Contribution of copy number to improve risk stratification of adult T-cell acute lymphoblastic leukemia patients enrolled in measurable residual disease-oriented trials

Authors

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Table S1. Prognostic impact of genetic alterations and associations assessed in the adult T-ALL cohort

Alteration/ Genetic Association	Frequency of alteration		Time point OS prob. (years)	OS (CI95%)		p value
	Patients with alteration (%)	Patients without alteration (%)		Patients with alteration	Patients without alteration	
CDKN2A/B (CNV)	67/107 (62.6)	40/107 (37.4)	5	40 (27-53)	31 (14-50)	0.50
PHF6 (SNV & CNV)	28/107 (26.2)	81/107 (75.7)	5	47 (25-66)	36 (24-48)	0.99
FBXW7 (SNV & CNV)	23/108 (21.3)	85/108 (78.7)	5	51 (25-72)	34 (22-46)	0.13
PTEN (SNV & CNV)	22/109 (20.2)	87/109 (79.8)	5	30 (9-55)	38 (26-50)	0.85
PTEN (SNV)	13/116 (11.2)	103/116 (88.9)	5	27(5-58)	38 (27-49)	0.92
PTEN (CNV)	12/107 (11.2)	95/107 (88.8)	5	46 (17-71)	36 (25-48)	0.97
BCL11B (SNV & CNV)	18/107 (16.8)	89/107 (83.2)	5	35 (12-60)	38 (26-50)	0.49
del(6q) (CNV)	16/107 (15.0)	91/107 (85.0)	5	46 (21-69)	36 (24-47)	0.73
CDKN1B (SNV & CNV)	14/107 (13.1)	93/107 (86.9)	5	44 (16-69)	36 (25-48)	0.56
