Adults with Philadelphia chromosome–like acute lymphoblastic leukemia frequently have *IGH-CRLF2* and *JAK2* mutations, persistence of minimal residual disease and poor prognosis

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Philadelphia chromosome–like acute lymphoblastic leukemia in adults is characterized by *IGH-CRLF2* and *JAK2* mutations, persistence of minimal residual disease and poor prognosis

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Running Head: Characterization of Ph-like ALL in adults

Supplementary Figure legends

Supplementary Figure 1: Distribution of *CRLF2* expression in the microarray data set and visualization of the cut off defining high expression

The expression of *CRLF2* in the data set and the cut off defining high expression are shown.

Supplementary Figure 2: Age dependent distribution of major molecular subtypes in B-cell precursor ALL

Pie charts showing the age dependent distribution of the frequency of major molecular subtypes in ALL.

Supplementary Figure 3: Expression of *CRLF2* in B-precursor ALL

The expression of *CRLF2* is shown by boxplot in major molecular subgroups of adult ALL patients.

Supplementary Figure 4: Distribution of mutations in *JAK2* in Ph-like ALL

Schematic presentation of the location of *JAK2* mutations. The horizontal bar represent the full linear polypeptide sequence from amino acid 1 to 1132 of *JAK2* (NM_004972). Amino acid numbering is given around the bars. The SH2-domain (amino acids 400-481) and the two protein tyrosine kinase (PTK) domains (amino acids 545-805 and 849-1123) are indicated in blue. Mutations are shown by black and green dots.

Supplementary Figure 5 A-F: Remission duration and overall survival of Ph-like and remaining BCP-ALL patients in several subgroups

Remission duration (RD) and overall survival (OS) in ALL patients treated in GMALL trials 06/99 and 07/03. Comparison of the Ph-like ALL subgroup with remaining BCP-ALL patients (Ph-negative, MLL-t negative, non-Ph-like) in patients A/B: classified as standard risk and C/D: classified as high risk according to GMALL recommendations. E/F shows only patients without stem cell transplantation (SCT) in first complete remission (CR1).

Supplementary Figure 6: IGH-CRLF2 and/or JAK2 mutations identify a subset of Ph-like ALL with high specificity

Prediction of Ph-like ALL including the analysis of the *IGH-CRLF2*, *MLL*- and *BCR-ABL1*-translocations and *JAK2*-PTK mutations.

Supplementary Tables

Supplementary Table S1: Patient characteristics

Variable	
No. of patients	207
Median age, years (range)	42 (16-84)
Male sex, no. (%)	111 (54)
White-cell count, G/l, median (range)	34 (1-500)
pre-B/c ALL, no. (%)	166 (80)
pro-B ALL, no. (%)	41 (20)
Ph positive ALL, no. (%)	72 (35)
MLL-rearrangement, no. (%)	40 (19)
IGH-CRLF2, no. (%)	6 (7)
IGH-t, no. (%)	7 (9)
P2RY8-CRLF2, no. (%)	2 (1)
TEL(*ETV6*)-*AML1*(*RUNX1*), no. (%)	2 (1)
TCF3-PBX1 (*E2A-PBX1*), no. (%)	3 (1)
High hyperdiploidy (51 to 65), no. (%)	7 (3)
Hypodiploidy (<44 chromosomes), no. (%)	1 (0.5)

Supplementary Table S2: Probe sets excluded from the analysis of Ph-like ALL

Probe set	**Gene**
1552316_a_at	GIMAP1
1554228_a_at	C8orf56
1554876_a_at	S100Z
1555486_a_at	FLJ14213
1556113_at	DKFZp451A211
1556114_a_at	DKFZp451A211
1557403_s_at	ARHGEF12
1558329_at	NFKBIL2
1559035_a_at	AHR
1560492_at	CRADD
1561092_at	KLHDC4
1561507_at	FFAR1
1562433_at	FLJ10489
1563573_at	ARHGEF3
1564077_at	LOC285513
1565598_at	FLJ20273
1568598_at	KAZALD1

Supplementary Table S3: Comparison of the St Jude and GMALL classification approaches

GEO patient ID	ALL_type_GMALL	ALL_type_St Jude	Array type	Class Labels	Predicted Class Labels	Predicted Class 1	Predicted Class 2
ALL_patient_1	Other	Other	A+B	1	1	1	0
ALL_patient_2	Other	Other	A+B	1	1	1	0
ALL_patient_3	Other	Other	A+B	1	1	1	0
ALL_patient_4	Ph-like	Ph-like	A+B	1	2	0.01	0.99
ALL_patient_5	Other	Other	A+B	1	1	1	0
ALL_patient_6	Ph-like	Ph-like	A+B	1	2	0.033	0.967
ALL_patient_7	Other	Other	A+B	1	1	1	0
ALL_patient_8	Other	Other	A+B	1	1	1	0
ALL_patient_9	Other	Other	A+B	1	1	1	0
ALL_patient_10	Other	Other	A+B	1	1	1	0
ALL_patient_11	Ph-like	Ph-like	A+B	1	2	0	1
ALL_patient_12	MLL	MLL	A+B	1	1	1	0
ALL_patient_13	MLL	MLL	A+B	1	1	1	0
ALL_patient_14	MLL	MLL	A+B	1	1	1	0
ALL_patient_15	MLL	MLL	A+B	1	1	1	0
ALL_patient_16	MLL	MLL	A+B	1	1	1	0
ALL_patient_17	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_18	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_19	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_20	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_21	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_22	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_23	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_24	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_25	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_26	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_27	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_28	MLL	MLL	A+B	1	1	1	0
ALL_patient_29	Other	Other	A+B	1	1	1	0
ALL_patient_30	Other	Other	A+B	1	1	1	0
ALL_patient_31	MLL	MLL	A+B	1	1	1	0
ALL_patient_32	MLL	MLL	A+B	1	1	1	0
ALL_patient_33	MLL	MLL	A+B	1	1	1	0
ALL_patient_34	MLL	MLL	A+B	1	1	1	0
ALL_patient_35	MLL	MLL	A+B	1	1	1	0
ALL_patient_36	MLL	MLL	A+B	1	1	1	0
ALL_patient_37	MLL	MLL	A+B	1	1	1	0
ALL_patient_38	MLL	MLL	A+B	1	1	1	0
ALL_patient_39	MLL	MLL	A+B	1	1	1	0
ALL_patient_40	MLL	MLL	A+B	1	1	1	0
ALL_patient_41	MLL	MLL	A+B	1	1	1	0
ALL_patient_42	MLL	MLL	A+B	1	1	1	0

