SUPPLEMENTARY INFORMATION FOR:

Exome sequencing identifies mutation in *CNOT3* and ribosomal genes *RPL5* and *RPL10* in T-cell acute lymphoblastic leukemia

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This .pdf document includes:

Supplementary Note

Supplementary Figure 1-9

Supplementary tables 1-4, 6 and 8-11

The following supplementary files are available as separate .xls files:

Supplementary table 5

Supplementary table 7

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List of supplementary documents:

Supplementary Note: Leukemia samples

Supplementary Figure 1: Comparison of somatic SNV filtering strategies

Supplementary Figure 2: The number of somatic mutations increases with age

Supplementary Figure 3: The number of mutations does not correlate with outcome

Supplementary Figure 4: Overview of mutations in recurrently but not significantly mutated genes in T-ALL samples

Supplementary Figure 5: Mutations in 15 identified candidate T-ALL driver genes in 17 T-ALL cell lines

Supplementary Figure 6: Localization of Rpl10 and Rpl5 proteins in the 60S ribosomal subunit

Supplementary Figure 7: DNA and RNA Sanger results RPL10 and CNOT3 mutations

Supplementary Figure 8: RPL10 mutated residues are close to the catalytic center of the ribosome

Supplementary Figure 9: T-ALL associated RPL10 mutants impair proliferation and ribosome biogenesis in yeast cells

Supplementary Table 1: Description patient set exome sequencing

Supplementary Table 2: Average alignment results over 123 samples

Supplementary Table 3: Sequencing and mapping statistics of the 123 samples

Supplementary Table 4: Detected SNV and INDEL numbers

Supplementary Table 5: Protein-altering (A) somatic SNVs and (B) somatic INDELs in 39 diagnosis-remission pairs

Supplementary Table 6: 20 significantly mutated genes

Supplementary Table 7: Protein-altering SNVs and INDELs in 15 candidate genes in (A) diagnosis-only samples and (B) cell lines

Supplementary Table 8: Patient characteristics *CNOT3* (NM_014516.3) mutated cases

Supplementary Table 9: Patient characteristics *RPL* mutated cases

Supplementary Table 10: Association between candidate driver mutations and clinico-biological features

Supplementary Table 11: *RPL10*, *RPL5* and *CNOT3* PCR and sequencing primers

Supplementary note

Leukemia samples

T-ALL patient samples were collected at various institutions. All patients have given their informed consent and all samples were obtained according to the guidelines of the local ethical committees. This study was approved by the ethical committee of the University Hospital Leuven. Diagnosis of T-ALL was based on morphology, cytochemistry and immunophenotyping according to the World Health Organization and European Group for the Immunological Characterization of Leukemias criteria. A detailed description of the clinico-biological characteristics of the analyzed patient samples is provided in Supplementary table 1.

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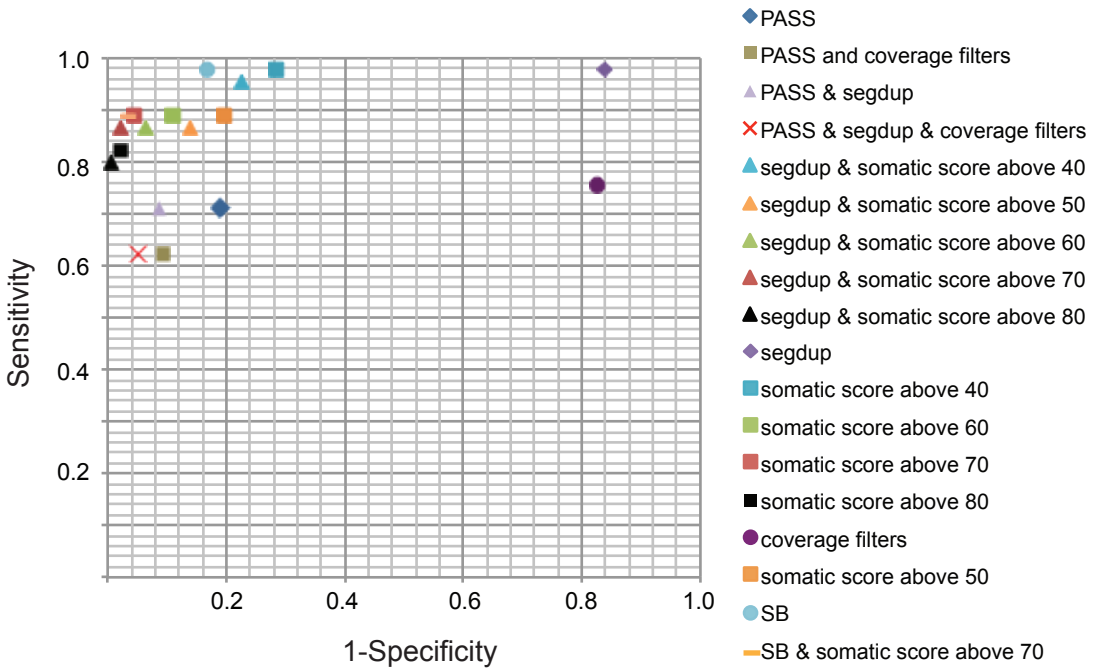
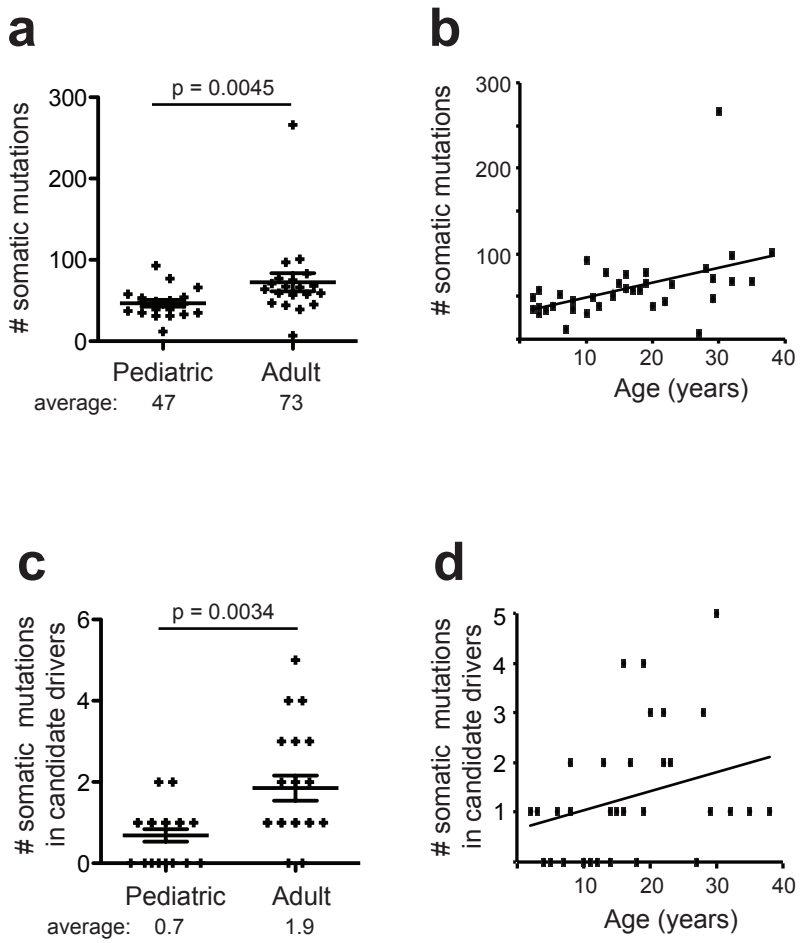


Suppl. Figure 1. Comparison of somatic SNV filtering strategies.
Variant quality filtering is denoted as 'PASS' (referring to the quality tag for high quality variants predicted by VQSR). Coverage filtering is defined as depth of coverage ≥ 10 reads in diagnosis and remission, and variant allele frequency ≥ 20% in diagnosis and ≤ 5% in remission. For repeat region filtering ('segdup' in the legend), all variants in segmental duplication regions are removed. The final filtering strategy used in the rest of this work is indicated with a red square.



Suppl. Figure 2. The number of somatic mutations increases with age. (**a**) Box plot showing the number of somatic mutations in pediatric (age ≤ 15 years) and in adult (age ≥ 16) T-ALL samples. Average and s.e.m. is indicated on the plots. The reported p-value tests whether there is a significant difference between mutation number in adults versus children and was calculated using a 2-tailed Wilcoxon signed rank test. Group size pediatric: n=19; adult: n=20. (**b**) Dot plot representing the number of somatic mutations versus patient age. (**c**) Box plot showing the number of somatic mutations in candidate driver genes in pediatric and in adult T-ALL patients. Average and s.e.m. is indicated on the plots. The reported p-value tests whether there is a significant difference between mutation number in adults versus children and was calculated using a 2-tailed Wilcoxon signed rank test. Group size pediatric: n=19; adult: n=20. (**d**) Dot plot representing the number of somatic mutations in candidate driver genes versus patient age.

