List of Supplementary Data

Table S1. Minimally deleted regions (MDR) in recurrent deletions.

Name	Range	kbp	Type	Genes
3p loss	chr3:47,002,496-47,641,149	639	loss	*CCDC12*, *NRADDP*, *SETD2*, *KIF9*, *KIF9-AS*, *KLHL18*, *PTPN23*, *SCAP*, *ELP6*, *CSPG5*
4p loss	chr4:29,549,906-30,935,298	1385	loss	*PCDH7*
8p loss	chr8:22,467,144-27,420,442	4953	loss	*EGR3*, *DOCK5*, *U4*, *STC1*, and 44 other genes
9p loss	chr9:21,325,815-21,359,498	34	loss	*KLHL9*, *IFNA6*
17p loss	chr17:7,549,591-7,583,945	34	loss	*ATP1B2*, *TP53*

Table S2. Clinical features of the patients in this study.

	Wild type	Del(17p)	p-value
n	208	69	
Age at Diagnosis	54 (32-78)	61 (38-86)	2.2e-05
RAI Stage at Sampling			
stage 0	62 (32%)	5 (8%)	6.1e-05
stage 1	82 (42%)	23 (36%)	0.38
stage 2	32 (17%)	8 (12%)	0.55
stage 3	7 (4%)	12 (19%)	2.7e-04
stage 4	10 (5%)	16 (25%)	2.9e-05
Maximum lymph node size (long axis, cm), at Sampling	2.5 (0-18.6)	3.4 (0-22)	2.2e-05
>5 cm	22 (15%)	21 (37%)	0.002
>10 cm	5 (4%)	3 (5%)	0.69
B2M, Median	2.3 (1.1-7.5)	3.9 (1.6-16.5)	1.4e-09
B2M, > ULN	69 (39%)	51 (81%)	5.3e-09
Treatments Prior to Sampling			
Median number	1 (1-7)	3 (1-8)	0.002
BTK inhibitors	3 (1%)	0 (0%)	0.58
PI3K inhibitors	3 (1%)	0 (0%)	0.58
Bendamustine Based	2 (1%)	15 (22%)	2.2e-08
Fludarabine Based	29 (14%)	31 (45%)	3.6e-07
Anti-CD20 Antibody	28 (13%)	36 (52%)	4e-10
BCL2 inhibitors	0 (0%)	0 (0%)	
High Dose Methyl Prednisolone (HDMP)	3 (1%)	4 (6%)	0.067
Lenalidomide	2 (1%)	2 (3%)	0.26
Alemtuzumab	3 (1%)	1 (1%)	1
Treatments After Sampling			
Median number	1.5 (1-7)	2 (1-8)	0.5
BTK inhibitors	19 (9%)	11 (16%)	0.12
PI3K inhibitors	5 (2%)	3 (4%)	0.42
Bendamustine Based	23 (11%)	2 (3%)	0.05
Fludarabine Based	72 (35%)	8 (12%)	1.9e-04
Anti-CD20	98 (47%)	44 (64%)	0.018
BCL2 inhibitors	4 (2%)	8 (12%)	0.002
HDMP	16 (8%)	37 (54%)	5.1e-15
Lenalidomide	12 (6%)	0 (0%)	0.04
Alemtuzumab	16 (8%)	35 (51%)	1.1e-13

ULN: upper limit of normal; HDMP: high-dose methylprednisolone.
Numbers are medians followed by percentage or range of values in parenthesis.

Table S3. Overall survival is correlated with total copy number events and somatic mutations (Stratified by treatment status at sampling). (n=99)

Univariable model	**HR**	**95% CI**		**p-value**	**C-index**
Tot no. of copy number events: high vs low	3.85	1.35	11.0	0.0012	0.765
Tot no. of mutations: high vs low	6.82	2.09	22.21	0.0014	0.750
Multivariable model					
Tot no. of copy number events: high vs low	5.749	1.93	17.11	0.0017	0.850
Tot no. of mutations: high vs low	9.14	2.66	31.41	0.00045	

Cutoff values for total number of mutations: 21; total number of CNA events: 4.

Table S4. Details of the *RPS15* mutations in this study.

Hugo Symbol	Sample Code	FISH Del17p	Genome Change	Protein Change	Alt	Ref	Treatment
RPS15	CW163	Yes	g.chr19:1440458G>C	p.K145N	6	10	Previously untreated
RPS15	CW224	No	g.chr19:1440438T>G	p.S139A	20	43	Previously untreated
RPS15	CW32	No	g.chr19:1440417G>A	p.G132S	5	5	Previously untreated
RPS15	SS171	Yes	g.chr19:1440414C>T	p.P131S	11	34	Previously untreated
RPS15	SS181a	Yes	g.chr19:1440439C>T	p.S139F	19	53	Previously untreated
RPS15	SS190	Yes	g.chr19:1440432C>G	p.H137D	19	17	Previously treated
RPS15	SS201	No	g.chr19:1440414C>T	p.P131S	13	21	Previously untreated
RPS15	SS202	Yes	g.chr19:1440429A>G	p.T136A	28	25	Never treated
RPS15	SS185	Yes	g.chr19:1440457A>T	p.K145M	19	26	Previously treated

Alt: alternative allele read count. Ref: reference allele read count.

Figure S1. IGV screen shot showing 17p deletions. The minimally deleted region (MDR) is marked between the red lines.