RPL22 (CNV)	14/107 (13.1)	93/107 (86.9)	4	17 (1-50)	42 (31-53)	0.17
CTCF (SNV & CNV)	13/107 (12.1)	94/107 (87.9)	5	35 (9-63)	38 (26-49)	0.85
RUNX1 (SNV & CNV)	11/107 (10.3)	96/107 (89.7)	5	49 (16-75)	36 (25-47)	0.72
RPL5 (SNV & CNV)	10/108 (9.3)	98/108 (90.7)	5	37 (6-69)	38 (26-49)	0.92
RB1 (CNV)	10/107 (9.3)	97/107 (90.7)	5	40 (10-70)	37 (26-49)	0.41
MYB (CNV)	10/107 (9.3)	97/107 (90.7)	5	39 (7-71)	37 (26-48)	0.63
PTPN2 (CNV)	8/107 (7.5)	99/107 (92.5)	5	73 (28-93)	34 (23-45)	0.19
ELF1 (CNV)	8/107 (7.5)	99/107 (92.5)	2	50 (15-78)	50 (39-60)	0.62
STIL-TAL1 (CNV)	7/107 (6.5)	100/107 (93.5)	5	54 (13-83)	36 (25-47)	0.41
WT1 (SNV & CNV)	7/107 (6.5)	100/107 (93.5)	5	51 (12-81)	36 (25-47)	0.37
LEF1 (SNV & CNV)	6/107 (5.6)	101/107 (94.4)	5	44 (7-79)	37 (26-48)	0.89
CREBBP (SNV & CNV)	6/107 (5.6)	101/107 (94.4)	4	17 (1-52)	42 (31-52)	0.15
Trisomy 10 (CNV)	6/107 (5.6)	101/107 (94.4)	5	67 (20-90)	35 (24-46)	0.43
del(19p13.2) (CNV)	5/107 (4.7)	102/107 (95.3)	3	30 (1-72)	45 (35-55)	0.88
del(19p13.3) (CNV)	5/107 (4.7)	102/107 (95.3)	5	33 (1-77)	37 (26-48)	0.31
dup(5q) (CNV)	5/107 (4.7)	102/107 (95.3)	3	60 (13-88)	44 (33-54)	0.85
NUP214-ABL1 (CNV)	5/107 (4.7)	102/107 (95.3)	5	40 (5-75)	38 (27-49)	0.80
