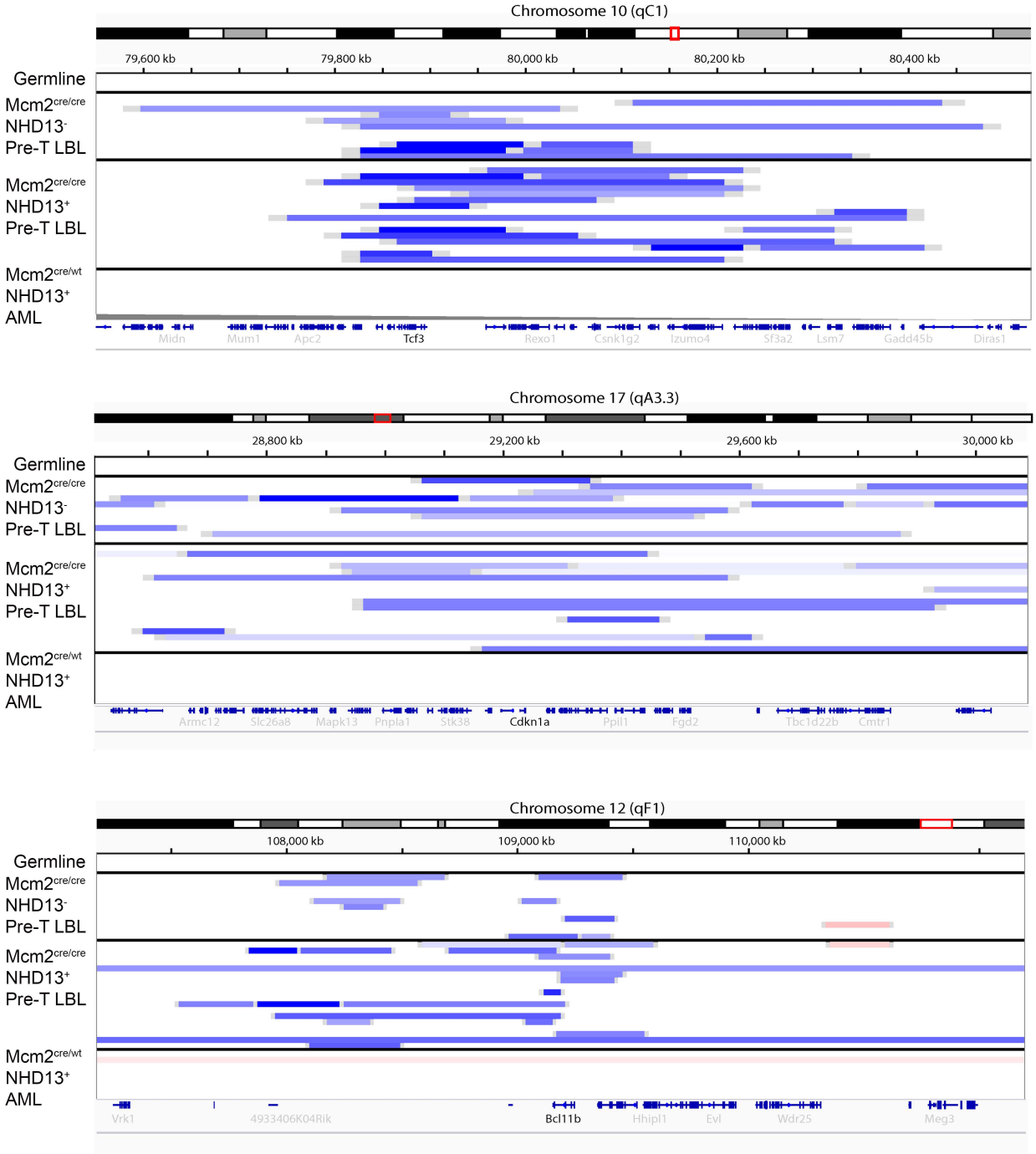
Supplemental Figure 1. *Mcm2* protein expression is decreased in thymus of Mcm2$^{cre/cre}$ mice. Western blot analysis of protein extracts from one month old mouse thymus. Genotypes are indicated. The ratio of *Mcm2* band intensity to tubulin band intensity is indicated.



Supplemental Figure 2. Histologic and immunohistochemical analysis of pre-T LBL. Hematoxylin and eosin (H&E) and CD3 immunohistochemistry of infiltrated liver, kidney and lung from representative pre-T LBL(n=16). Scale bar, 300 μm(low power). Scale bar, 100 μm(high power).