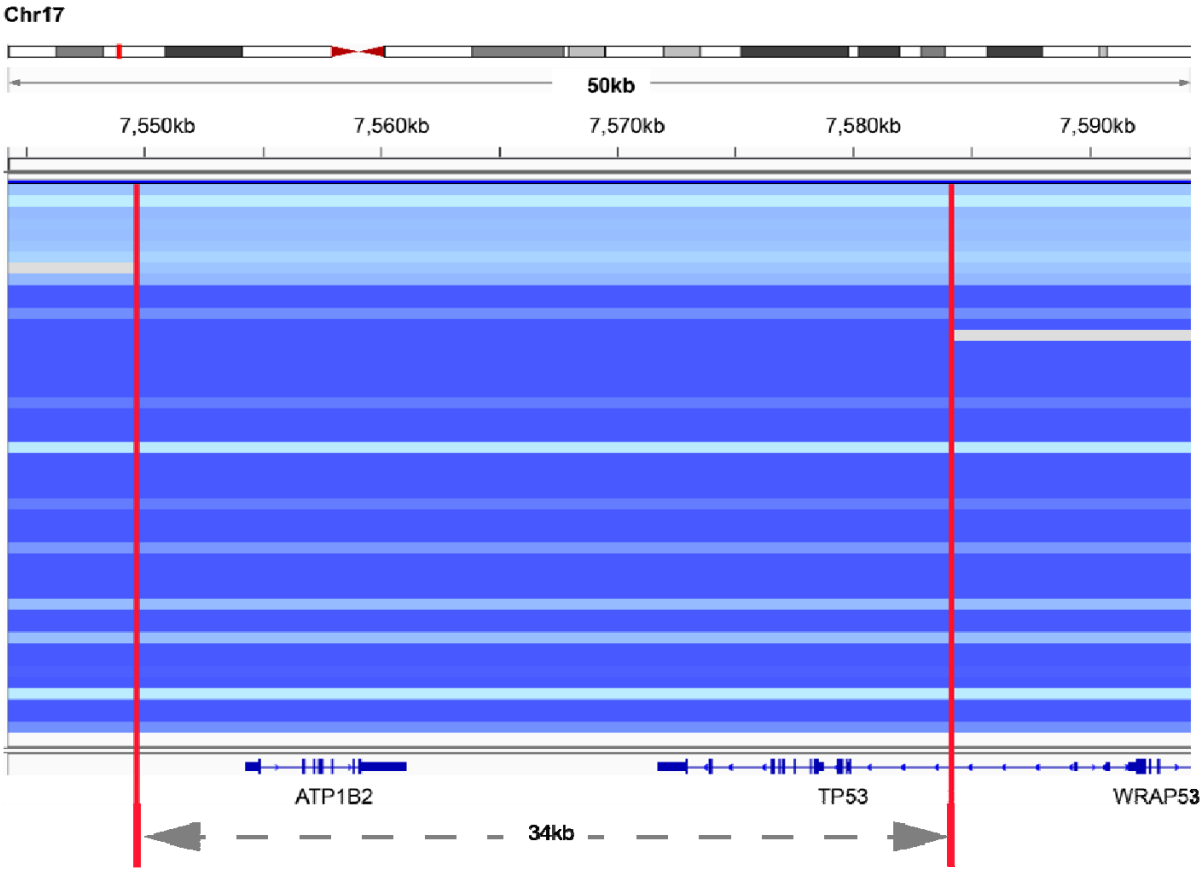


Figure S2. Overview of CNAs in the tumor samples of 200 independent CLL patients.

Each vertical track represents the copy number status of one tumor sample. The copy number value is color-coded as shown in the legend. The green line separates the 17p wild type samples from the 17p deletion samples. Samples are arranged by their treatment status.

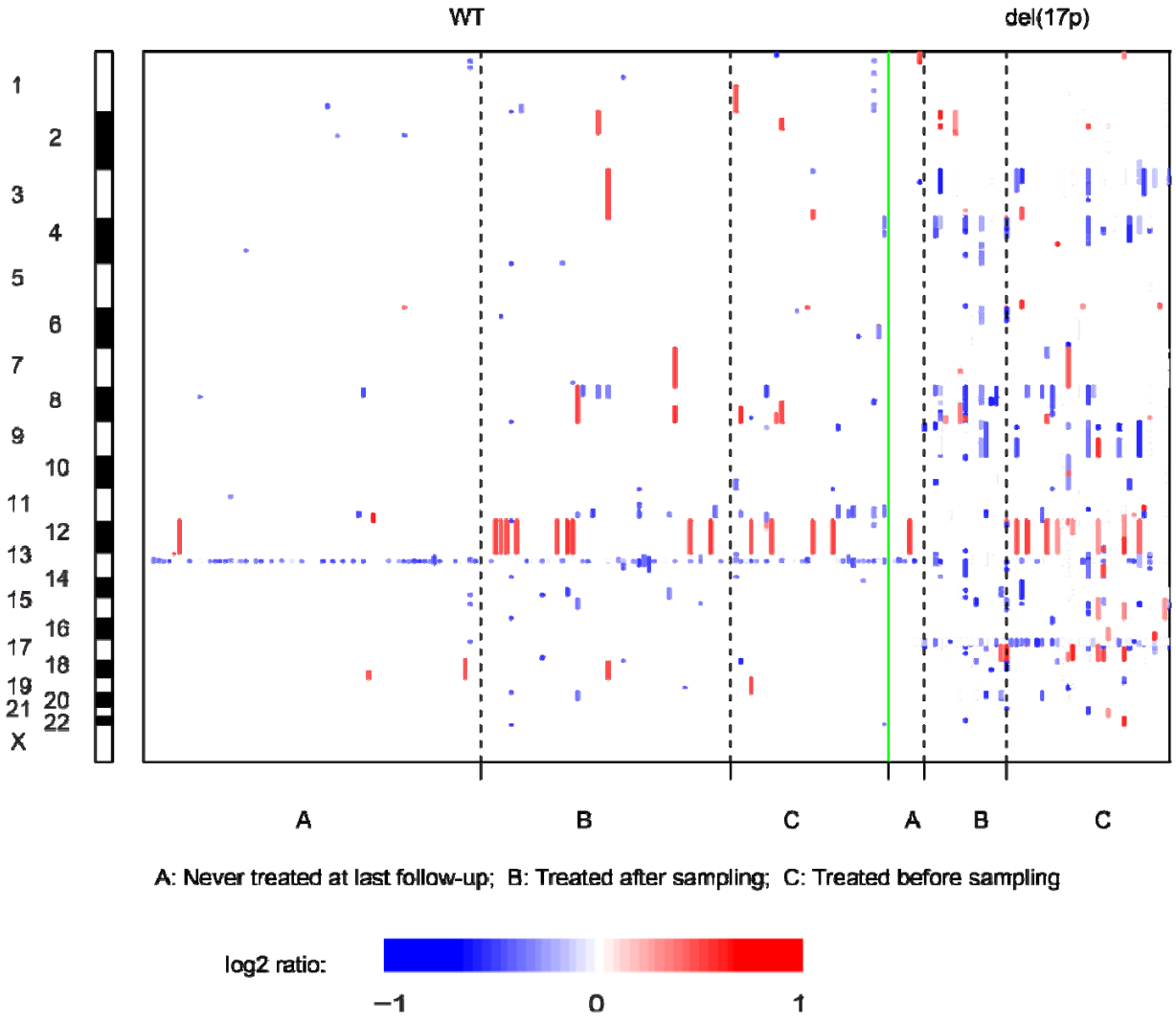


Figure S3. CNAs and somatic mutations in the 99 patients with both WES and SNP profiles. A-C: Correlations between numbers of CNA and somatic mutations. Blue lines represent linear fitting of the data points. D: Overall survival in patient groups stratified by total CNAs and somatic mutations. Cutoff for CNAs is 4 events, Cutoff for mutations is 21.