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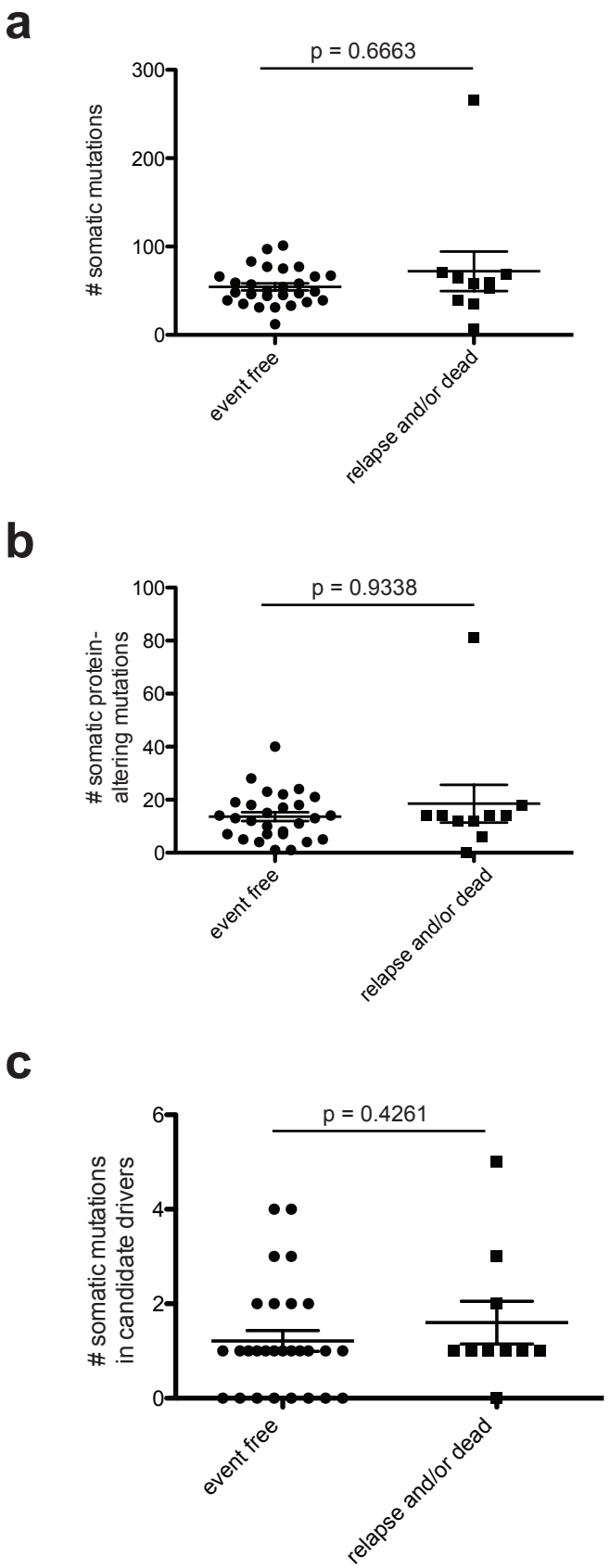
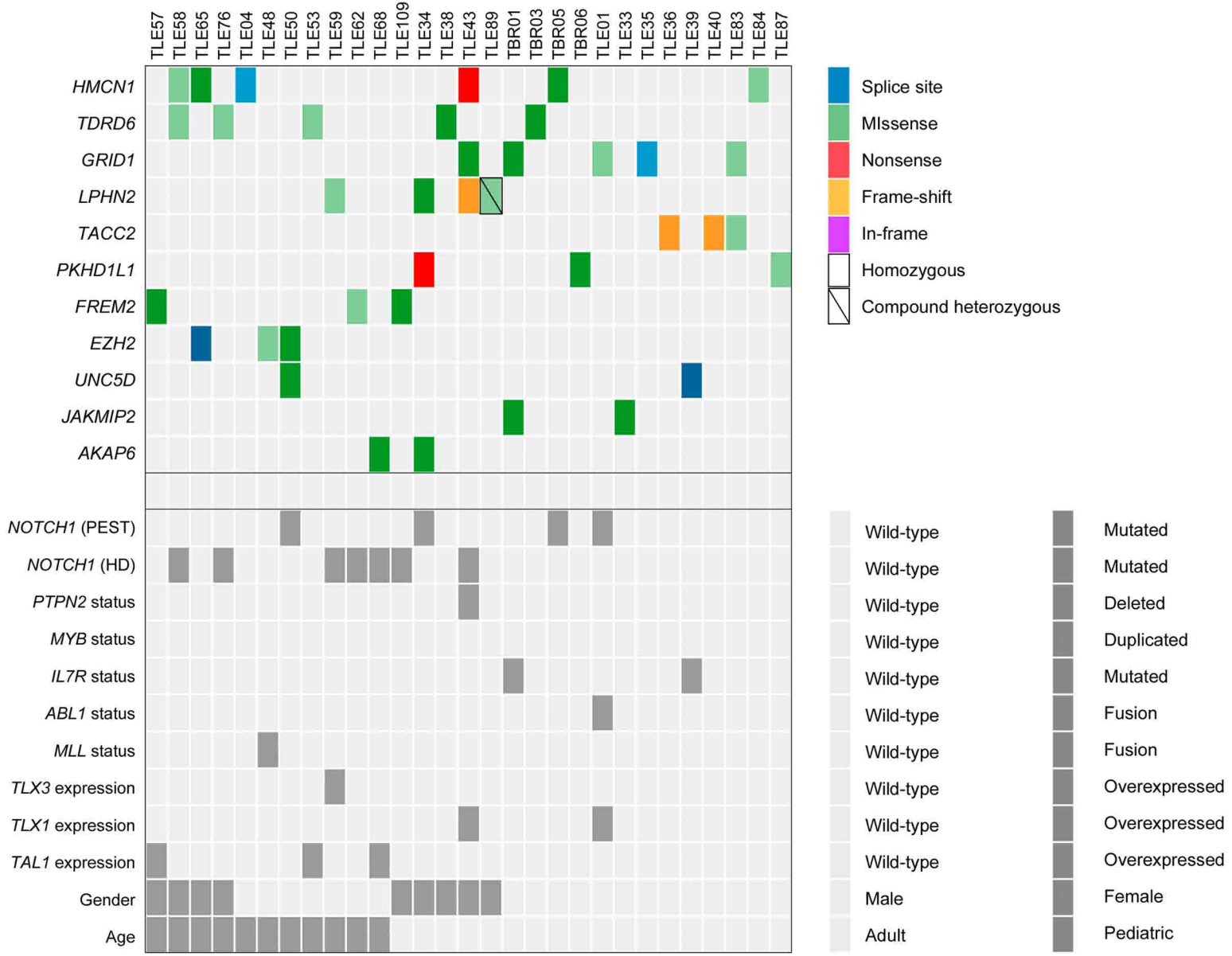
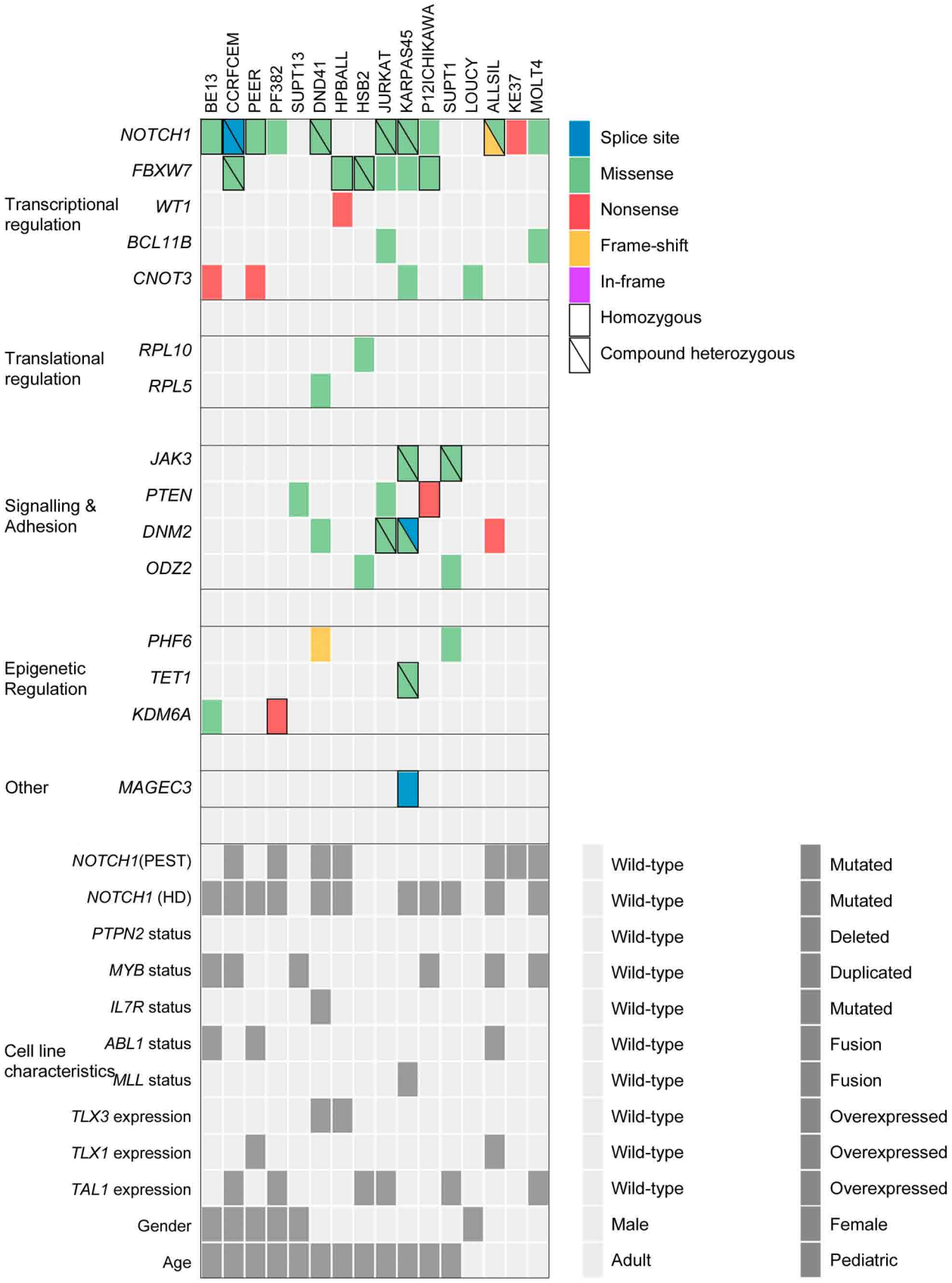


Suppl. Figure 3. The number of mutations does not correlate with outcome.
(**a-c**) Box plots showing number of somatic mutations (**a**), number of protein-altering somatic mutations (**b**) and number of somatic mutations in candidate driver genes (**c**) in patients that did not undergo an event versus patient that relapsed and/or died due to T-ALL. Average and s.e.m. is indicated on the plots. All reported p-values test whether there is a significant difference between mutation number in event free versus relapsed and/or leukemia induced dead patiens and were calculated using a 2-tailed Wilcoxon singed rank test. Group size event free: n=28; relapse and/or dead: n=10.