Gain of X (CNV)	5/107 (4.7)	102/107 (95.3)	5	27 (1-69)	38 (27-49)	0.55
Trisomy 19 (CNV)	5/107 (4.7)	102/107 (95.3)	5	60 (13-88)	36 (26-47)	0.70
RB1* & *BCL11B	7/107 (6.5)	100/107 (93.5)	5	34 (0-72)	38 (27-49)	0.56

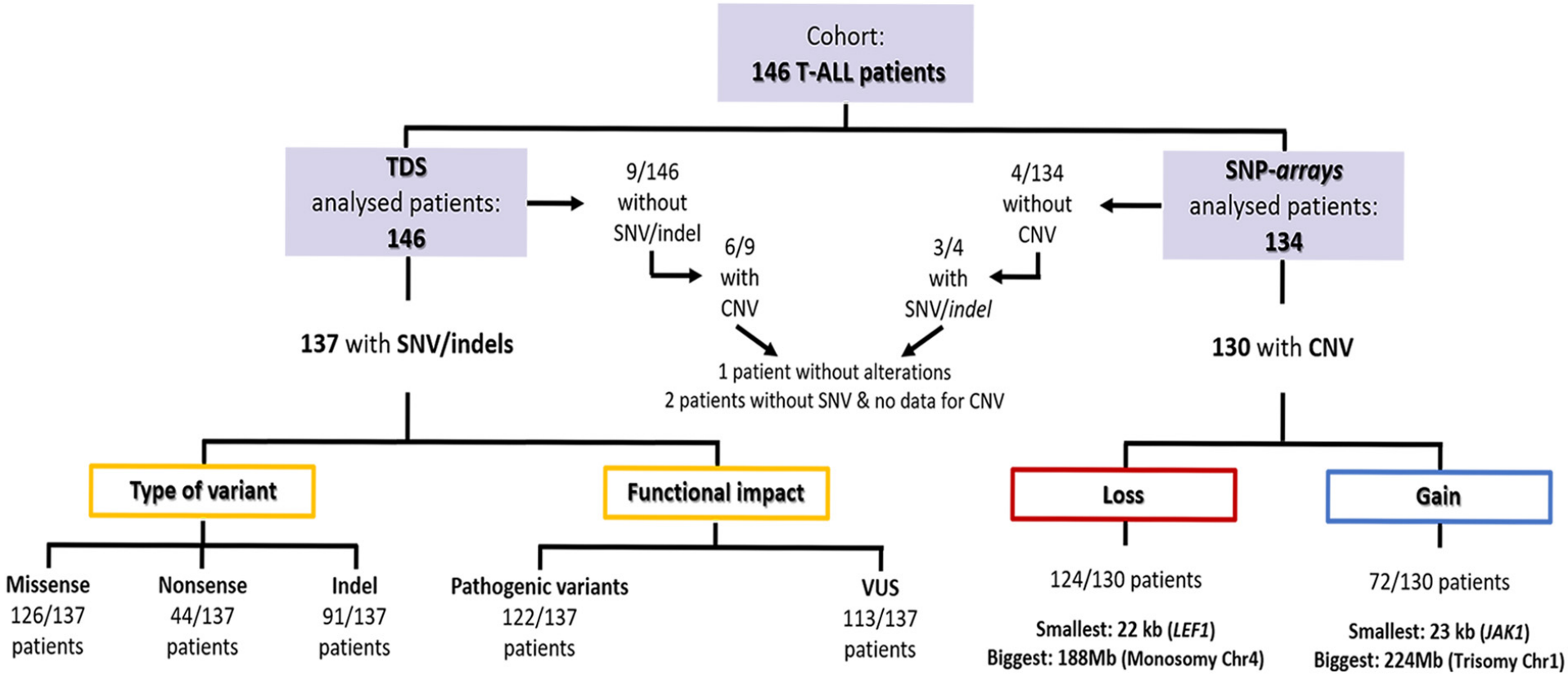
RB1* & *CDKN2A/B	10/107 (9.3)	97/107 (90.7)	5	40 (10-70)	37 (26-49)	0.41
RB1* & *NOTCH1	10/107 (9.3)	97/107 (90.7)	5	40 (10-70)	37 (26-49)	0.41
BCL11B* & *NOTCH1	18/107 (16.8)	89/107 (83.2)	5	35 (12-60)	38 (26-50)	0.49
BCL11B* & *CDKN2A/B	17/107 (15.9)	90/107 (84.1)	5	30 (17-43)	40 (28-52)	0.70
JAK3* & *JAK1	8/107 (7.5)	99/107 (92.6)	5	37 (17-57)	38 (32-44)	0.80
JAK3* & *PHF6	9/107 (8.4)	98/107 (91.6)	5	26 (10-42)	38 (32-44)	0.26
ETP-ALL *& N/KRAS*	6/108 (5.6)	102/108 (94.4)	5	33 (13-53)	40 (34-46)	0.45
Cortical *& RB1*	9/102 (9.7)	93/102 (91.2)	5	47 (28-66)	40 (34-46)	0.42
Cortical *& CDKN1B*	12/102 (11.8)	90/102 (88)	5	52 (36-68)	38 (32-44)	0.3

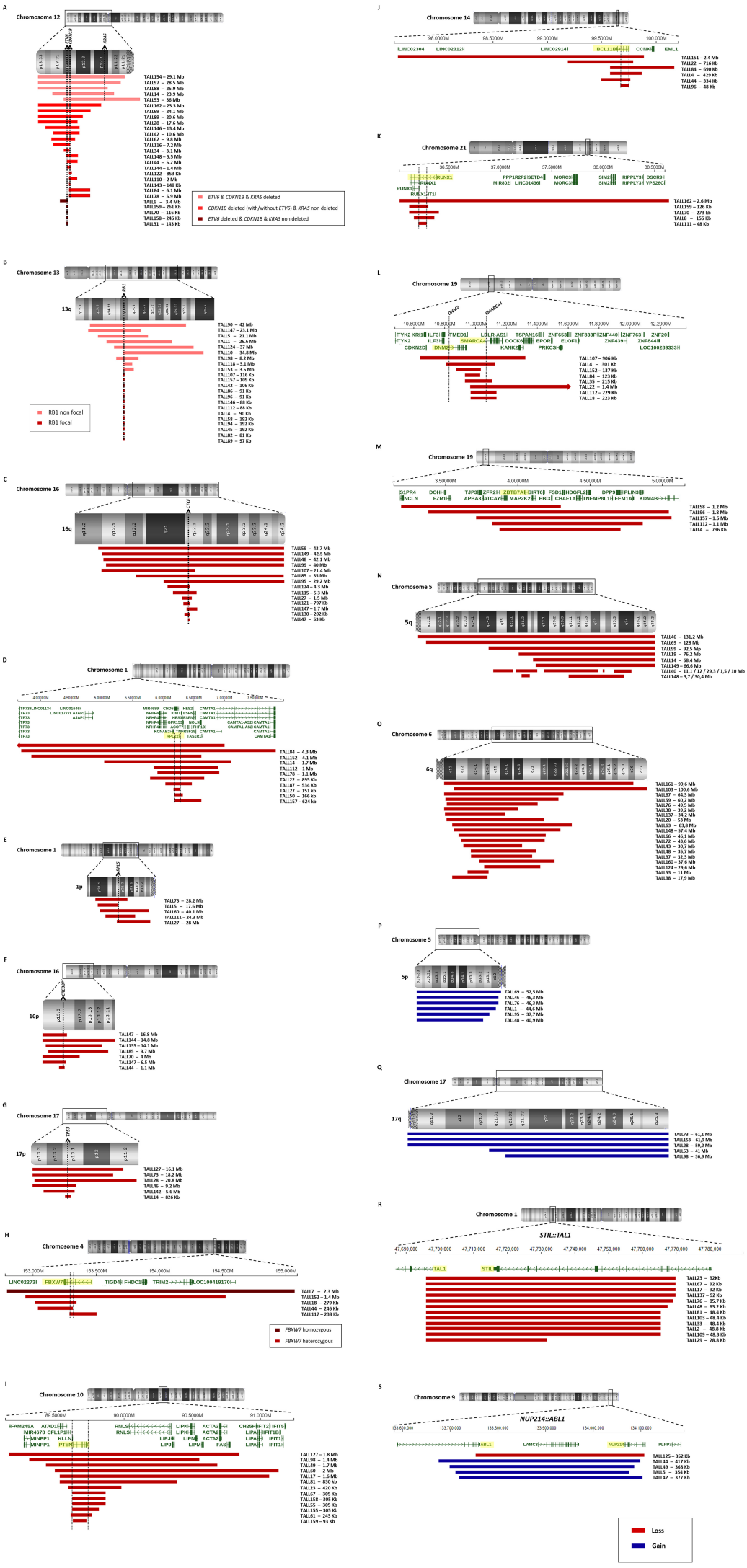
Results for alterations and genetic associations affecting ≥ 5 are shown. Results expressed as median of OS; SNV: single nucleotide variant; CNV: copy number variation. OS: overall survival; CI: confidence interval.