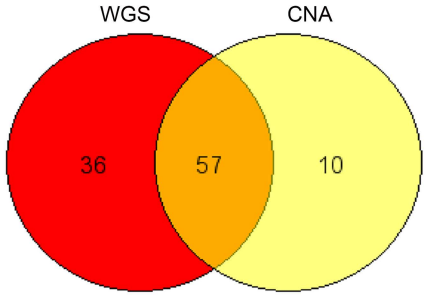


Supplemental Figure 3. Copy number gain and loss in Mcm2$^{cre/cre}$ pre-T LBL. (A)CNA of control, germline (tail) from the *Mcm2* colony compared to reference C57bl6 genome (mm9). **(B)**CNA of typical pre-T LBL sample. **(C)**Number of deletions in pre-T LBL (Mcm2$^{cre/cre}$NHD13^{-}(n=11) and Mcm2$^{cre/cre}$NHD13^{+}(n=18)). NS: no significant. One tailed Student's t test . Error bars represent standard deviation. **(D)**Number of deletions and gains in pre-T LBL(n=29). Error bars represent standard deviation. One tailed Student's t test, *** p<0.001.

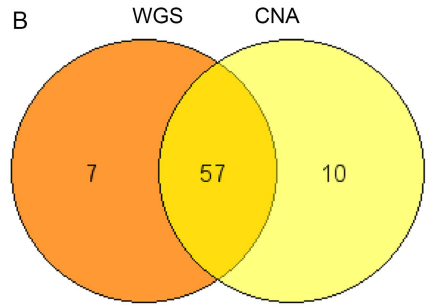


Supplemental Figure 4. Recurrent deletions involving *Tcf3*, *Cdkn1a*, and *Bcl11b*. Presentation of chromosomal regions as in Figure 2,B-C.