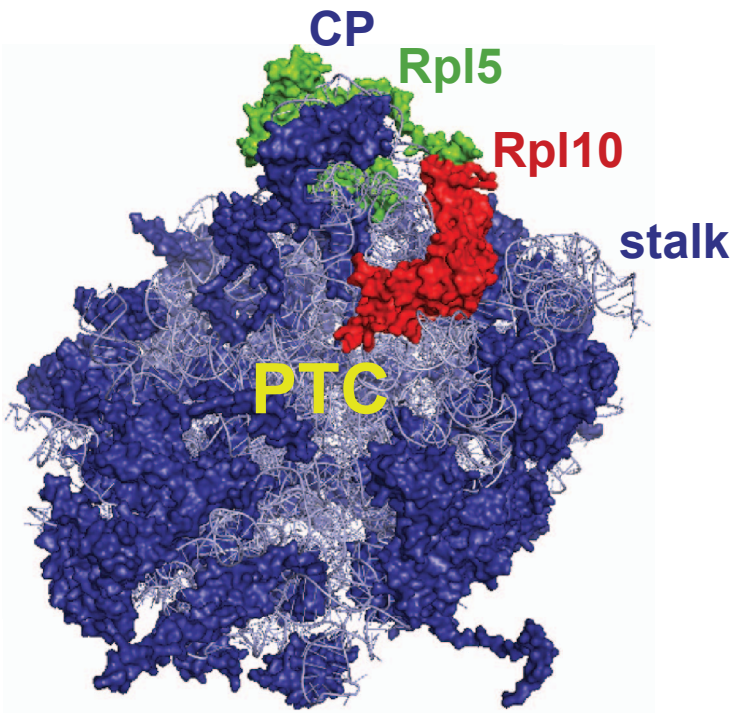


Suppl. Figure 4. Overview of mutations in recurrently but not significantly mutated genes in T-ALL samples

Mutations observed in 11 genes that were recurrently mutated in at least 2 of the diagnosis-remission pairs but that were not significantly mutated as determined by GenomeMuSiC. For clarity, only samples harboring mutations in any of these 11 genes are shown in the figure. Each type of mutation is indicated with a different color as indicated in the legend and symbols for homozygous and compound heterozygous mutations are explained. Mutations with no indication are heterozygous. All mutations shown in this figure were validated by conventional Sanger sequencing. Relevant patient characteristics (identified by Sanger sequencing, karyotyping, or gene expression) are included at the bottom of the heatmap. Mutations in *NOTCH1* were hard to identify by exome sequencing due to the low coverage of *NOTCH1* exons. *NOTCH1* mutations detected by Sanger sequencing are indicated at the bottom of the heatmap under patient characteristics.



Suppl. Figure 5. Mutations in 15 identified candidate T-ALL driver genes.
Mutations observed in the 15 selected candidate T-ALL driver genes in 17 sequenced T-ALL cell lines. Each type of mutation is indicated with a different color as indicated in the legend and symbols for homozygous and compound heterozygous mutations are explained. Mutations with no indication are heterozygous. All mutations shown in this figure were validated by conventional Sanger sequencing. Relevant cell line characteristics (identified by Sanger sequencing, karyotyping, or gene expression) are included at the bottom of the heatmap. Mutations in *NOTCH1* were hard to identify by exome sequencing due to the low coverage of *NOTCH1* exons. *NOTCH1* mutations detected by Sanger sequencing are indicated at the bottom of the heatmap under cell line characteristics.



Suppl. Figure 6. Localization of Rpl10 and Rpl5 proteins in the 60S ribosomal subunit.
The figure shows the 'crown view' of the rRNA and proteins of the yeast 60S ribosomal subunit with indication of Rpl10 and Rpl5 proteins. PTC: peptidyltransferase center; CP: central protuberance. This model is based on the yeast 3Å crystal structure (PDB entries 3U5E and 3U5D).

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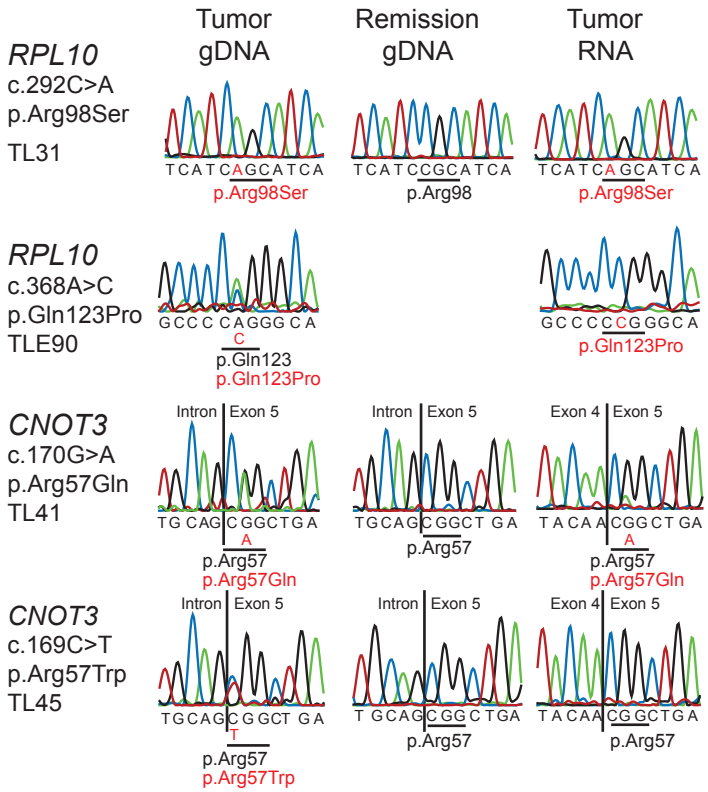
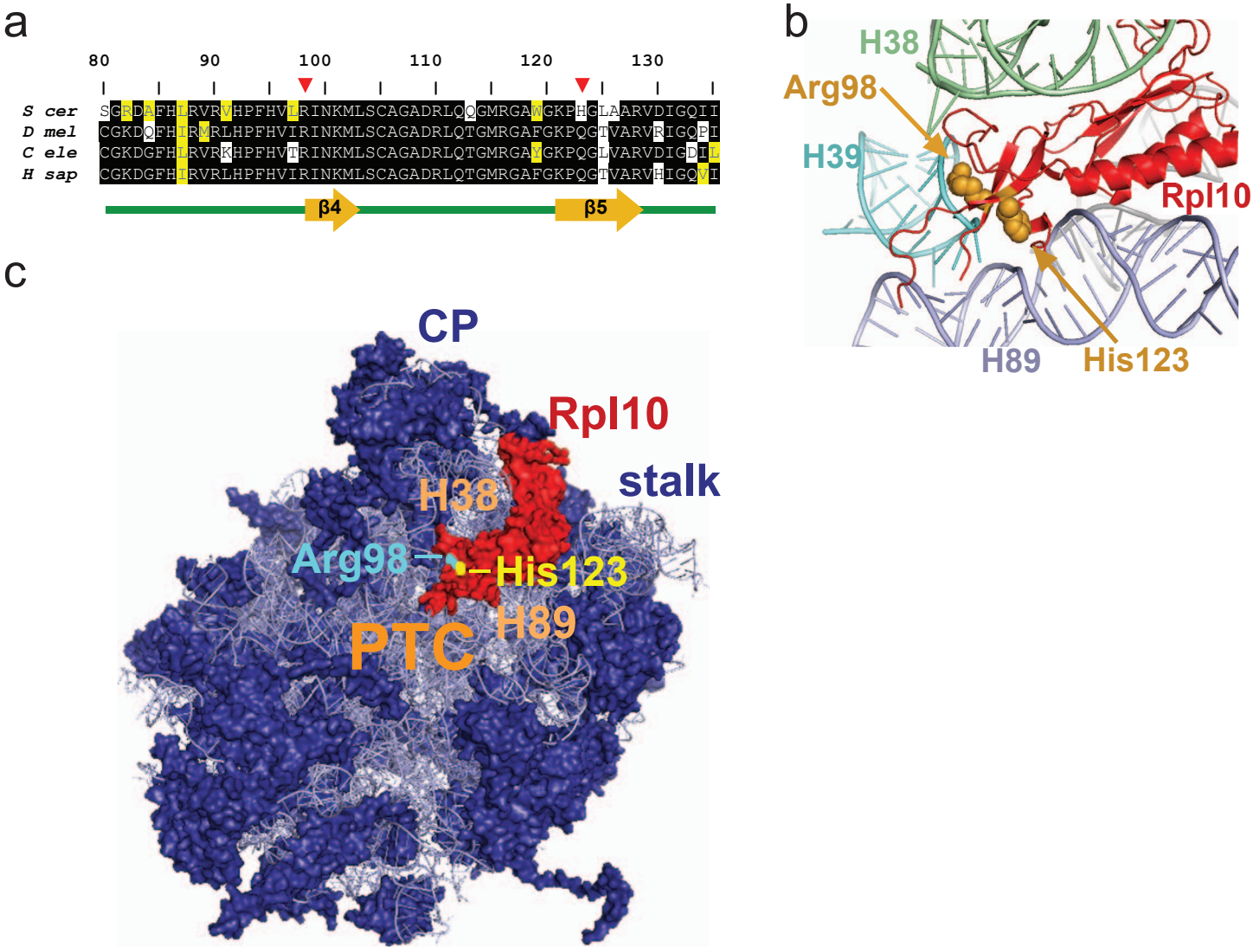
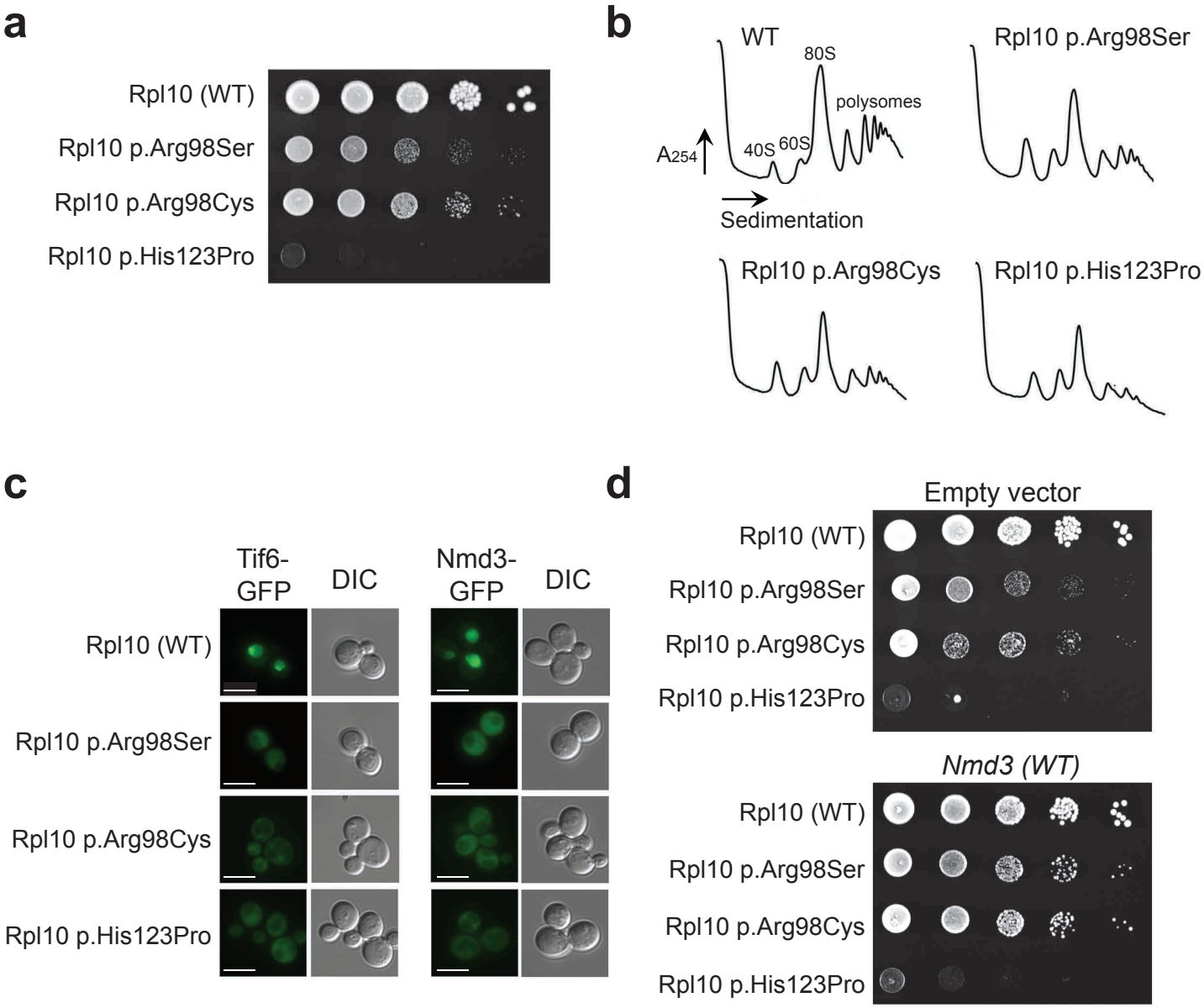