SUPPLEMENTARY FIGURE LEGEND

Figure S1. Genetic study flow-Chart. Distribution of patients included in the study cohort according to the alterations detected by TDS and SNP-arrays. SNV functional impact classification was defined according to previously reported criteria[1]. TDS: Target Deep Sequencing; SNP: Single Nucleotide Polymorphism; SNV: Single Nucleotide Variant; CNV: Copy Number Variation.

Figure S2. CNV and subgroups: Size and positions of the different alterations are shown for the different groups. (A) del(12p): each subgroup defined according to the affected deleted genes are represented in different colours. Position of deleted T-ALL driver genes is indicated by a dash line with an arrow. (B) del(13p): each subgroup defined according to the deleted genes are represented in different colours. Position of *RB1* is indicated by a dash line with an arrow. (C) del(16q): position of *CTCF* is indicated by a dash line with an arrow. (D) del(1)(p32.3;p36.33): position of *RPL22* is delimited by lines and highlighted in yellow. (E) del(1)(p11.2;p31.1): position of *RPL5* is indicated by a dash line with an arrow. (F) del(16p): position of *CREBBP* is indicated by a dash line with an arrow. (G) del(17p): position of *TP53* is indicated by a dash line with an arrow. (H) del(4)(q31.3): position of *FBXW7* is delimited by lines and highlighted in yellow. (I) del(10)(q23): position of *PTEN* is delimited by lines and highlighted in yellow. (J) del(14)(q32.2): position of *BLC11B* is delimited by lines and highlighted in yellow. (K) del(21)(q22.12): position of *RUNX1* is delimited by lines and highlighted in yellow. (L) del(19)(p13.2): position of *DNM2* and *SMARCA4* are indicated by a line and the genes are highlighted in yellow. (M) del(19)(p13.3): the name of the gene is highlighted in yellow. (N) del(5q). (O) del(6q). (P) dup(5p). (Q) dup(17q). (R) *STIL::TAL1* gene fusion. (S) *NUP214::ABL1* gene fusion. Losses are represented in red and gains in blue. CNVs and immunophenotype correlations found were: i) del(9p) affecting *CDKN2A/B* genes, del(12p) involving *CDKN1B* with or without *ETV6* deletions (Figure S1A), but not *KRAS,* and del(13q) restricted to *RB1* gene (Figure S1B), were associated with the cortical immunophenotype (OR=4.5, p=0.0002; OR= 7.6, p=0.0006; OR=7.3, p=0.002, respectively); ii) del(16q) involving *CTCF* (Figure S1C), was associated with a mature immunophenotype (OR=3.9; p=0.03).