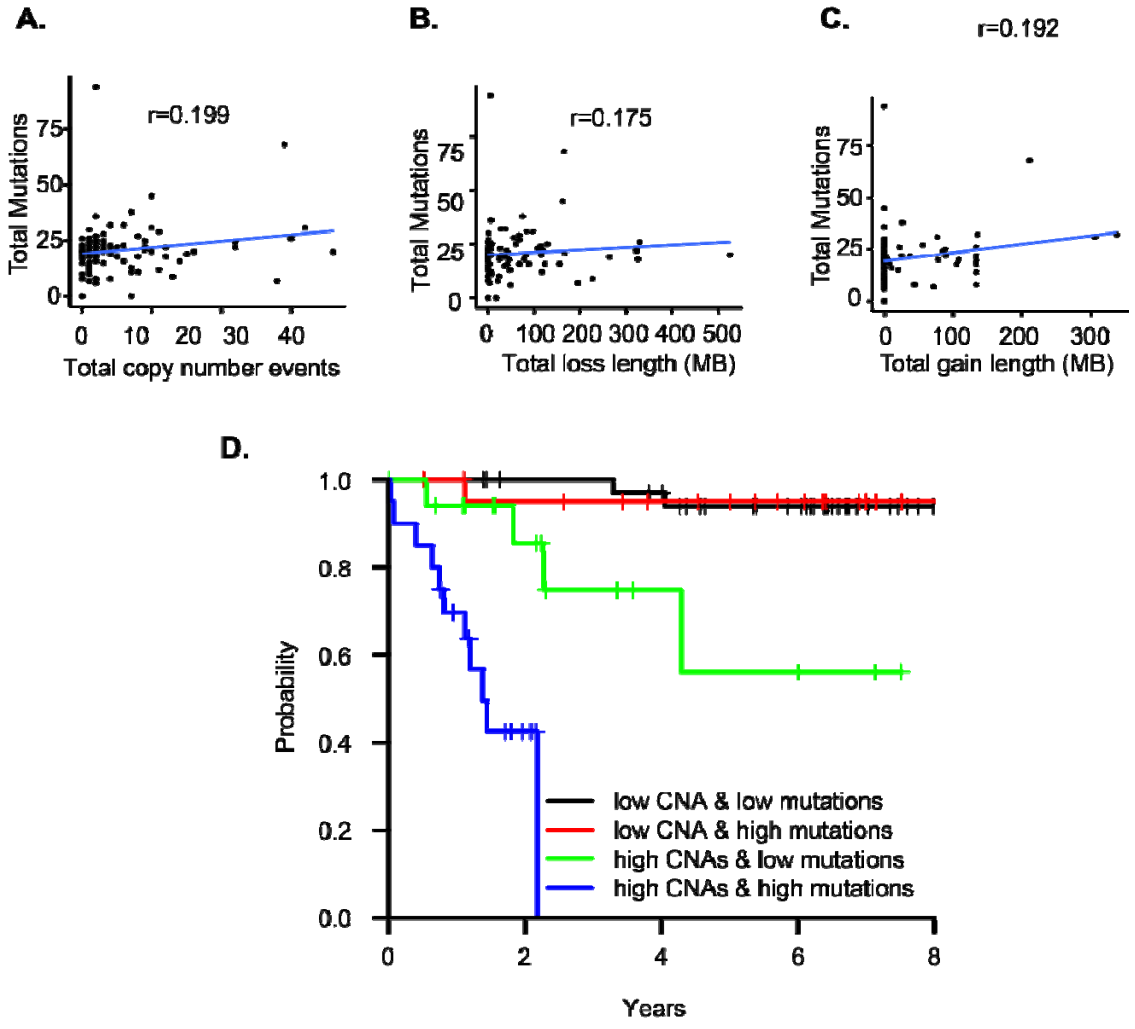


Figure S4. Analysis of *TP53* and *SF3B1* mutations. A. Heatmap of 59 tumor samples that have either *TP53* mutations or 17p deletions (single null) or both (double null). Two samples with *TP53* mutation but without 17p deletion were found to have copy neutral LOH and are therefore classified as double null. Samples without *TP53* disruption (i.e. wild type) are not shown in the heatmap (N= 117). B. Cancer cell fractions of the *SF3B1* mutations in each patient. C. Kaplan-Meier curves of OS by the clonality status of *SF3B1* mutations.

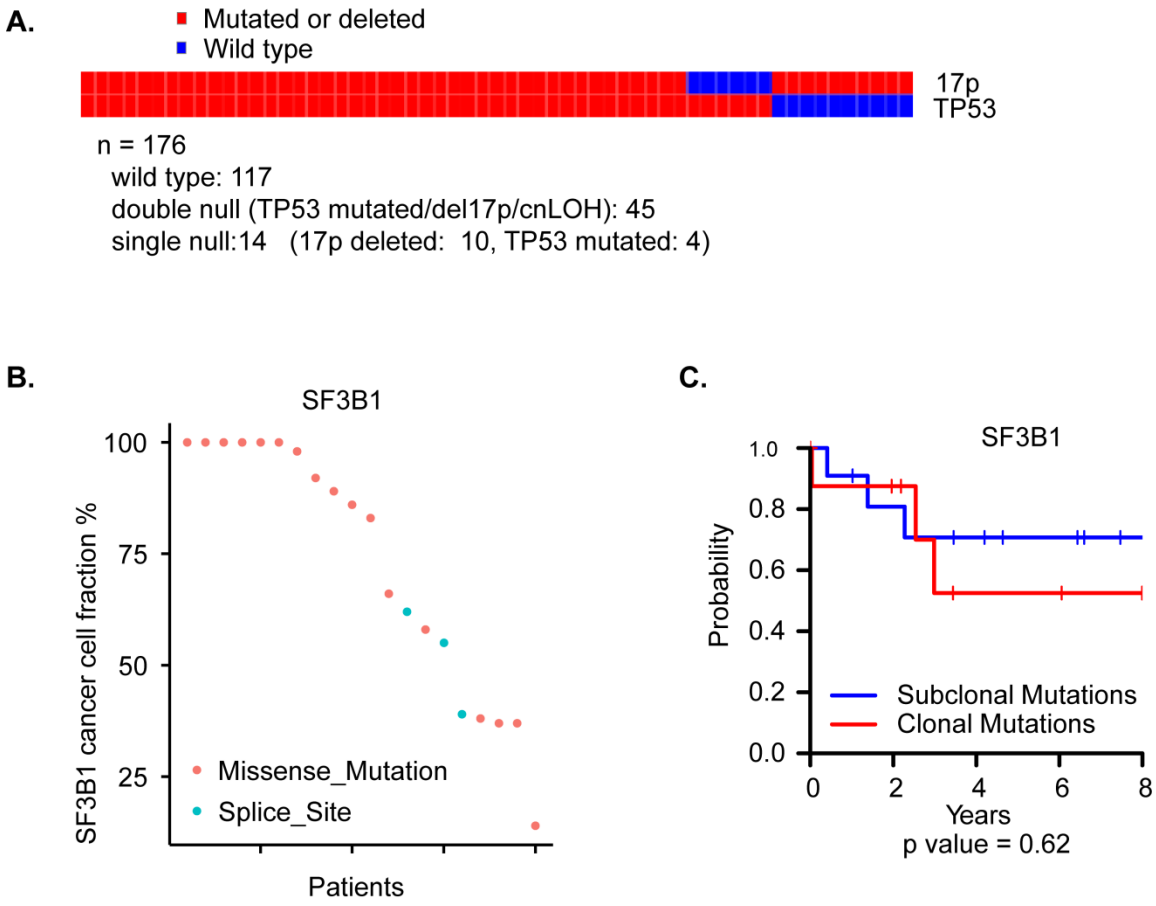


Figure S5. *RPS15* mutations. A. Sanger sequencing of genomic DNA confirming the C->T transition in a representative sample. B. Screenshot of RNA sequencing showing that a T->G mutation is transcriptionally expressed. C. Schematic representation of the 4 exons of *RPS15*, with *RPS15* mutations identified by WES. Exon lengths are not drawn to scale. D. Overall survival analysis of *RPS15* and del(17p).