Suppl. Figure 7. DNA and RNA Sanger results *RPL10* and *CNOT3* mutations.
Representative chromatograms illustrating presence or absence of indicated *RPL10* or *CNOT3* mutations in diagnostic or remission genomic DNA or diagnostic RNA.



Suppl. Figure 8. RPL10 mutated residues are close to the catalytic center of the ribosome.
(**a**) Alignment of Rpl10 protein sequence from yeast (*S cer*), Drosophila (*D mel*), nematodes (*C ele*) and human (*H sap*). Amino acid positions are given and Arg98 and Gln123 (or His123 in yeast) are indicated (▼). β-sheets in the secondary structure of Rpl10 are indicated under the alignment. (**b**) 3D representation of the region of yeast Rpl10 containing Arg98 and His123 and surrounding rRNA helices H38, H39 and H89. The figure shows that Rpl10 residues Arg98 and His123 are opposing residues in a beta-hairpin loop of Rpl10. (**c**) Model showing the position of Rpl10 and its residues Arg98 and His123 into the 60S yeast ribosomal subunit ('crown view'). The figure illustrates that Rpl10, and particularly residues Arg98 and His123, are close to the peptidyltransferase center (PTC) in the ribosome. For Reference, rRNA helices H38 and H89 that are also shown in panel (b) are indicated. CP: Central Protuberance. Modeling in panels (b) and (c) is based on the yeast 3Å crystal structure (PDB entries 3U5E and 3U5D).



Suppl. Figure 9. T-ALL associated RPL10 mutants impair proliferation and ribosome biogenesis in yeast cells. (**a**) Growth of conditional glucose-repressible Rpl10 yeast cells expressing wild-type (WT) Rpl10, or the T-ALL associated Rpl10 p.Arg98Ser, Rpl10 p.Arg98Cys and Rpl10 p.His123Pro mutants was compared by plating ten-fold serial dilutions. (**b**) Polysome profiles for Rpl10 WT, Rpl10 p.Arg98Ser, Rpl10 p.Arg98Cys and Rpl10 p.His123Pro yeast cells were carried out as described for Fig 4b with the exception that the Rpl10 alleles were expressed in a glucose-repressible Rpl10 strain shifted to glucose for six hours. (**c**) Fluorescence microscopy of Tif6-GFP or Nmd3-GFP for the indicated yeast cells was done as described in the legend to Fig 4c. Scale bars: 5 μm. (**d**) Rpl10 WT, Rpl10 p.Arg98Ser, Rpl10 p.Arg98Cys and Rpl10 p.His123Pro yeast cells were transformed with empty vector or vector WT Nmd3. Ten-fold serial dilutions were grown.

Supplementary Table 1. Description patient set exome sequencing

	Sex	Age	WBC (x10^9/l)	immunophenotype	Karyotype	*NOTCH1* status	remission sequenced	clinical status
TLE01	M	16	455	cortical	46, XY [20]	PEST	no	dead after relapse
TLE02	M	2	108	cortical	46,XY [20]	HD + PEST	yes	dead after relapse
TLE03	M	20	120	Pre-T	46,XY [10]	HD	yes	dead after relapse
TLE04	M	5	10	cortical	46,XY [21]	wt	no	CR1
TLE05	M	13	5,4	mature	46,XY [9]	wt	no	CR1
TLE06	M	18	10	Pre-T	46,XY [8]	HD	no	dead after relapse
TLE07	M	3	23	cortical	46,XY [25]	HD	yes	CR1
TLE08	M	18	N/A	NA	46,XY [10]	HD + PEST	no	NA
TLE09	F	7	61	cortical	46,XX [7]	HD	yes	CR1
TLE10	F	32	87	mature	46, XX [10]	wt	yes	dead after relapse
TLE29	M	4	5	cortical	46,XY [7]	wt	yes	CR1
TLE31	F	5	15	cortical	46, XY, inv(3)(p11;p22) [15]	wt	yes	CR1
TLE32	M	10	7	cortical	46,XY [15]	wt	yes	N/A
TLE33	M	29	18	cortical	46,XY,+M1(=?+21),+M2,with non-systematic loss [CP5](5)	wt	yes	CR1 after allotransplant