Cohort:
146 T-ALL patients
TDS
analysed patients:
146
9/146
without
SNV/indel
6/9
with
CNV
4/134
without
CNV
3/4
with
SNV/indel
SNP-arrays
analysed patients:
134
137 with SNV/indels
1 patient without alterations
2 patients without SNV & no data for CNV
130 with CNV
Type of variant
Functional impact
Loss
Gain
Missense
126/137
patients
Nonsense
44/137
patients
Indel
91/137
patients
Pathogenic variants
122/137
patients
VUS
113/137
patients
124/130 patients
Smallest: 22 kb (LEF1)
Biggest: 188Mb (Monosomy Chr4)
72/130 patients
Smallest: 23 kb (JAK1)
Biggest: 224Mb (Trisomy Chr1)


A
Chromosome 12
ETV6
KRAS
TALL154 – 29,1 Mb
TALL97 – 28,5 Mb
TALL88 – 25,9 Mb
TALL114 – 23,9 Mb
TALL53 – 36 Mb
TALL162 – 23,3 Mb
TALL69 – 24,1 Mb
TALL89 – 20,6 Mb
TALL28 – 17,6 Mb
TALL146 – 13,4 Mb
TALL62 – 10,6 Mb
TALL62 – 9,8 Mb
TALL116 – 7,2 Mb
TALL34 – 3,1 Mb
TALL148 – 5,5 Mb
TALL64 – 5,2 Mb
TALL144 – 1,4 Mb
TALL122 – 853 Kb
TALL110 – 2 Mb
TALL143 – 168 Kb
TALL84 – 6,1 Mb
TALL78 – 5,9 Mb
TALL6 – 3,4 Mb
TALL159 – 261 Kb
TALL70 – 116 Kb
TALL158 – 245 Kb
TALL31 – 143 Kb
ETV6 & CDKN1B & KRAS deleted
CDKN1B deleted (with/without ETV6) & KRAS non deleted
ETV6 deleted & CDKN1B & KRAS non deleted
B
Chromosome 13
RB1
13q
TALL90 – 42 Mb
TALL147 – 23,1 Mb
TALL5 – 21,1 Mb
TALL1 – 26,6 Mb
TALL124 – 37 Mb
TALL10 – 34,8 Mb
TALL98 – 8,2 Mb
TALL118 – 3,1 Mb
TALL53 – 3,5 Mb
TALL107 – 116 Kb
TALL157 – 109 Kb
TALL42 – 106 Kb
TALL86 – 91 Kb
TALL96 – 91 Kb
TALL146 – 88 Kb
TALL112 – 88 Kb
TALL4 – 90 Kb
TALL58 – 192 Kb
TALL94 – 192 Kb
TALL45 – 192 Kb
TALL82 – 81 Kb
TALL89 – 97 Kb
RB1 non focal
RB1 focal
C
Chromosome 16
CTCF
16q
TALL59 – 43,7 Mb
TALL149 – 42,5 Mb
TALL48 – 42,1 Mb
TALL99 – 40 Mb
TALL107 – 21,4 Mb
TALL85 – 35 Mb
TALL95 – 29,2 Mb
TALL126 – 4,9 Mb
TALL115 – 5,3 Mb
TALL27 – 1,5 Mb
TALL121 – 797 Kb
TALL147 – 1,7 Mb
TALL130 – 202 Kb
TALL47 – 53 Kb
D
Chromosome 1
TALL84 – 4,3 Mb
TALL152 – 4,1 Mb
TALL14 – 1,7 Mb
TALL112 – 1 Mb
TALL78 – 1,1 Mb
TALL22 – 895 Kb
TALL87 – 534 Kb
TALL27 – 153 kb
TALL50 – 166 kb
TALL157 – 624 kb
E
Chromosome 1
PAX7
1p
TALL73 – 28,2 Mb
TALL5 – 17,6 Mb
TALL60 – 40,1 Mb
TALL111 – 24,3 Mb
TALL27 – 28 Mb
F
Chromosome 16
CREBBP
16p
TALL47 – 16,8 Mb