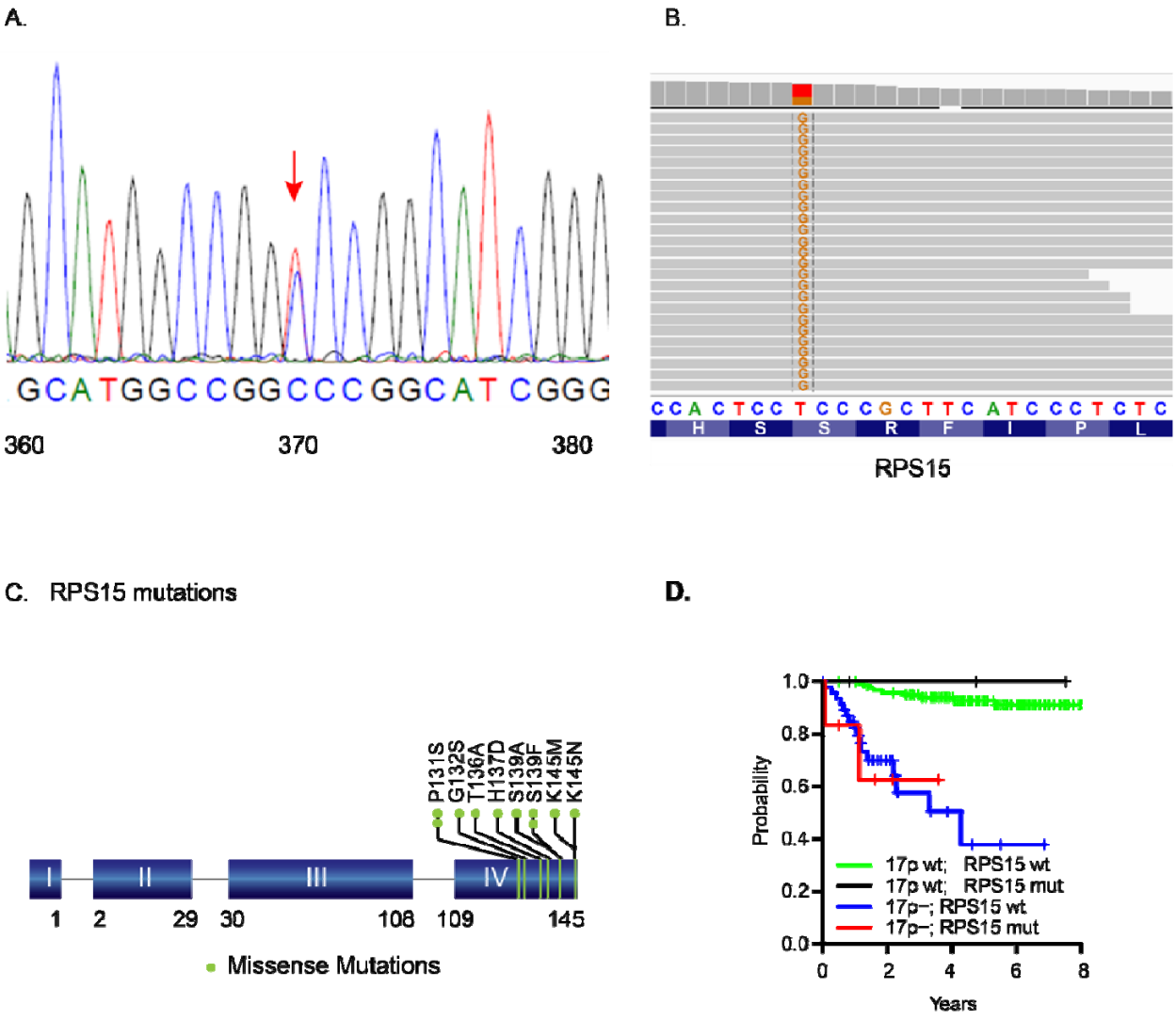


Figure S6. GISTIC analysis discovered novel recurrent deletions in chromosomal 3p, 4p, 8p and 9p in del(17p) CLL. The green lines indicate the q value cutoff of 0.05.