A



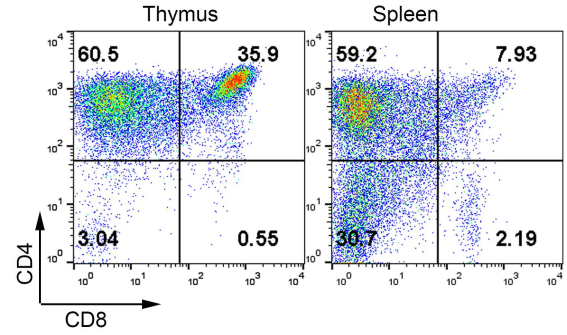
B



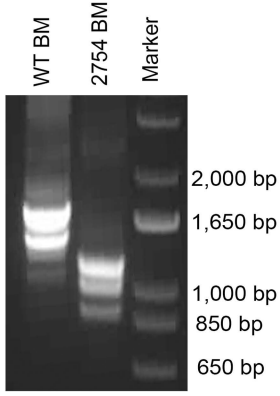
C

	% concordance for deletions >125 kb
2739 BM	100%
2754 BM	100%
2883 Thy	68%

D



E

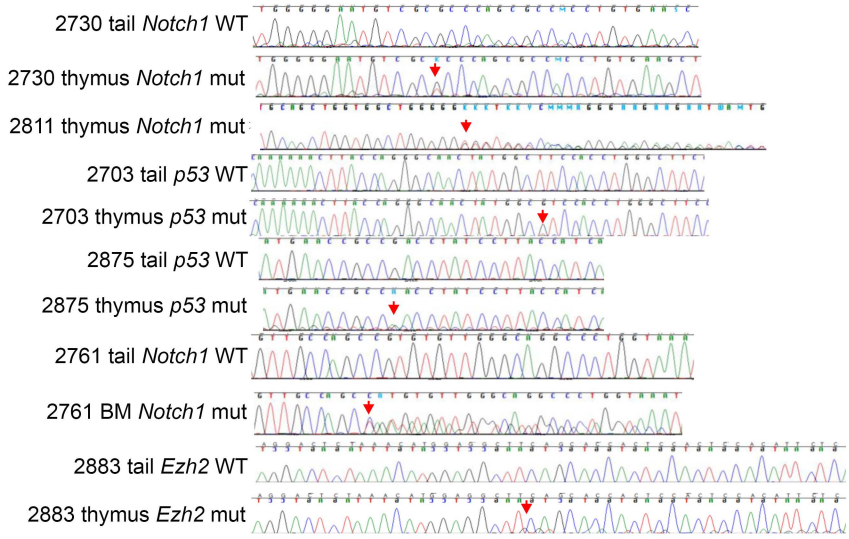


F

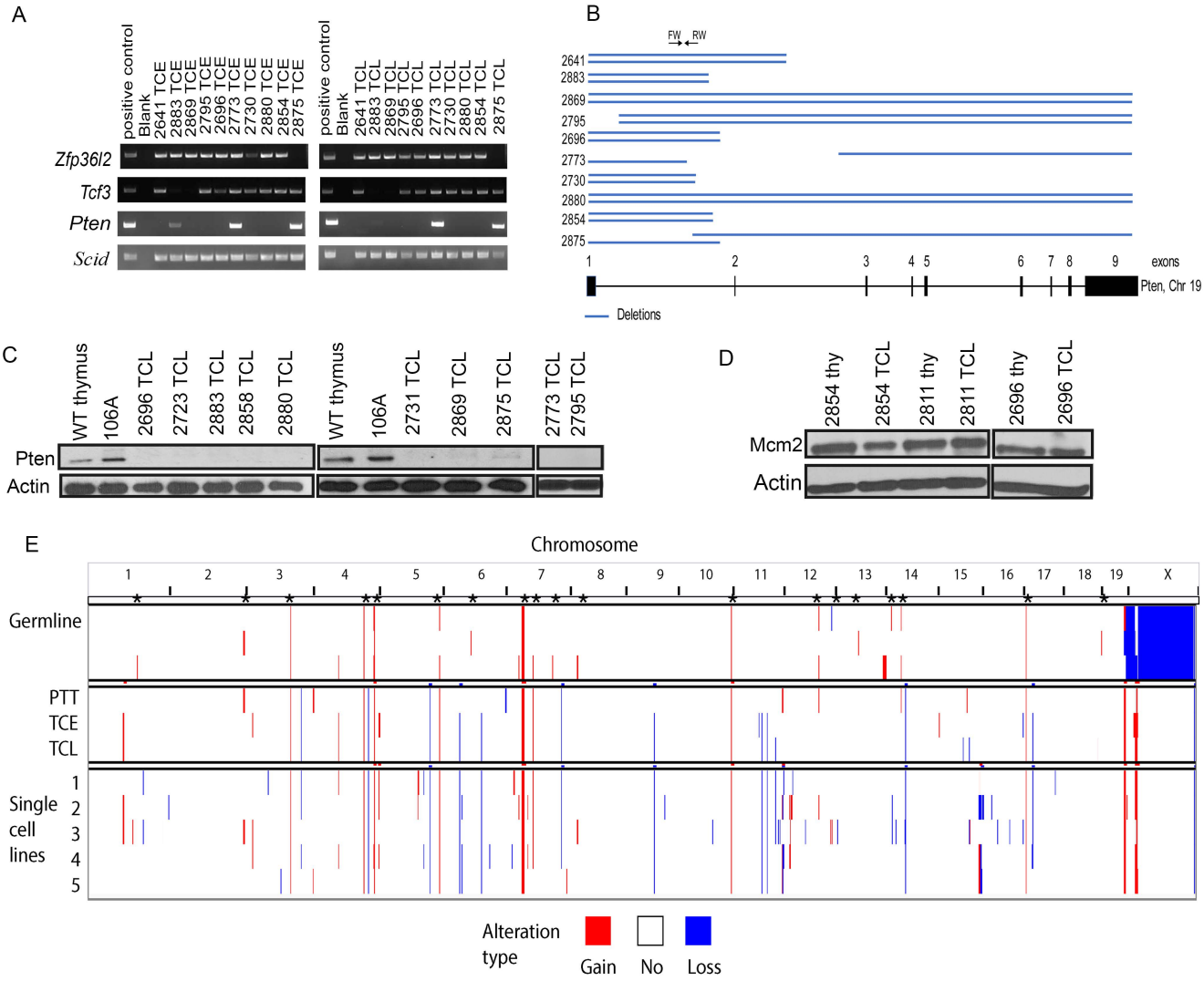
	2754 BM
Ikzf1 ex3-6	CAAGAGTGATCGAGGCATGGTTGGTAAGCCTCACAAATGT
Ikzf1 ex3-7	CAAGAGTGATCGAGGCATGGTCATTAAGGAAGAAACTAAC
Ikzf1 ex3-8	CAAGAGTGATCGAGGCATGGGAGACAAGTGCCTGTCAGAC

G

Supplemental Figure 5. Correlation of deletions between sparse WGS and conventional WGS, and *Ikzf1* deletion identified by conventional WGS. (A)Correlation of deletions identified by WGS and CNA analysis in three tumors analyzed. **(B)**Correlation of deletions in WGS (>125 kb) and CNA analysis for the three tumors analyzed. **(C)**Percent concordance for deletions >125 kb between CNA and WGS analysis (defined as deletions found in both CNA and WGS assay divided by deletions found in WGS assay) for samples 2739 BM, 2854 BM and 2883 thymus. **(D)**Flow cytometry plots of 2883 thymus and spleen stained with CD4 and CD8. **(E)**Expression of aberrantly spliced *Ikzf1* mRNA in 2754 BM. **(F)**Sequence results for Figure E, demonstrating mRNA species that lack exons 4 and 5. **(G)**Schematic representation of *Ikzf1* (ENSMUSG00000018654) splice variants (*Ikzf1* WT and *Ikzf1* mut1-3 isoforms generated by deletion in 2754 BM).