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TLE34	F	19	1	Pre-T	54-58,XX,-9,-13,-18,-21,+2M1[M1=?der(4)t(1;4)(p31;q26)], +M2,+M3,+M4,+M5,+R,+11-15MAR[CP5] [5]; 46,XX [5]	PEST	yes	CR1 after autotransplant
TLE35	M	41	62	Pre-T	46, XY, ADD(1)(p36)[3]/46, XY[12]	wt	no	dead after relapse
TLE36	M	16	57	cortical	46,XY [19]	wt	yes	CR1
TLE37	M	37	59	mature	45,XY,add(4)(p16),del(5)(p13p15),?der(7)(p),del(9)(p12p21), add(11)(p11),del(11)(p11p14),add(14)(p13),-21 [9]; 46,XY [1]	wt	no	dead after relapse
TLE38	F	22	206	cortical	46,X,add(X)(q21),del(5)(q12q32),del(7)(q22q33), add(19)(q13)[8]	wt	yes	CR1
TLE39	M	17	405	cortical	NA	wt	yes	CR1
TLE40	M	38	13	cortical	46,XY [5]	wt	yes	CR1
TLE41	M	16	186	cortical	45,X,-Y, t(10;12)(p12;q21)[10]	PEST	yes	dead after relapse
TLE42	M	23	81	cortical	48, XY, t(3;11)(p12;p15), t(7;10)(q35;q24), t(8;10)(q21;q21), +11, +12 [5]	wt	yes	dead
TLE43	F	30	46	cortical	46,XX,add(9)(p13),t(10;14) (q23;q11),del(12)(p12)[1]; 46,XX,idic(9)(p13),t(10;14),del(12) [8]	HD	yes	dead after relapse
TLE44	F	29	13	cortical	46,X,t(X;10)(p23;q23),del(7)(q22q34)[4],del(12(p11p12)[4], del(17)(q22)[2] [CP5][5]; 46,XX [8]	HD + PEST	yes	dead after relapse
TLE45	M	22	52	cortical	46,XY [3]; 46,XY,del(1)(p21p31),ins(6;?)(q22;?),t(10;14)(q25;q11) [3]	wt	yes	CR1
TLE47	M	34	8	cortical	NA	PEST	no	dead after relapse
TLE48	M	7	28	c-T-ALL	47,XY,add(6)(q27),t(10;11)(q23;q23),+der(10) t(10;11) [7]; 46,XY [3]	wt	no	CR1
TLE50	M	12	185	Pre-T	46,XY [25]	wt	yes	CR1
TLE51	M	6	52	Pre-T	47, XY, del(6)(q21), +8 [12] / 46, XY [4]	wt	yes	dead after relapse
TLE53	M	13	350	pre-T	46, XY [12]	wt	no	dead
TLE54	F	15	8,17	Cortical	92,XXXX,DEL(6)(q14q16),del(9)(p11),t(14;20) (q11;p12) [17]; 46, XX [7]	wt	yes	CR1
TLE55	M	3	162	cortical	46,XY [12]	HD	yes	CR1

TLE56	M	7	251,5	mature	46, XY [33]	PEST	no	CR1
TLE57	F	8	123	mature	46, XX, der(19)?t(1;19)(q41;p13)[3], 46, XX [12]	wt	yes	CR1
TLE58	F	9	128,5	mature	46,XX,t(1;9)(p13;p21),add(5)(q21),?del(7)(q31q33), der(16)t(1;16)(q21;p11)[6]; 46, XX[2]	HD	no	CR1 after allotransplant
TLE59	M	7	3,8	pre-T	47,XY,del(6)(q23q26)[2],+8,del(12)(p12p13),del(13)(q13q21) [4]; 46, XY [6]	HD	no	CR1 after allotransplant
TLE60	M	3	541,2	pre-T	46, XY [20]	wt	yes	dead after relapse
TLE61	M	13	N/A	NA	46, XY [11]	wt	yes	CR1
TLE62	M	7	N/A	cortical	91, XXYY, -3, 4del(9)(p13) [8]; 46, XY, 2del(9)(p13) [1]	HD	no	CR1
TLE63	M	11	18	pre-T	46,XY,der(2).ISH(WCP2+,WCP9P+),der(5)t(5;9)(q33;q31), del(9)(q12q33),der(9)del(9)(p13p22)t(2;9)(q22;q21), der(11)t(9;11)(q?;p15),inv(14)(q11q32) [3]; 46,SL,del(1)(q21q31) [1]	wt	yes	CR1
TLE64	F	8	18	cortical	46,XX,del(7)(p12p21) [9]	wt	yes	CR1
TLE65	F	14	8	mature	45,XX,-3,der(9)t(3;9)(p12;p21) [6]; 46, XX [4]	wt	yes	CR1
TLE66	F	2	248	cortical	46,XX [10]	HD	yes	CR1
TLE67	M	14	518	Pre-T	46,XY,t(7;9)(p14;q34) [5]; 46,XY,del(6)(q16q24) [3]	HD	yes	CR1
TLE68	M	10	48	mature	46,XY, t(1;14)(p32;q11),t(6;10)(q14;q23), t(8;12)(p11;p12) [6]; 46,XY [4]	HD	yes	CR1
TLE76	F	9	105	NA	NA	HD	no	CR1
TLE78	M	19	347	mature	NA	HD	no	dead after relapse
TLE79	M	22	20	NA	46,XY [20]	wt	no	dead
TLE80	M	41	358	NA	NA	HD	no	CR1
TLE82	F	19	5	Pre-T	NA	wt	no	CR1
TLE83	M	17	173	NA	46,XY,del(6)(q21q25)[4]/46,XY[16] [20]	wt	no	dead after relapse

TLE84	M	46	10	NA	45,XY,add(1)(p13),add(6)(q?24),-8,del(11)(q23), der(12)t(12;18)(q10;q10),-18,+mar1[cp3]/46,XY[3] [6]	wt	no	dead
TLE85	M	2	208	NA	46,XY,add(5)(p13),del(6)(q21q2?5),add(7)(q?32),add(8)(q2?4), add(11)(q21),add(14)(q2?4)[6]/46,XY[4] [10]	HD	no	dead
TLE87	M	20	8	c-T-ALL	52,XY,+?X,+8,+10,+11,+13,+19[11]/46,XY[9] [20]	HD	no	dead after relapse
TLE89	F	72	34	NA	40~44,X,-X,del(3)(q21),-5,add(6)(q2?3),add(7)(p1?),-8,-9, add(12)(p13),-13,-14,add(16)(p13),i(17)(q10), +i(17)(q10),add(21)(p11),+1~6mar[cp11]/46,XX[2] [13]	wt	no	dead
TLE 90	F	10	30,6	NA	NA	HD	no	CR1
TLE91	NA	16	4	immature	NA	wt	no	CR1
TLE92	M	23	448	NA	46,XY [14]	wt	no	dead after relapse
TLE109	F	28	83,6	Pre-T/cortical	47, XX,+9,?DEL(22)(Q11),INC[2][2]; 46,XX[15]	HD	yes	CR1
TLE110	M	27	89	cortical	46,XY,t(10;14)(q24;q11),DEL(12)(p12)[4]	wt	yes	CR2
TBR01	M	35	8,5	NA	46,XY (20);	wt	yes	CR1
TBR03	M	18	33	cortical	t(1;14)(p32;q11), del(9)(p12) (3); 46,XY (13)	wt	yes	CR1
TBR05	M	32	11	Pre-T	46,XY	PEST	no	CR1
TBR06	M	16	11	cortical	NA	wt	yes	CR1
TBR08	M	19	5,2	pre-T	46,XY (4)	HD	yes	CR1
TBR09	M	45	7,2	mature	NA	wt	no	CR1 after autotransplant

Supplementary Table 2. Average alignment results over 123 samples

	Average ± St. Dev.	Range
Number of high-quality aligned bases (Gbp)	7.1 ± 2.5	3.9 – 17.2
Mean target coverage	109.12 ± 31.8	51.3 - 239
Percentage of bases covered by at least 2 reads (%)	95.7 ± 0.8	92.5 – 97.3
Percentage of bases covered by at least 10 reads (%)	91.0 ± 2.0	81.5 – 95.7
Percentage of bases covered by at least 20 reads (%)	84.9 ± 3.8	68.7 – 94.1

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Supplementary Table 3. Sequencing and mapping statistics of the 123 samples

	Sample	Average Coverage	Number of HQ aligned bases	%2x	%10x	%20x
Diagnosis-remission pairs	TLE02	115,97	6434773318	95,76	91,48	86,10
	TLE02R	105,02	7832528909	95,30	90,03	83,81
	TLE03	116,49	6552282192	95,28	91,08	86,02
	TLE03R	123,52	6977981481	96,24	91,93	86,52
	TLE07	116,27	6571887395	95,00	90,47	85,09
	TLE07R	119,27	6740263910	94,93	90,92	86,28
	TLE09	117,46	6715668652	95,83	91,78	86,71
	TLE09R	114,47	6628660943	95,87	91,15	85,15
	TLE10	130,20	7421870724	94,55	89,68	84,31
	TLE10R	115,87	6811622486	94,57	89,63	84,07
	TLE29	208,40	11166444607	97,12	94,82	92,08
	TLE29R	140,18	8756733946	96,21	93,03	89,22
	TLE31	102,92	5609763248	96,56	92,16	85,84
	TLE31R	130,73	9114214164	95,91	92,11	87,95
	TLE32	105,34	5841357239	96,50	92,09	85,99
	TLE32R	99,88	5540056431	96,44	92,13	86,07
	TLE33	108,86	5930415357	96,61	92,68	87,11
	TLE33R	77,05	6063512277	96,67	92,76	87,29
	TLE34	107,98	9257512617	92,85	84,29	76,66
	TLE34R	106,01	8155053405	95,13	89,83	83,82
	TLE36	109,54	8436956125	95,77	91,95	87,42
	TLE36R	164,90	13801288412	95,90	92,01	87,94
	TLE38	113,46	6635778977	96,40	92,17	86,77
	TLE38R	118,39	6893839625	95,80	91,41	86,13
	TLE39	98,78	5337604507	96,11	91,18	84,41
	TLE39R	119,09	6778665723	95,92	90,91	85,17
	TLE40	175,66	13870515334	96,08	93,14	90,30
	TLE40R	103,03	8471524518	92,94	84,63	76,97
	TLE41	97,87	5290970095	96,27	91,45	84,88
	TLE41R	97,65	7784769138	95,13	89,34	82,71
	TLE42	93,04	7379808751	94,65	88,23	80,94
	TLE42R	77,88	5933401140	94,72	87,84	79,58
	TLE43	96,00	4119112509	95,57	89,22	80,35
	TLE43R	115,00	7067266260	95,99	91,31	85,59
	TLE44	157,37	11262196695	97,06	94,93	92,44
	TLE44R	199,40	11140664707	97,14	95,20	92,98
	TLE45	99,60	5361441689	96,28	91,60	84,96
	TLE45R	73,60	6108833952	94,62	88,04	79,73
	TLE50	105,84	6232620442	96,52	92,20	86,58
	TLE50R	117,57	6737868380	95,84	90,38	84,22
	TLE51	204,47	11647824116	96,94	94,44	91,71
	TLE51R	103,49	8825090203	94,51	88,33	81,70