TALL144 – 14,8 Mb
TALL135 – 14,1 Mb
TALL85 – 9,7 Mb
TALL70 – 4 Mb
TALL147 – 6,5 Mb
TALL44 – 1,1 Mb
G
Chromosome 17
TP53
17p
TALL127 – 16,1 Mb
TALL73 – 18,2 Mb
TALL28 – 20,8 Mb
TALL46 – 9,2 Mb
TALL142 – 5,6 Mb
TALL14 – 826 Kb
H
Chromosome 4
FBXW7
TALL7 – 2,3 Mb
TALL152 – 1,4 Mb
TALL18 – 279 Kb
TALL44 – 246 Kb
TALL117 – 238 Kb
FBXW7 homozygous
FBXW7 heterozygous
I
Chromosome 10
PTEN
TALL127 – 1,8 Mb
TALL98 – 1,4 Mb
TALL49 – 1,7 Mb
TALL60 – 2 Mb
TALL17 – 1,6 Mb
TALL81 – 830 kb
TALL23 – 420 kb
TALL67 – 305 Kb
TALL158 – 305 Kb
TALL55 – 305 Kb
TALL155 – 305 Kb
TALL61 – 243 Kb
TALL159 – 93 kb
J
Chromosome 14
BCL11B
TALL151 – 2,4 Mb
TALL22 – 716 Kb
TALL84 – 690 Kb
TALL6 – 429 Kb
TALL44 – 334 Kb
TALL96 – 48 Kb
K
Chromosome 21
RUNX1
TALL162 – 2,6 Mb
TALL159 – 126 Kb
TALL70 – 273 kb
TALL8 – 155 Kb
TALL111 – 48 Kb
L
Chromosome 19
DNMT1
SMARCA4
TALL107 – 906 Kb
TALL6 – 301 Kb
TALL152 – 137 Kb
TALL84 – 123 Kb
TALL95 – 215 Kb
TALL22 – 1,4 Mb
TALL112 – 229 Kb
TALL18 – 223 Kb
M
Chromosome 19
TALL58 – 1,2 Mb
TALL96 – 1,8 Mb
TALL157 – 1,5 Mb
TALL112 – 1,1 Mb
TALL4 – 796 Kb
N
Chromosome 5
5q
TALL46 – 131,2 Mb
TALL69 – 128 Mb
TALL99 – 92,5 Mb
TALL19 – 76,2 Mb
TALL14 – 68,4 Mb
TALL149 – 66,6 Mb
TALL40 – 11,1 / 12 / 29,3 / 1,5 / 10 Mb
TALL148 – 3,7 / 30,4 Mb
O
Chromosome 6
6q
TALL161 – 99,6 Mb
TALL103 – 100,6 Mb
TALL67 – 64,3 Mb
TALL59 – 60,2 Mb
TALL76 – 49,5 Mb
TALL38 – 39,2 Mb
TALL137 – 34,2 Mb
TALL20 – 53 Mb
TALL63 – 63,8 Mb
TALL168 – 57,4 Mb
TALL66 – 46,1 Mb
TALL72 – 45,6 Mb
TALL43 – 30,7 Mb
TALL48 – 35,7 Mb
TALL97 – 32,3 Mb
TALL160 – 57,6 Mb
TALL124 – 29,6 Mb
TALL153 – 11 Mb
TALL98 – 17,9 Mb
P
Chromosome 5
5p
TALL69 – 52,5 Mb
TALL46 – 46,3 Mb
TALL76 – 46,3 Mb
TALL1 – 44,6 Mb
TALL95 – 37,7 Mb
TALL48 – 30,9 Mb
Q
Chromosome 17
17q
TALL73 – 61,1 Mb
TALL153 – 61,9 Mb
TALL28 – 59,2 Mb
TALL53 – 41 Mb
TALL98 – 36,9 Mb
R
Chromosome 1
STIL::TAL1
TAL1
STIL
TALL23 – 92kb
TALL67 – 92 Kb
TALL17 – 92 Kb
TALL137 – 92 Kb
TALL76 – 85,7 Kb
TALL48 – 63,2 Kb
TALL81 – 48,4 Kb
TALL103 – 48,4 Kb
TALL53 – 48,4 Kb
TALL2 – 48,8 Kb
TALL109 – 48,3 Kb
TALL29 – 28,8 Kb
S
Chromosome 9
NUP214::ABL1
ABL1
NUP214
TALL125 – 352 Kb
TALL44 – 417 Kb
TALL49 – 368 Kb
TALL5 – 354 Kb
TALL42 – 377 Kb
Loss
Gain