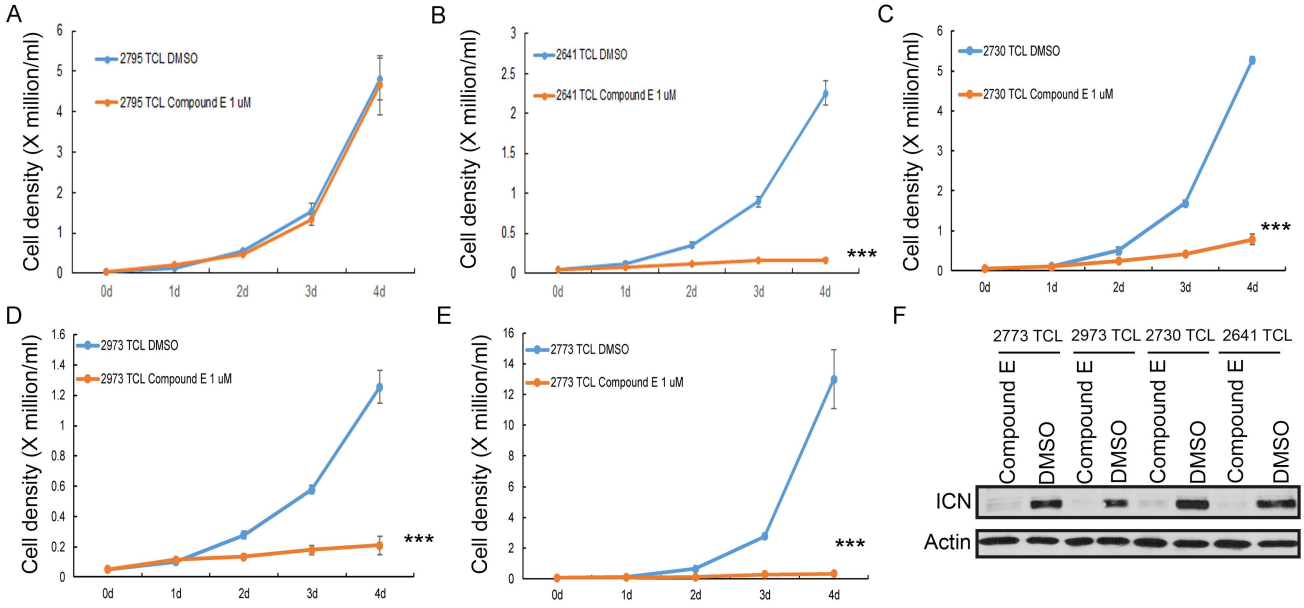
Supplemental Figure 6. Acquired mutations in tumor tissue compared with WT control (tail DNA) from identical mouse which develop pre-T LBL. Sequence chromatograms reveal the presence of mutations (red arrows) in *Notch1*, *Tp53*, and *Ezh2*.