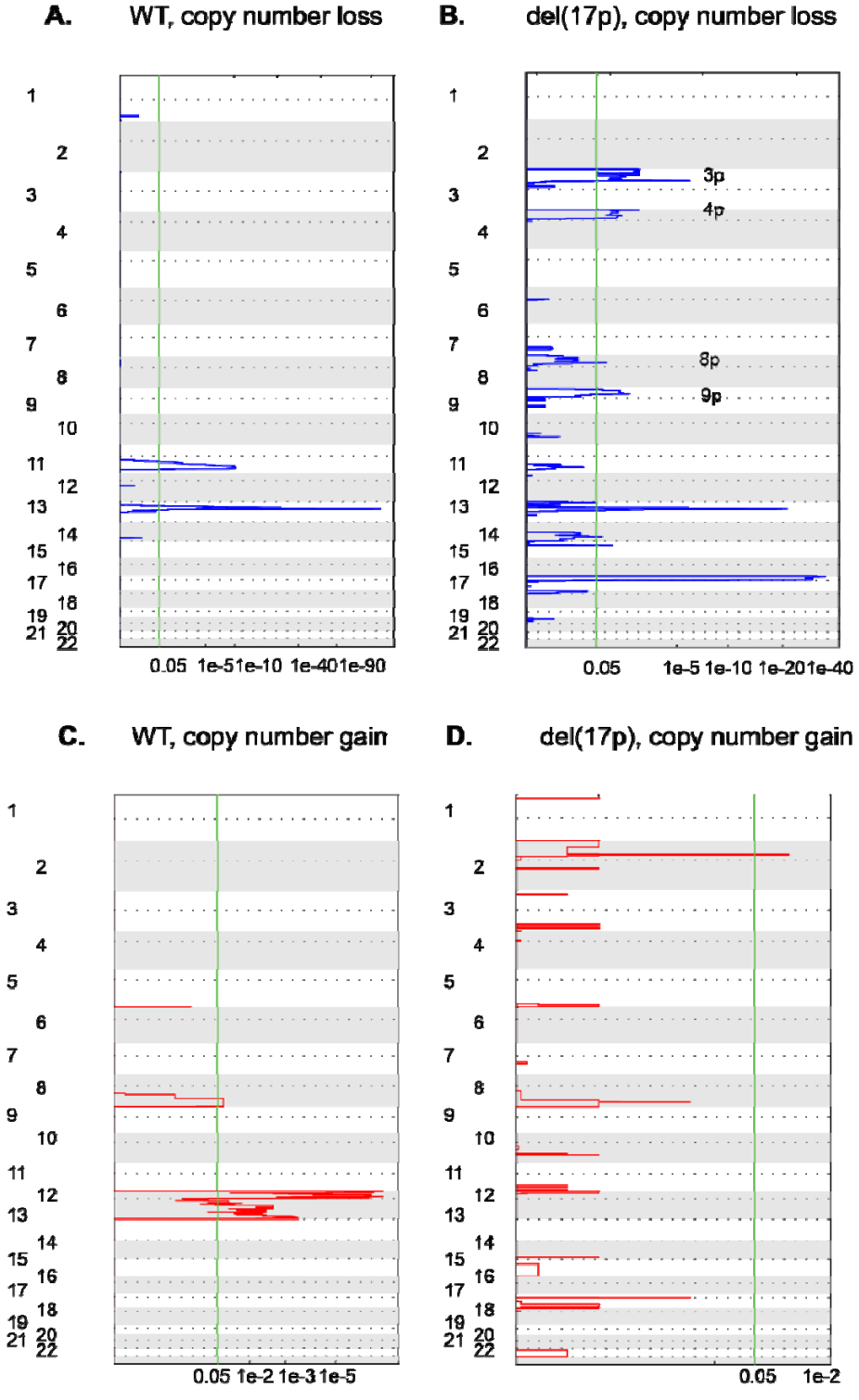


Figure S7. Association of del(17p) and chromosomal deletions at 8p, 3p, 4p, and 9p.

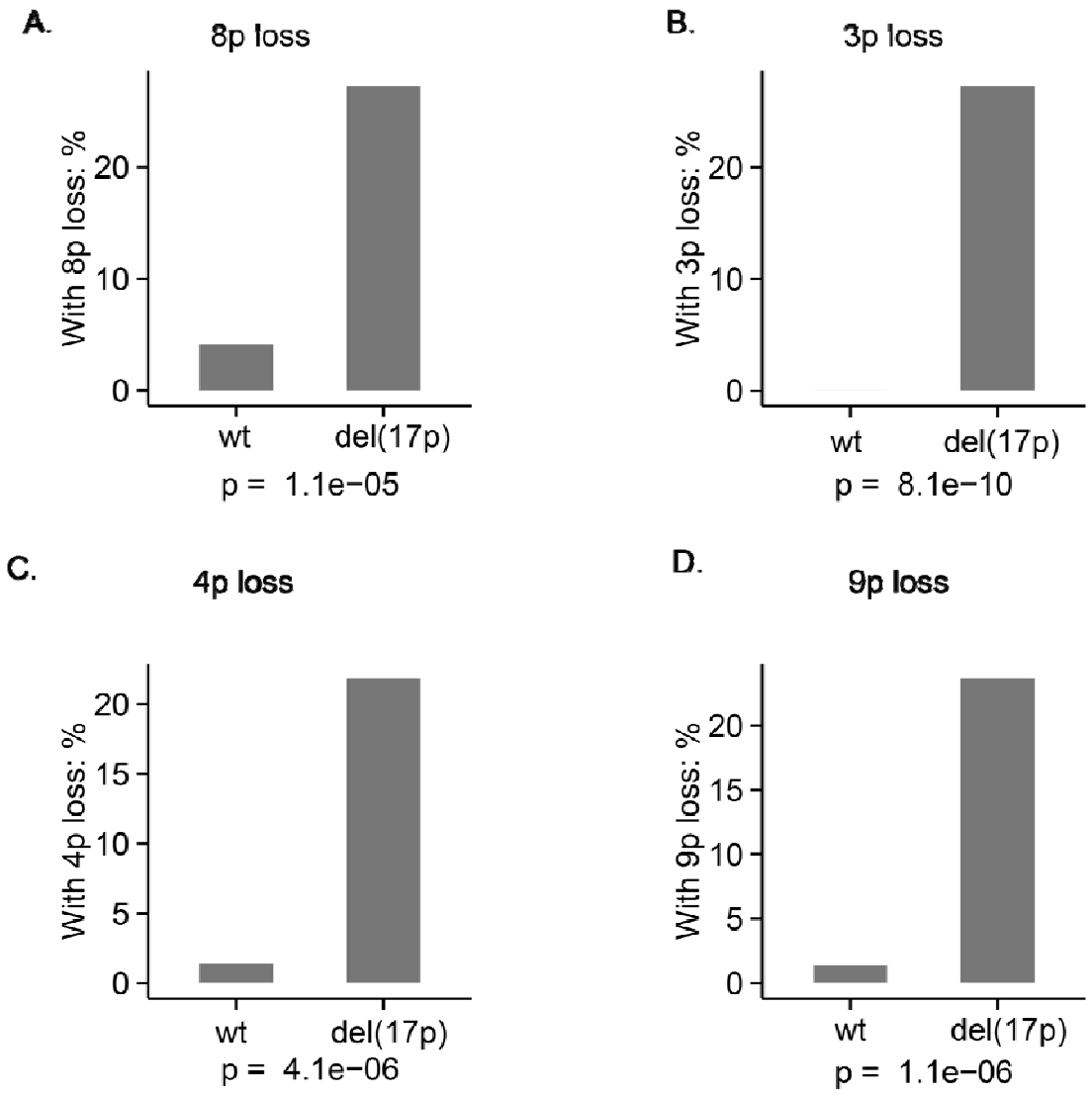


Figure S8. Overall survival in del(17p) patients with recurrent deletions. A. 17p wt vs del(17p). B. del(17p) alone vs del(17p) with 3p-. C. del(17p) alone vs del(17p) with 4p-. D. del(17p) alone vs del(17p) with 9p.