Diagnosis-remission pairs	TLE54	103,17	5592702430	96,31	92,03	86,10
	TLE54R	101,20	7747517288	94,86	88,94	82,31
	TLE55	104,84	5731912169	96,48	92,13	86,15
	TLE55R	122,28	9556978938	95,44	91,09	86,12
	TLE57	102,24	8067777512	94,67	88,62	81,98
	TLE57R	51,32	3926150993	92,50	81,46	68,74
	TLE60	88,73	6933172263	93,93	89,81	84,77
	TLE60R	92,32	7159382496	95,02	91,52	87,26
	TLE61	81,60	4519726087	95,79	89,91	82,11
	TLE61R	183,82	14423403800	95,95	92,48	89,13
	TLE63	101,73	5621508025	96,34	91,40	84,74
	TLE63R	124,74	9417945019	95,46	91,54	87,18
	TLE64	105,47	5779977325	96,30	91,68	85,52
	TLE64R	122,61	9343211056	95,77	92,36	88,57
	TLE65	53,32	4255758220	93,72	86,70	76,32
	TLE65R	126,19	7401926715	96,17	91,77	86,52
	TLE66	239,04	17226531022	97,26	95,65	94,07
	TLE66R	224,95	16590397799	97,34	95,71	94,08
	TLE67	108,78	6013449699	96,49	92,16	86,31
	TLE67R	125,59	9333634272	95,21	92,41	89,38
	TLE68	95,51	5588455253	96,12	90,74	83,61
	TLE68R	115,01	6467764161	96,47	91,86	86,20
	TLE109	84,30	6641112642	95,37	89,93	82,64
	TLE109R	124,91	9429949759	96,42	93,47	89,67
	TLE110	91,46	6705886758	95,83	91,95	86,35
	TLE110R	114,73	8288756821	96,05	92,80	88,57
	TBR01	102,01	5666167563	96,40	91,72	85,31
	TBR01R	89,52	6363460796	96,13	92,24	86,45
	TBR03	103,01	5423082617	96,40	91,63	85,04
	TBR03R	66,48	6489214656	96,09	90,17	81,05
	TBR05	109,52	6335234031	96,67	92,80	87,41
	TBR05R2	135,72	9666385539	96,29	93,00	89,01
	TBR06	81,02	5722009683	95,73	90,71	83,30
	TBR06R	92,11	6642728915	95,81	91,57	85,43
	TBR08	83,10	5910976132	95,92	91,53	84,91
	TBR08R	66,56	6026709986	96,03	90,01	80,80
Diagnosis-only	TLE01	119,25	6734469242	96,14	91,92	86,77
	TLE04	144,52	8150064536	96,08	92,88	89,06
	TLE05	116,68	6879914028	95,63	90,14	84,06
	TLE06	116,21	6722108090	95,43	90,62	84,87
	TLE08	121,48	6852485845	95,67	90,65	84,82
	TLE35	112,95	9091739373	94,64	91,48	88,26
	TLE37	96,02	5203144234	96,31	91,35	84,45
	TLE47	97,89	5264105494	96,23	91,26	84,40
	TLE48	104,75	5658759914	96,37	91,75	85,41
	TLE53	104,34	5617924241	96,44	91,91	85,66

Diagnosis-only	TLE56	105,08	5675514463	96,52	92,13	86,06
	TLE58	163,72	11224449086	97,09	94,99	92,52
	TLE59	100,32	5279422808	96,31	91,29	84,38
	TLE62	98,44	5301124302	96,15	90,92	83,98
	TLE76	118,42	8982789768	93,25	90,03	85,92
	TLE78	136,14	10393955120	96,35	93,56	90,06
	TLE79	106,37	8201070607	96,23	92,86	88,18
	TLE80	76,32	5483240222	95,66	90,89	83,52
	TLE82	83,41	5988879782	95,74	91,54	85,34
	TLE83	112,15	7956463149	96,19	93,10	88,83
	TLE84	131,19	9659821995	96,39	93,75	90,38
	TLE85	111,12	8198682650	96,14	92,51	87,65
	TLE87	74,93	5472259002	95,59	90,16	82,10
	TLE89	110,93	7893400404	95,82	92,08	87,13
	TLE90	98,52	7669801970	94,83	89,06	82,37
	TLE91	107,25	7804471198	95,83	92,00	86,91
	TLE92	71,18	5076931079	95,40	90,00	81,86
	TBR09	75,83	5620548171	95,74	90,17	81,98
Cell lines	BE13	80,02	4389579074	95,96	89,90	80,94
	HSB2	76,83	4111507226	96,09	90,23	81,25
	KARPAS45	78,83	4299191762	96,04	89,61	80,38
	SUPT1	83,03	4423428632	95,84	89,65	81,07
	ALLSIL	80,40	4268499678	95,85	89,61	80,85
	DND41	81,44	4351377003	95,88	89,86	81,38
	HPBALL	136,69	7846101056	94,80	90,85	86,41
	JURKAT	79,18	4284636749	95,95	89,91	81,07
	KE37	77,62	4104120108	95,98	89,00	79,05
	MOLT4	77,23	4260634262	95,60	88,66	79,35
	P12ICHIKAWA	77,56	4257956827	95,75	89,49	80,51
	PEER	78,57	4222938259	95,36	88,31	79,06
	SUPT13	76,15	4105548930	95,79	89,39	80,12
	TALL1	76,07	4220878568	95,81	89,34	80,16
	PF382	77,69	4142895290	95,48	88,91	79,89
	CCRFCEM	116,08	6657193739	95,69	91,56	86,36
	LOUCY	130,34	7589136310	95,45	91,57	87,11

Supplementary Table 4. Detected SNV and INDEL numbers

Supplementary Table 4A. Number of somatic SNVs and INDELs observed in 39 samples

Sample	# somatic SNVs	# somatic INDELs	Total # of somatic variations	#of protein altering somatic SNVs	#of protein altering somatic INDELs	Total # of protein altering somatic variations	
TLE02	28	7	35	6	0	6	
TLE03	35	4	39	13	1	14	
TLE07	4	27	31	0	5	5	
TLE09	5	7	12	0	1	1	
TLE10	51	17	68	14	4	18	
TLE29	24	9	33	1	0	1	
TLE31	37	2	39	4	0	4	
TLE32	9	84	93	0	9	9	
TLE33	40	7	47	17	1	18	
TLE34	66	153	66	19	61	19	*
TLE36	27	32	59	6	4	10	
TLE38	33	12	45	17	5	22	
TLE39	53	5	58	20	1	21	
TLE40	38	63	101	0	14	14	
TLE41	53	6	59	11	1	12	
TLE42	64	253	64	14	27	14	*
TLE43	250	16	266	76	5	81	
TLE44	46	25	71	12	2	14	
TLE45	37	7	44	10	2	12	
TLE50	30	9	39	13	0	13	
TLE51	40	13	53	10	4	14	
TLE54	61	5	66	13	1	14	
TLE55	35	2	37	8	0	8	
TLE57	35	316	35	13	103	13	*
TLE60	30	28	58	6	6	12	
TLE61	74	3	77	15	0	15	

* the INDEL calls from these samples are excluded from further analysis

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Supplementary Table 4A (continued). Number of somatic SNVs and INDELs observed in 39 samples

Sample	# somatic SNVs	# somatic INDELs	Total # of somatic variations	#of protein altering somatic SNVs	#of protein altering somatic INDELs	Total # of protein altering somatic variations
TLE63	44	5	49	4	3	7
TLE64	44	2	46	11	0	11
TLE65	35	19	54	6	1	7
TLE66	34	14	48	2	3	5
TLE67	47	3	50	7	0	7
TLE68	23	8	31	3	1	4
TLE109	69	14	83	20	4	24
TLE110	0	7	7	0	0	0
TBR01	63	4	67	26	2	28
TBR03	52	5	57	17	0	17
TBR05	86	11	97	37	3	40
TBR06	45	30	75	11	7	18
TBR08	63	14	77	20	3	23

Supplementary Table 4B. Number of SNVs and INDELs observed in 28 diagnosis-only samples

Sample	#of SNVs	#of INDELs	Total # of variation	#of protein altering SNVs	#of protein altering INDELs	Total # of protein altering variations
TLE01	3683	58	3741	274	7	281
TLE04	3433	44	3477	179	6	185
TLE05	3959	45	4004	193	8	201
TLE06	3602	66	3668	201	12	213
TLE08	3791	42	3833	198	4	202
TLE35	12118	132	12250	280	11	291
TLE37	5704	32	5736	256	6	262
TLE47	5983	40	6023	263	7	270
TLE48	9229	50	9279	298	5	303
TLE53	6040	40	6080	271	2	273

Supplementary Table 4B (continued). Number of SNVs and INDELs observed in 28 diagnosis-only samples

Sample	#of SNVs	#of INDELs	Total # of variation	#of protein altering SNVs	#of protein altering INDELs	Total # of protein altering variations
TLE56	6306	49	6355	303	6	309
TLE58	14013	114	14127	401	18	419
TLE59	8323	33	8356	333	8	341
TLE62	5326	47	5373	232	6	238
TLE76	16973	64	17037	262	5	267
TLE78	14446	124	14570	251	12	263
TLE79	9487	108	9595	194	16	210
TLE80	5052	80	5132	211	8	219
TLE82	5922	86	6008	221	8	229
TLE83	6097	117	6214	212	15	227
TLE84	8393	123	8516	236	18	254
TLE85	8717	113	8830	219	11	230
TLE87	4769	77	4846	188	8	196
TLE89	8113	110	8223	236	15	251
TLE90	25753	494	26247	996	117	1113
TLE91	8047	102	8149	217	10	227
TLE92	5400	90	5490	212	10	222
TBR09	5489	100	5589	307	8	315