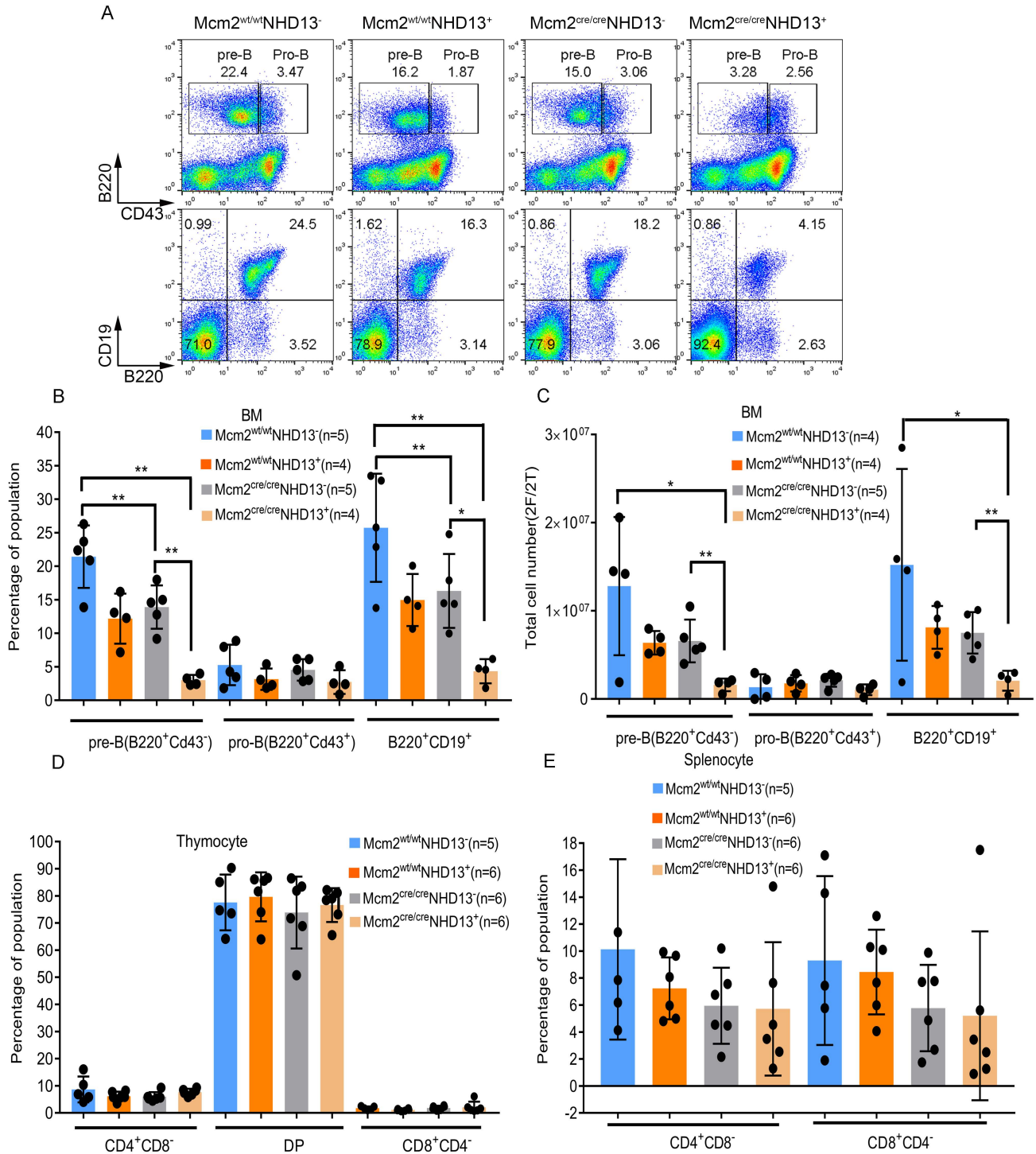
Supplemental Figure 7. PCR amplification of *Pten*, *Tcf3*, and *zfp36l2* in TCE and TCL, and CNA for single cell sub-clones (TCC) of the Mcm2$^{cre/cre}$NHD13^{-} Pre-T LBL cell line 2696 (TCL). (A)PCR amplification of *Pten*, *Tcf3* and *zfp36l2* deleted region in 2875,2854,2880,2730,2773, 2696,2795,2869,2883, and 2641 TCL and TCE. **(B)**Schematic of mouse *Pten* (ENSMUSG00000013663), exons 1 to 9. Location of primer of *Pten* for figure A are indicated. Blue line indicate the deleted region of *Pten* two allele in Figure A. **(C)**Expression of *Pten* in TCL. WT thymus and 106A cell line were positive controls. The lanes were grouped from different gels. **(D)**Expression of *Mcm2* in primary tumor and TCL of 2854,2811 and 2696 mice. The lanes were run on the same gel but were noncontiguous. **(E)**CNA for single cell sub-clones (TCC) of the Mcm2$^{cre/cre}$ Pre-T LBL cell line 2696 (TCL). Color code as in Figure 2A.

Sample Name	Junction	Sequence
2880 Thy	ex2-ex28	CACTGAAGCCTGTGTGTGAGCCGGTGGAGCC
2963 Thy	ex2-ex28	CACTGAAGCCTGTGTGTGAGCCGGTGGAGCC
2748 Thy	ex15-ex28	CTCTGCCATATACAGGTGAGCCGGTGGAGCC
2973 Thy	ex15-ex28	CTCTGCCATATACAGGTGAGCCGGTGGAGCC
2773 TCL	ex2-ex28	CACTGAAGCCTGTGTGTGAGCCGGTGGAGCC
2773 TCL	ex2-ex27	CACTGAAGCCTGTGTGACAACCGGCAATGTG
2008 Thy	ex2-ex28	CACTGAAGCCTGTGTGTGAGCCGGTGGAGCC
2897 Thy	ex2-ex28	CACTGAAGCCTGTGTGTGAGCCGGTGGAGCC