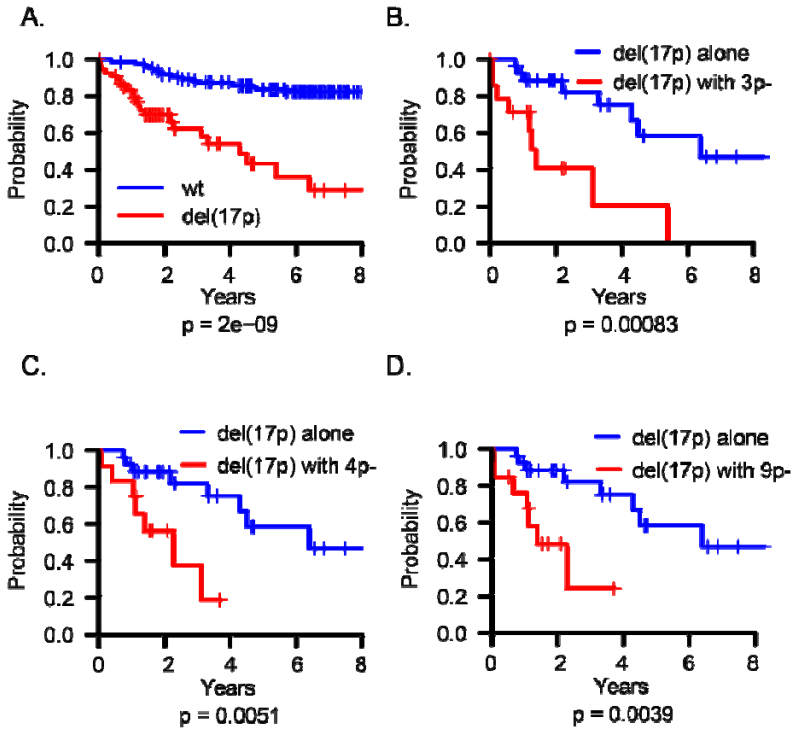


Figure S9. IGV screen shot showing 3p deletions. The MDR is marked between the red lines.

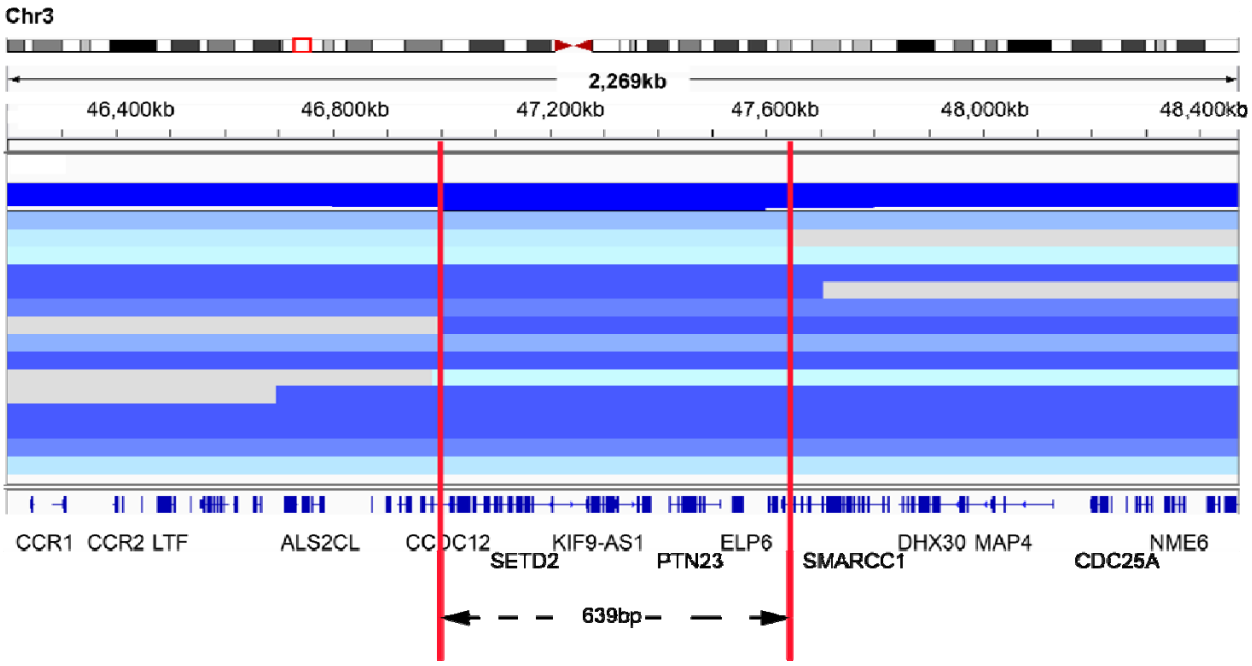


Figure S10. IGV screen shot showing 4p deletions. The MDR is marked between the red lines.

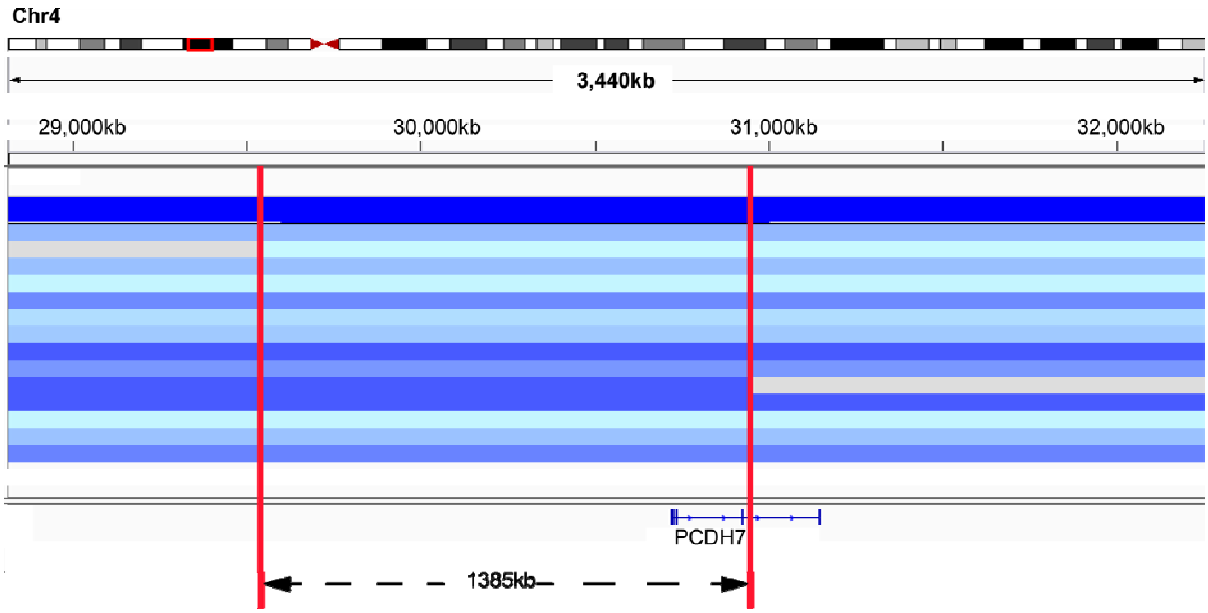


Figure S11. IGV screen shot showing 8p deletions. The MDR is marked between the red lines.