Supplementary Table 4C. Number of SNVs and INDELs observed in 17 T-ALL cell lines

Sample	#of SNVs	#of INDELs	Total # of variation	#of protein altering SNVs	#of protein altering INDELs	Total # of protein altering variations
BE13	7127	58	7185	553	17	570
HSB2	10400	281	10681	1522	162	1684
KARPAS45	23897	110	24007	6094	43	6137
SUPT1	18056	371	18427	3481	211	3692
ALLSIL	6099	52	6151	424	11	435

Supplementary Table 4C (continued). Number of SNVs and INDELs observed in 17 T-ALL cell lines

Sample	#of SNVs	#of INDELs	Total # of variation	#of protein altering SNVs	#of protein altering INDELs	Total # of protein altering variations
DND41	13220	230	13450	2295	122	2417
HPBALL	4772	49	4821	519	13	532
JURKAT	21269	517	21786	4627	309	4936
KE37	5863	50	5913	296	8	304
MOLT4	9195	123	9318	1190	47	1237
12ICHIKAW	5475	54	5529	405	11	416
PEER	6342	38	6380	420	7	427
SUPT13	4932	50	4982	268	11	279
TALL1	6343	38	6381	347	12	359
PF382	9640	63	9703	1705	18	1723
CCRFCEM	12838	544	13382	2735	234	2969
LOUCY	4185	63	4248	292	9	301

Supplementary Table 6. 20 significantly mutated genes

Gene	SNVs	Indels	P-value_FCPT	P-value_LRT	P-value_CT	FDR_FCPT	FDR_LRT	FDR_CT
PHF6	6	3	0	0	0	0	0	0
FBXW7	5	0	2,57E-07	3,96E-12	6,24E-12	0,002407843	3,72E-08	5,85E-08
WT1	1	2	0,00073945	9,05E-08	1,13E-07	1	0,000566306	0,00036233
JAK3	3	1	0,000233854	2,28E-07	7,40E-08	1	0,001071297	0,00036233
DNM2	3	1	0,000302891	3,18E-07	1,01E-07	1	0,001101975	0,00036233
PTEN	2	1	0,000693405	7,65E-07	1,16E-07	1	0,001794413	0,00036233
CNOT3	3	1	0,000638879	9,11E-07	2,11E-07	1	0,001899338	0,000554231
NOTCH1	4	0	0,000401731	3,15E-06	2,36E-07	1	0,004554007	0,000554231
BCL11B	3	0	0,001866336	3,52E-07	5,94E-07	1	0,001101975	0,001134205
TET1	2	2	0,000967204	1,59E-06	6,04E-07	1	0,002987512	0,001134205
KDM6A	1	2	0,002808411	6,23E-07	1,19E-06	1	0,001670034	0,002029813
PPP1R15A *	0	2	0,034115052	2,13E-06	2,12E-05	1	0,003641867	0,03323959
ODZ2	3	0	0,017372204	1,10E-05	2,36E-05	1	0,013784452	0,034006298
TLR1	1	1	0,039179024	3,38E-05	2,63E-05	1	0,037312701	0,035324464
RPL10	2	0	0,040560182	2,94E-06	3,99E-05	1	0,004554007	0,049932595
ST8SIA2 *	2	0	0,070211284	8,37E-06	1,06E-04	1	0,011218891	0,124716068
RPL5	2	0	0,072064094	1,03E-04	1,32E-04	1	0,087716644	0,145751954
FAM55A *	1	0	0,250917229	1,00E-04	1,51E-04	1	0,087716644	0,157793458
MAGEC3	2	0	0,097310584	1,60E-05	0,000164696	1	0,018784018	0,162719158
MTMR8 *	2	0	0,100203907	0,000190863	0,000176446	1	0,143315041	0,165612115

* the gene is not recurrently mutated across different samples (the gene has either one mutation, or several mutations in the same sample).

Supplementary Table 8. Patient characteristics *CNOT3* (NM_014516.3) mutated cases

patient	cohort	nucleotide change	amino acid change	Somatic	sex	age (y)	WBC (x10^9/l)	blast %	immune phenotype	karyotype	CDKN2A*
TLE39	exome	c.170G>A	p.Arg57Gln	yes	M	17	405	93	cortical	NA	NA
TLE41	exome	c.169C>T	p.Arg57Trp	yes	M	16	186	97	cortical	45,X,-Y, t(10;12)(p12;q21)[10]	NA
TLE43	exome	c.13_14insG	p.Arg5Fs	yes	F	30	46	93	cortical	46,XX,add(9)(p13),t(10;14) (q23;q11),del(12)(p12)[1]; 46,XX,idic(9)(p13),t(10;14),del(12) [8]	-/+
TLE45	exome	c.169C>T	p.Arg57Trp	yes	M	22	52	59	cortical	46,XY [3]; 46,XY,del(1)(p21p31),ins(6;?)(q22;?),t(10;14)(q25;q11) [3]	NA
TL21	confirmation	c.477delC	p.Asp159Fs	NA	M	31	131	99	cortical	NA	+/-
TL41	confirmation	c.170G>A	p.Arg57Gln	yes	M	4	260	93	cortical	46,XY[8]/ failure	-/-
TL45	confirmation	c.169C>T	p.Arg57Trp	yes	F	43	159	100	cortical	46,XX,inv(7)(p15q34)[9]	-/-
ALEK127	confirmation	c.170G>A	p.Arg57Gln	NA	M	42	NA	NA	NA	NA	NA

* no deletion on 4K CGH-array but does not excude very focal deletions or mutations

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Supplementary Table 8 (continued). Patient characteristics *CNOT3* (NM_014516.3) mutated cases

patient	NOTCH1	transcription factors	other	patient outcome	survival (months)
TLE39	wt	TLX1	*IL7R* mutant	CR	66+
TLE41	mutant	MLL	*IL7R* mutant	dead after relapse	18
TLE43	mutant	TLX1	*PTPN2* deletion, *PHF6* mutant	dead after relapse	30
TLE45	wt	TLX1	*PTEN* mutant	CR	75+
TL21	NA	TAL-RB	deletion *LMO2*	NA	NA
TL41	mutant	CALM-AF10		CR	NA
TL45	mutant	HOXA	*PTPN2* deletion	CR	NA
ALEK127	NA	NA		NA	NA

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Supplementary Table 9. Patient characteristics RPL mutated cases

patient	cohort	gene	nucleotide change	amino acid change	Somatic	sex	age (y)	WBC (x10^9/l)	blast %	karyotype
TLE07	exome	*RPL10* (NM_006013.3)	c.292C>A	p.Arg98Ser	yes	M	3	23	55	46,XY [25]
TLE08	exome	*RPL10* (NM_006013.3)	c.292C>A	p.Arg98Ser	yes	M	18	NA	NA	46,XY [10]
TLE54	exome	*RPL10* (NM_006013.3)	c.292C>A	p.Arg98Ser	yes	F	15	8	100	92,XXXX,DEL(6)(q14q16),del(9)(p11), t(14;20) (q11;p12) [17]; 46, XX [7]
TLE61	exome	*RPL10* (NM_006013.3)	c.292C>A	p.Arg98Ser	yes	M	13	NA	89	46, XY [11]
TLE62	exome	*RPL10* (NM_006013.3)	c.292C>A	p.Arg98Ser	yes	M	7	NA	71	91, XXYY, -3, 4del(9)(p13) [8]; 46, XY, 2del(9)(p13) [1]
TLE90	exome	*RPL10* (NM_006013.3)	c.368A>C	p.Gln123Pro	NA	F	10	31	NA	NA
TL29	confirmation	*RPL10* (NM_006013.3)	c.292C>A	p.Arg98Ser	NA	F	6	92	84	46,XX[20]
TL31	confirmation	*RPL10* (NM_006013.3)	c.292C>A	p.Arg98Ser	yes	M	8	28	93	46,XY,del(9)(p11)[20]/46,XY[8]
TL74	confirmation	*RPL10* (NM_006013.3)	c.292C>T	p.Arg98Cys	yes	M	8	27	78	46,XY[30]
ALEK45	confirmation	*RPL10* (NM_006013.3)	c.292C>A	p.Arg98Ser	NA	M	9	NA	NA	NA
ALEK84	confirmation	*RPL10* (NM_006013.3)	c.292C>A	p.Arg98Ser	NA	F	3	NA	NA	NA
TLE39	exome	*RPL5* (NM_000969.3)	c.535C>T	p.Arg179*	yes	M	17	405	93	NA
TLE43	exome	*RPL5* (NM_000969.3)	c.188A>G	p.Gln63Arg	yes	F	30	46	93	46,XX,add(9)(p13),t(10;14)(q23;q11), del(12)(p12)[1]; 46,XX,idic(9)(p13),t(10;14), del(12) [8]
TL61	confirmation	*RPL5* (NM_000969.3)	c.175_176delGA	p.Arg58Fs	NA	M	10	157	92	+19, 9p+
TL58	confirmation	*RPL5* (NM_000969.3)	c.634delAinsGC	p.Met212Fs	yes	F	4	NA	NA	47,XX,del(9)(p12),+9p+