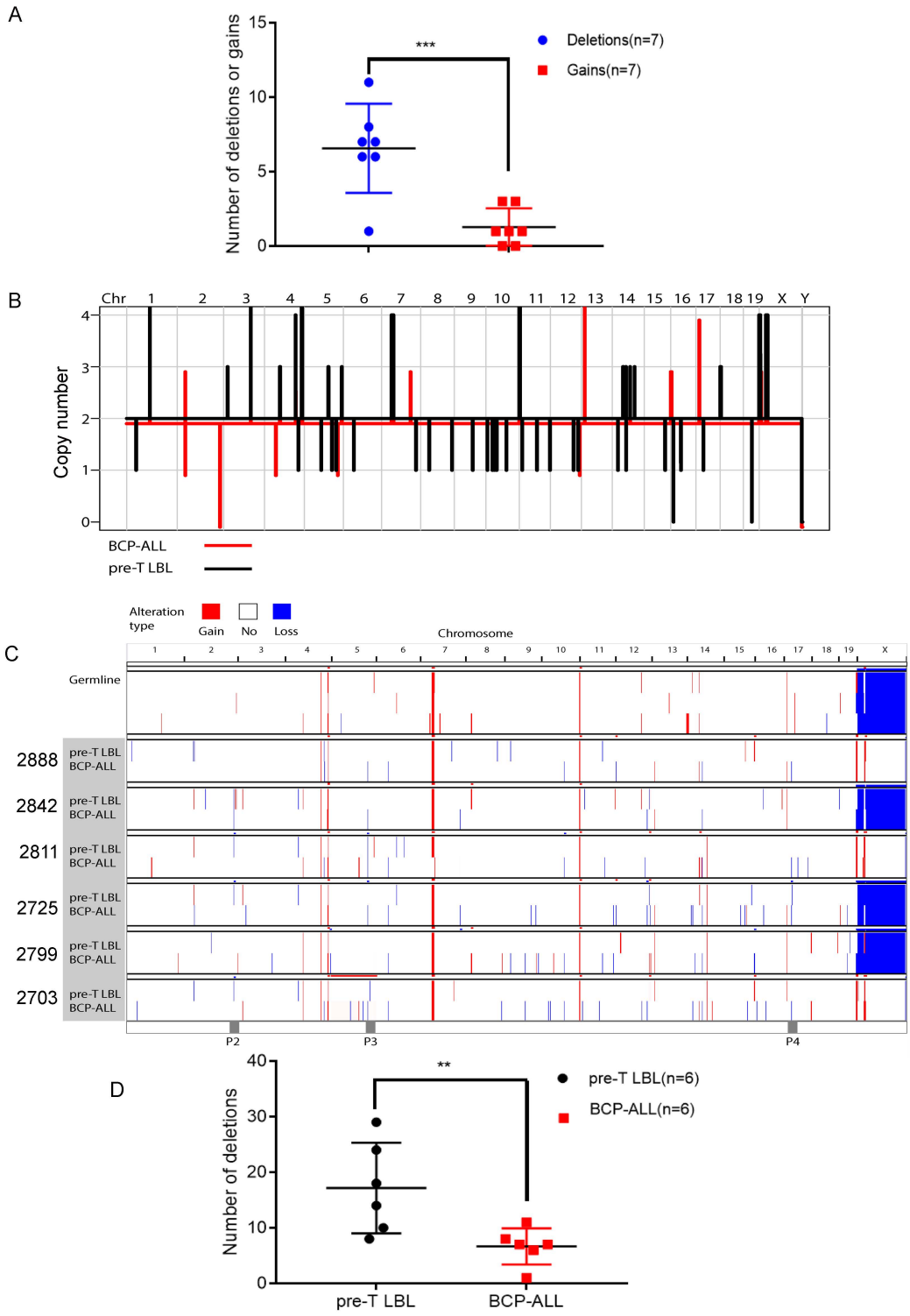
Supplemental Figure 8. Sequence results for Figure 4B