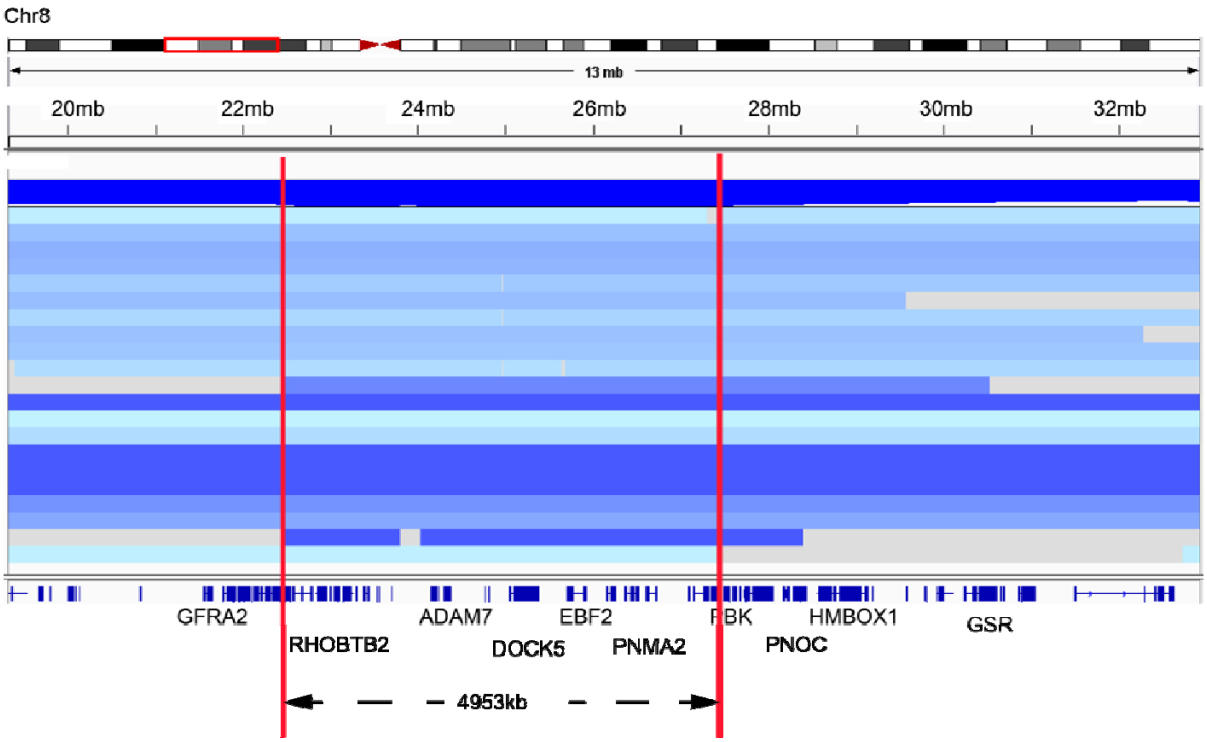


Figure S12. IGV screen shot showing 9p deletions. The MDR is marked between the red lines.

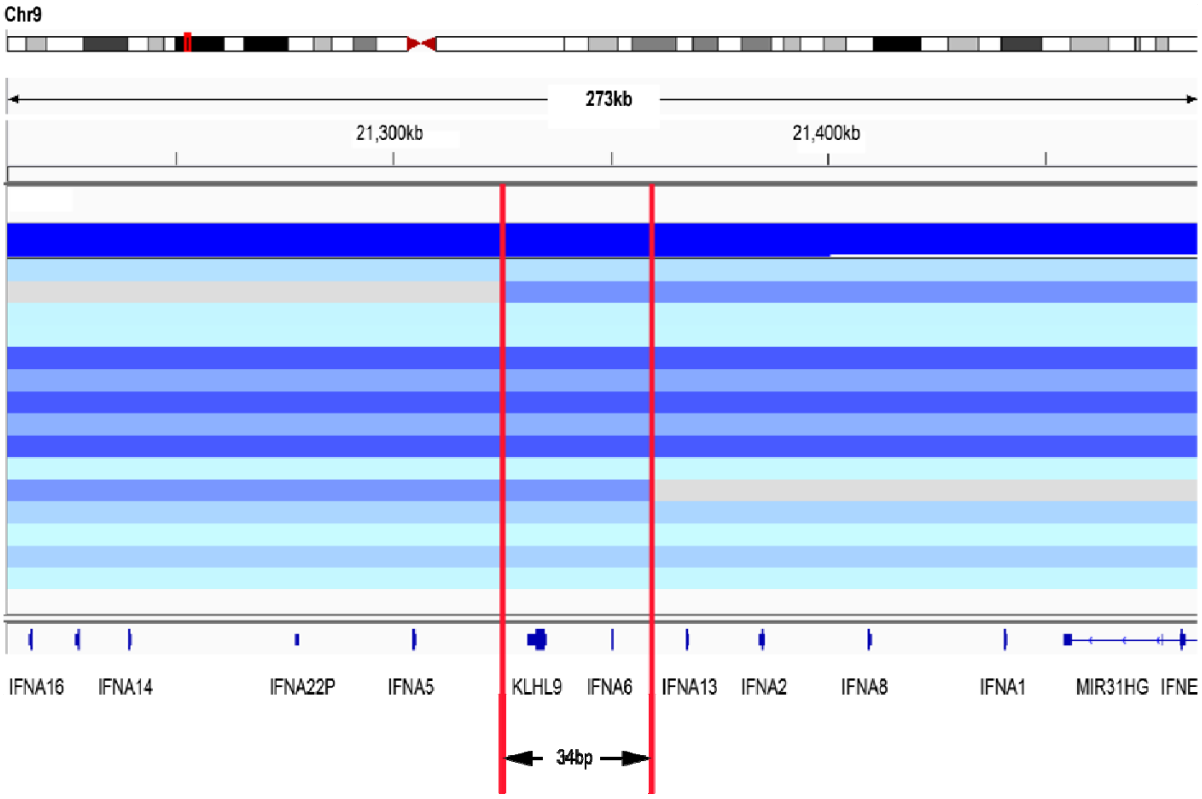


Figure S13. Association between number of CNAs and complex karyotype (CKT).