Supplementary Table 9 (continued). Patient characteristics RPL mutated cases

patient	immune phenotype	*CDKN2A**	*NOTCH1*	transcription factors**	other	patient outcome	survival (months)
TLE07	cortical	NA	mutant	-		CR	193+
TLE08	NA	-/-	mutant	-		NA	NA
TLE54	cortical	NA	wt	NA		CR	193+
TLE61	NA	+/+	wt	-		CR	67+
TLE62	cortical	-/-	mutant	-		CR	63+
TLE90	NA	NA	mutant	NKX2.1		CR	39+
TL29	cortical	-/-	mutant	SIL-TAL1	*MYB* duplication	NA	NA
TL31	cortical	-/-	NA	TAL-RB	del(11p)/*LMO2*, *PHF6* deletion	CR	NA
TL74	cortical	-/-	mutant	TLX3		CR, relapse, patient died	NA
ALEK45	NA	NA	NA	NA		NA	NA
ALEK84	NA	NA	NA	NA		NA	NA
TLE39	mature	NA	wt	TLX1	*IL7R* mutant	CR	66+
TLE43	cortical	-/+	mutant	TLX1	*PTPN2* deletion, *PHF6* mutant	CR, relapse, patient died	30
TL61	mature	-/-	mutant	TLX3		NA	NA
TL58	cortical	-/-	NA	TLX1		NA	NA

* no deletion on 4K CGH-array but does not excude very focal deletions or mutations
** the sign '-' indicates negative for TLX1, TLX3 and SIL-TAL1

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Supplementary Table 10. Association between candidate driver mutations and clinicobiological features

AGE		# adult (≥16 y) patients	# pediatric (≤15) patients	P value 2-tailed Fisher's test
NOTCH1	mutant	15	14	p=0.6300
n=67	wild type	22	16	
FBXW7	mutant	7	1	p=0.0657
n=67	wild type	30	29	
WT1	mutant	2	5	p=0.4334
n=67	wild type	35	25	
BCL11B	mutant	4	1	p=0.3700
n=67	wild type	33	29	
CNOT3	mutant	7	1	**p=0.0107**
n=211	wild type	82	121	
RPL10	mutant	1	10	**p=0.0268**
n=211	wild type	88	112	
RPL5	mutant	2	2	p=1.0000
n=211	wild type	87	120	
JAK3	mutant	4	3	p=1.0000
n=67	wild type	33	27	
PTEN	mutant	3	1	p=0.6220
n=67	wild type	34	29	
DNM2	mutant	1	3	p=0.3179
n=67	wild type	36	27	

Supplementary Table 10 (continued). Association between candidate driver mutations and clinicobiological features

AGE		# adult (≥16 y) patients	# pediatric (≤15) patients	P value 2-tailed Fisher's test
ODZ2	mutant	1	1	p=1.0000
n=67	wild type	36	29	
PHF6	mutant	11	1	**p=0.0083**
n=67	wild type	26	29	
TET1	mutant	3	1	p=0.6220
n=67	wild type	34	29	
KDM6A	mutant	3	0	p=0.2469
n=67	wild type	34	30	
MAGEC3	mutant	2	0	p=0.4980
n=67	wild type	35	30	

***NOTCH1* status**		# NOTCH1 wt patients	# NOTCH1 mut patients	P value 2-tailed Fisher's test
FBXW7	mutant	5	3	p=1.0000
n=67	wild type	33	26	
WT1	mutant	4	3	p=1.0000
n=67	wild type	34	26	
BCL11B	mutant	0	5	**p=0.0123**
n=67	wild type	38	24	
CNOT3	mutant	2	6	p=0.1369
n=84	wild type	43	33	

Supplementary Table 10 (continued). Association between candidate driver mutations and clinicobiological features

***NOTCH1* status**		# NOTCH1 wt patients	# NOTCH1 mut patients	P value 2-tailed Fisher's test
RPL10	mutant	3	6	P=0.2918
n=84	wild type	42	33	
RPL5	mutant	1	2	p=0.5948
n=84	wild type	44	37	
JAK3	mutant	5	2	p=0.6899
n=67	wild type	33	27	
PTEN	mutant	4	0	p=0.1273
n=67	wild type	34	29	
DNM2	mutant	2	2	p=1.0000
n=67	wild type	36	27	
ODZ2	mutant	0	2	p=0.1836
n=67	wild type	38	27	
PHF6	mutant	4	8	p=0.1078
n=67	wild type	34	21	
TET1	mutant	2	2	p=1.0000
n=67	wild type	36	27	
KDM6A	mutant	1	2	p=0.5744
n=67	wild type	37	27	
MAGEC3	mutant	2	0	p=0.5016
n=67	wild type	36	29	

Supplementary Table 11. *RPL10*, *RPL5* and *CNOT3* PCR and sequencing primers and siRNA sequence

Amplicon name	Target gene	Amplicon size (bp)	Forward primer	Reverse primer	Comment
*CNOT3*_Ex2-3	*CNOT3* (NM_014516.3)	392	tttaccagccagggaatacg	ctggtcaacacccagaggtc	PCR + Sequencing of gDNA
*CNOT3*_Ex4	*CNOT3* (NM_014516.3)	233	ggtcctcgagtccctagcat	gcagtccactctcccagttc	PCR + Sequencing of gDNA
*CNOT3*_Ex5	*CNOT3* (NM_014516.3)	248	gaactgggagagtggactgc	gtgaccttcccacctctctg	PCR + Sequencing of gDNA
*CNOT3*_Ex6-7	*CNOT3* (NM_014516.3)	489	gtctgctggcccttagtcag	ccaactcccaggagcataaa	PCR + Sequencing of gDNA
*CNOT3*_Ex8-9	*CNOT3* (NM_014516.3)	594	actgaggacaggttctgtgg	cagatttgtctcctcgagtcc	PCR + Sequencing of gDNA
*CNOT3*_Ex10	*CNOT3* (NM_014516.3)	199	cattcagagattggcggttc	ctcaagatgcctttgggaag	PCR + Sequencing of gDNA
*CNOT3*_Ex11-12	*CNOT3* (NM_014516.3)	739	ggacaaagatggagcctgag	cgcctctctgtttcaaaagg	PCR + Sequencing of gDNA
*CNOT3*_Ex13	*CNOT3* (NM_014516.3)	365	tgtgcagtctcccctctctc	gcagctagagacctggagga	PCR + Sequencing of gDNA
*CNOT3*_Ex14-15	*CNOT3* (NM_014516.3)	526	cctgtgtcaggctgcactt	actgcctcctccgtaagact	PCR + Sequencing of gDNA
*CNOT3*_Ex16	*CNOT3* (NM_014516.3)	344	tgtctgagcacccttttgat	cccaggagtgggaataggg	PCR + Sequencing of gDNA
*CNOT3*_Ex17	*CNOT3* (NM_014516.3)	298	tgatgtcctgccccattc	gaggcaagggagcagagg	PCR + Sequencing of gDNA
*CNOT3*_Ex18	*CNOT3* (NM_014516.3)	292	tgacacatccacagccctaa	cctccctccagtcttccag	PCR + Sequencing of gDNA
*RPL10*_Ex2	*RPL10* (NM_006013.3)	189	ttgctggttctcacacctttt	attgttttcagcggccatag	PCR + Sequencing of gDNA
*RPL10*_Ex3-4	*RPL10* (NM_006013.3)	290	aaagtgcctgttgggcttt	agtgtatgtgggtggggttg	PCR + Sequencing of gDNA
*RPL10*_Ex5	*RPL10* (NM_006013.3)	205	actcagccaacacagttccc	cagaccaagctcacctgtca	PCR + Sequencing of gDNA
*RPL10*_Ex6-7	*RPL10* (NM_006013.3)	589	agtgtacgcagcctgttggt	ccttccccgtcaagaatgta	PCR + Sequencing of gDNA
*RPL5*_Ex1	*RPL5* (NM_000969.3)	196	cttttcccacccccctagcgcc	gctagcaatctaacgccatcc	PCR + Sequencing of gDNA
*RPL5*_Ex2-3	*RPL5* (NM_000969.3)	500	gaccctagttgcttgtgaaacc	cacaccatgtgctttgcttc	PCR + Sequencing of gDNA
*RPL5*_Ex4	*RPL5* (NM_000969.3)	300	catctgtgtccatcaatgttttt	tgcagaaaactctccaagca	PCR + Sequencing of gDNA
*RPL5*_Ex5	*RPL5* (NM_000969.3)	384	ttccagatgtcagtggtcctt	tcggttatctccacagtcca	PCR + Sequencing of gDNA
*RPL5*_Ex6	*RPL5* (NM_000969.3)	389	agttggtcctttggttgcat	atgttacctgccccccaaaac	PCR + Sequencing of gDNA
*RPL5*_Ex7	*RPL5* (NM_000969.3)	296	tgagaatctggcttagaaggaca	tcacgcagagctagtgatcg	PCR + Sequencing of gDNA
*RPL5*_Ex8	*RPL5* (NM_000969.3)	289	ccttctgattgcaaagtcttaaa	aacacagaaatagttgctgttcat	PCR + Sequencing of gDNA
*CNOT3*_Arg57Gln/Trp	*CNOT3* (NM_014516.3)	184	gatatttggcagaagctcca	ttggttttggtctctcgttc	PCR + Sequencing of cDNA
*RPL10*_Arg98S	*RPL10* (NM_006013.3)	182	cccgaatttgtgccaataag	tcacatgctccttgttctgc	PCR + Sequencing of cDNA
*RPL10*_Gln123Pro	*RPL10* (NM_006013.3)	210	cacccctccacgtcatc	gtgaagccccacttctttga	PCR + Sequencing of cDNA

siRNA name	catalog number	company	sequence
mouse Rpl10	MMC.RNAI.N052835.12.2	IDT	ccaacaaauacaugguaaagagutg