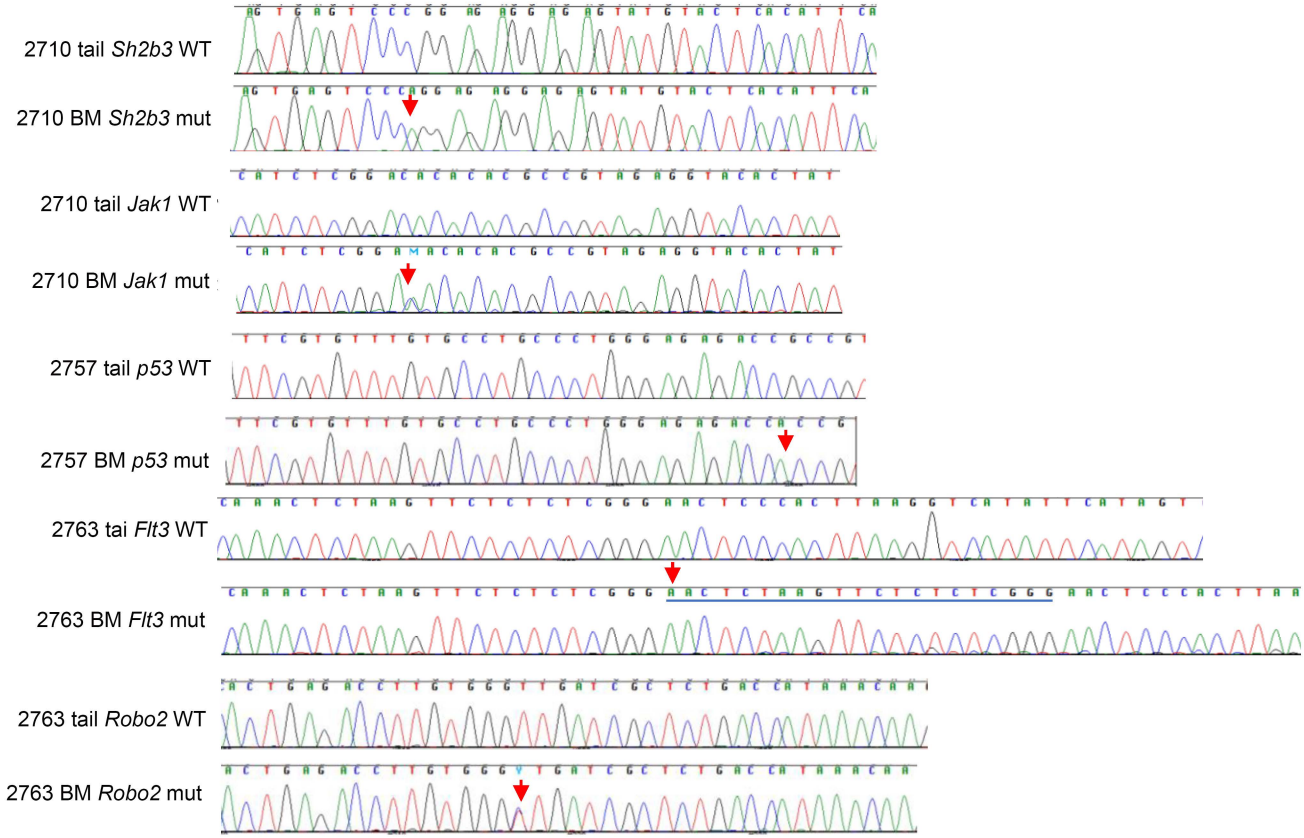
Supplemental Figure 9. T cell lines with interstitial deletions of *Notch1* are sensitive to Compound E. (A-E)Growth curves of 2795TCL(A) with WT *Notch1*, 2641TCL(B) with deleted exon 1-4, 2730TCL(C) with deleted exon 1-19, 2973TCL(D) with deleted exon 16-27 and 2773TCL(E) with deleted exon 3-27 treated with Compound E for 4 days. Cell number was assessed by trypan blue exclusion. Each point represents the mean ± standard deviation (SD; n=3). One tailed Students t test, ***, P<0.001. **(F)**Expression of ICN in pre-T LBL cell line (2773, 2730, 2973 and 2641 TCL) treated with Compound E or DMSO for 24hs.



Supplemental Figure 10. B and T cell differentiation of Mcm2$^{cre/cre}$NHD13+ mice. (**A**)Flow cytometry of Mcm2$^{wt/wt}$NHD13^{-}, Mcm2$^{wt/wt}$NHD13^{+}, Mcm2$^{cre/cre}$NHD13^{-} and Mcm2$^{cre/cre}$NHD13^{+} BM at age one month stained with the indicated antibodies. **(B)**Proportion of pro-B(CD43^{+}B220^{+}), pre-B(CD43^{-}B220^{+}) and B220^{+}CD19^{+} B cells shown in Figure A. **(C)**Total cell number of pro-B(CD43^{+}B220^{+}), pre-B(CD43^{-}B220^{+}) and B220^{+}CD19^{+} B cells shown in figure A in two femora and two tibiae (2F2T) of each mouse. **(D-E)**Proportion of CD4^{+}CD8^{-}, DP(CD4^{+}CD8^{+}) and CD4^{-}CD8^{+}cells in thymus (D) and spleen (E) of Mcm2$^{wt/wt}$NHD13^{-}, Mcm2$^{wt/wt}$NHD13^{+}, Mcm2$^{cre/cre}$NHD13^{-} and Mcm2$^{cre/cre}$NHD13^{+} at one month of age. Error bars represent standard deviation. One tailed Student's t test, *P<0.05; **P<0.01.