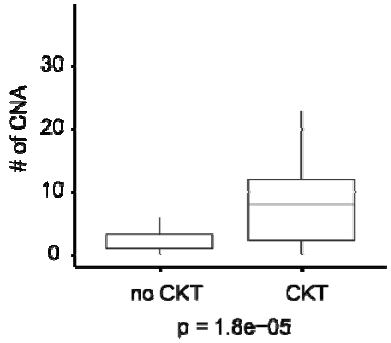
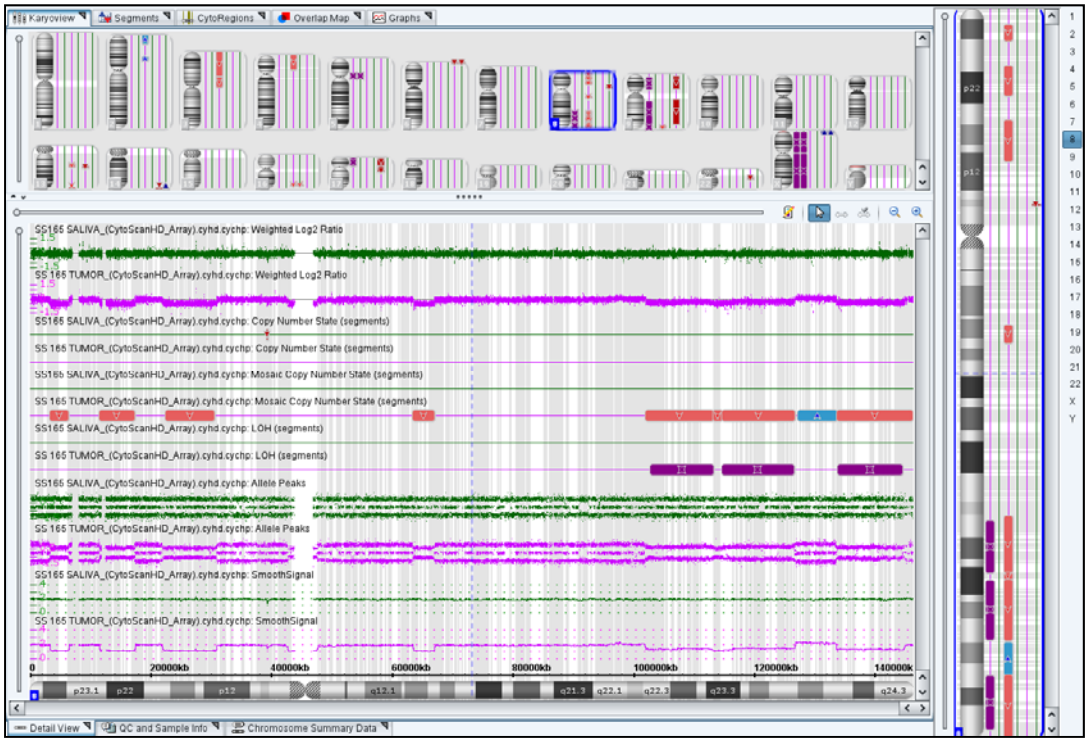


Figure S14. Chromothripsis in del(17p) CLL samples. Figure 14A depicts a likely chromothripsis event on chr8p in sample SS165. Figure 14B shows a likely chromothripsis event, followed by a likely chromoanasynthesis event in sample SS192. The karyotype is represented in the upper panel of both figures. The chromosomal alterations for the tumor sample (magenta) and the matched normal (green) are shown in the lower panel. Included tracks are weighted $\log_2$ ratio, copy number states (loss-red, gain-blue), mosaic copy number states, loss of heterozygosity (purple), allele peaks, smooth signal and the chromosome ideogram (expanded view also shown in the right panel). Chromothripsis is evident by the presence of alternating states of DNA copy number and allele ratios.

A.



B.

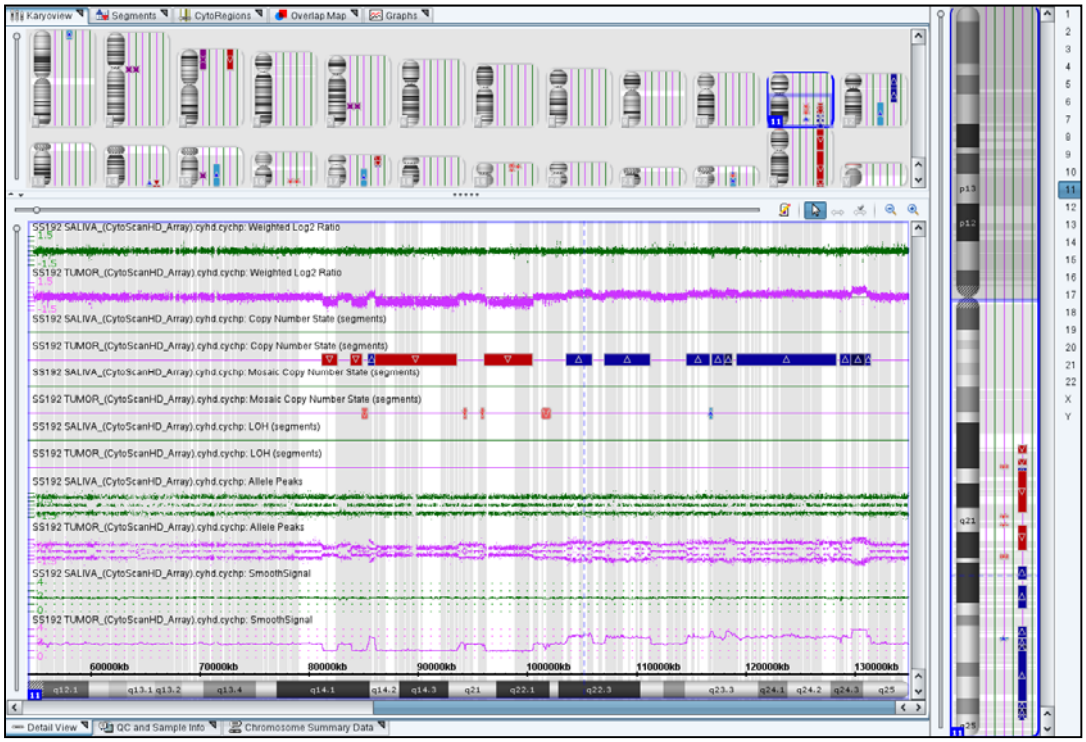

Karyoview
Segments
CytoRegions
Overlap Map
Graphs
SS192 SALIVA_(CytoScanHD_Array).cyhd.cychp: Weighted Log2 Ratio
SS192 TUMOR_(CytoScanHD_Array).cyhd.cychp: Weighted Log2 Ratio
SS192 SALIVA_(CytoScanHD_Array).cyhd.cychp: Copy Number State (segments)
SS192 TUMOR_(CytoScanHD_Array).cyhd.cychp: Copy Number State (segments)
SS192 SALIVA_(CytoScanHD_Array).cyhd.cychp: Mosaic Copy Number State (segments)
SS192 TUMOR_(CytoScanHD_Array).cyhd.cychp: Mosaic Copy Number State (segments)
SS192 SALIVA_(CytoScanHD_Array).cyhd.cychp: LOH (segments)
SS192 TUMOR_(CytoScanHD_Array).cyhd.cychp: LOH (segments)
SS192 SALIVA_(CytoScanHD_Array).cyhd.cychp: Allele Peaks
SS192 TUMOR_(CytoScanHD_Array).cyhd.cychp: Allele Peaks
SS192 SALIVA_(CytoScanHD_Array).cyhd.cychp: SmoothSignal
SS192 TUMOR_(CytoScanHD_Array).cyhd.cychp: SmoothSignal
60000kb
70000kb
80000kb
90000kb
100000kb
110000kb
120000kb
130000kb
Detail View
QC and Sample Info
Chromosome Summary Data

Figure S15. Sanger sequencing of *TP53* with cnLOH at 17p. Arrow indicates the A>G mutation in exon 5.