Supplemental Figure 11. CNA analysis for concurrent pre-T LBL and BCP-ALL in Mcm2$^{cre/cre}$NHD13^{+} mice. (A) Number of deletions and gains in Mcm2$^{cre/cre}$NHD13^{+} BCP-ALL (n=7). Error bars represent standard deviation. **(B)**one CNA example for comparison of pre-T LBL and BCP-ALL. **(C)**CNA analysis for concurrent pre-T LBL and BCP-ALL. For each pair, pre-T LBL and BCP-ALL are indicated. Color code as in Figure 2A. **(D)**Number of deletions in pre-T LBL and BCP-ALL from same mouse(n=6). Error bars represent standard deviation. One tailed Student's t test, ** p<0.01; *** p<0.001.



Supplemental Figure 12. Validation of Tier 1 mutations identified in Mcm2$^{cre/wt}$NHD13^{+} BCP-ALL WES. Tail (germline) and tumor sequence tracks are shown for the indicated genes. Mutations are indicated with red arrows.

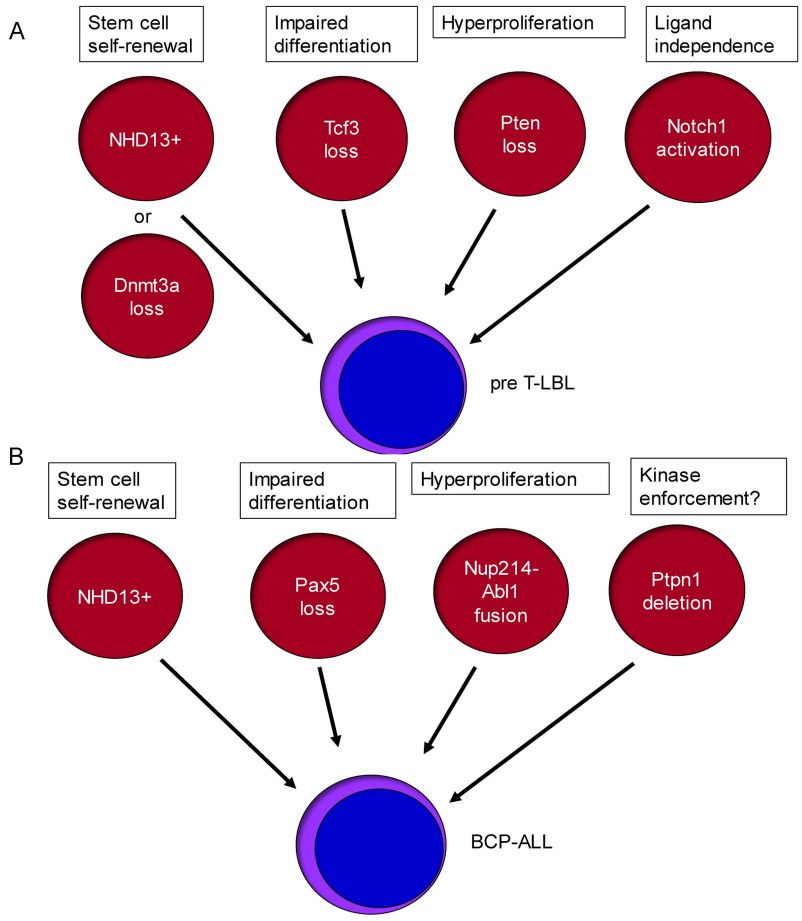
A

	200 bp window with mononucleotide repeat	200 bp window without mononucleotide repeat
WGS breakpoints	17	139
7332 random regions	421	6911
p Value(WGS vs Random)	0.009456	

B

	200 bp window with mononucleotide repeat	200 bp window without mononucleotide repeat
LCC breakpoints	44	446
7530 random regions	460	7070
p Value(LCC vs Random)	0.009671	

Supplemental Figure 13. Number of mononucleotide repeat immediately surrounding breakpoint junctions for WGS, LCC and random control. (A) Number of mononucleotide repeats surrounding 78 breakpoint junctions (100 nucleotides 5' and 100 nucleotide 3' of the breakpoint,156 windows) for WGS sequence and 7332 200bp random windows. **(B)**Number of mononucleotide repeats immediately surrounding 245 breakpoint junctions (100 nucleotides 5' and 100 nucleotide 3' of the breakpoint,490 windows) for LCC sequence and 7530 200bp random windows from chr 2,7, 10 and 19. p value is indicated (Fisher's Exact Test).



Supplemental Figure 14. Combinations of CNAs lead to T and B lymphocyte malignancies. **(A)***NHD13* transgene expression (or *Dnmt3a* deletion) leads to increased stem cell self-renewal, *Tcf3* deletion results in a block to thymocyte differentiation, *Pten* deletion leads to hyperproliferation, and *Notch1* 5' deletion leads to ligand-independent activation of *Notch1*. **(B)***NHD13* transgene activation leads to increased stem cell self-renewal, *Pax5* deletion results in a block to B lymphoid differentiation, *Nup214-Abl1* fusion leads to hyperproliferation, and *Ptpn1* deletion enforces kinase activation.