ALL_patient_43	MLL	MLL	A+B	1	1	1	0
ALL_patient_44	Other	Other	A+B	1	1	1	0
ALL_patient_45	Other	Border Ph-like	A+B	1	2	0.494	0.506
ALL_patient_46	Ph-like	Ph-like	A+B	1	2	0	1
ALL_patient_47	Ph-like	Ph-like	A+B	1	2	0	1
ALL_patient_48	Ph-like	Ph-like	A+B	1	2	0.079	0.921
ALL_patient_49	Other	Other	A+B	1	1	1	0
ALL_patient_50	Other	Other	A+B	1	1	1	0
ALL_patient_51	Other	Other	A+B	1	1	1	0
ALL_patient_52	Other	Other	A+B	1	1	1	0
ALL_patient_53	Ph-like	Ph-like	A+B	1	2	0	1
ALL_patient_54	Other	Other	A+B	1	1	1	0
ALL_patient_55	Ph-like	Ph-like	A+B	1	2	0.042	0.958
ALL_patient_56	Ph-like	Ph-like	A+B	1	2	0	1
ALL_patient_57	Other	Other	A+B	1	1	1	0
ALL_patient_58	Other	Other	A+B	1	1	1	0
ALL_patient_59	Other	Other	A+B	1	1	1	0
ALL_patient_60	Ph-like	Ph-like	A+B	1	2	0	1
ALL_patient_61	Ph-like	Ph-like	A+B	1	2	0	1
ALL_patient_62	Other	Other	A+B	1	1	1	0
ALL_patient_63	Other	Other	A+B	1	1	0.994	0.006
ALL_patient_64	Other	Other	A+B	1	1	1	0
ALL_patient_65	Other	Other	A+B	1	1	1	0
ALL_patient_66	Other	Other	A+B	1	1	1	0
ALL_patient_67	Ph-like	Ph-like	A+B	1	2	0	1
ALL_patient_68	Ph-like	Ph-like	A+B	1	2	0.001	0.999
ALL_patient_69	Ph-like	Ph-like	A+B	1	2	0.003	0.997
ALL_patient_70	Other	Other	A+B	1	1	0.999	0.001
ALL_patient_71	MLL	MLL	A+B	1	1	1	0
ALL_patient_72	MLL	MLL	A+B	1	1	1	0
ALL_patient_73	MLL	MLL	A+B	1	1	1	0
ALL_patient_74	MLL	MLL	A+B	1	1	1	0
ALL_patient_75	MLL	MLL	A+B	1	1	1	0
ALL_patient_76	MLL	MLL	A+B	1	1	1	0
ALL_patient_77	MLL	MLL	A+B	1	1	1	0
ALL_patient_78	MLL	MLL	A+B	1	1	1	0
ALL_patient_79	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_80	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_81	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_82	BCR-ABL1	BCR-ABL1	A+B	2	1	1	0
ALL_patient_83	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_84	BCR-ABL1	BCR-ABL1	A+B	2	1	1	0
ALL_patient_85	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_86	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_87	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_88	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_89	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1

ALL_patient_90	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_91	BCR-ABL1	BCR-ABL1	A+B	2	1	0.582	0.418
ALL_patient_92	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_93	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_94	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_95	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_96	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_97	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_98	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_99	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_100	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_101	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_102	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_103	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_104	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_105	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_106	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_107	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_108	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_109	BCR-ABL1	BCR-ABL1	A+B	2	2	0	1
ALL_patient_110	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_111	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_112	Other	Other	Plus 2.0	1	1	0.986	0.014
ALL_patient_113	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_114	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_115	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_116	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_117	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_118	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_119	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_120	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_121	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_122	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_123	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_124	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_125	Ph-like	Ph-like	Plus 2.0	1	2	0	1
ALL_patient_126	BCR-ABL1	BCR-ABL1	Plus 2.0	2	1	1	0
ALL_patient_127	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_128	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_129	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_130	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_131	Other	Other	Plus 2.0	1	1	0.963	0.037
ALL_patient_132	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_133	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_134	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_135	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_136	Other	Other	Plus 2.0	1	1	0.888	0.112

ALL_patient_137	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_138	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_139	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_140	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_141	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_142	Other	Other	Plus 2.0	1	1	0.94	0.06
ALL_patient_143	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_144	Ph-like	Ph-like	Plus 2.0	1	2	0	1
ALL_patient_145	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_146	Ph-like	Ph-like	Plus 2.0	1	2	0.001	0.999
ALL_patient_147	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_148	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_149	Ph-like	Ph-like	Plus 2.0	1	2	0.012	0.988
ALL_patient_150	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_151	Ph-like	Ph-like	Plus 2.0	1	2	0	1
ALL_patient_152	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_153	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_154	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_155	Ph-like	Ph-like	Plus 2.0	1	2	0.006	0.994
ALL_patient_156	Ph-like	Ph-like	Plus 2.0	1	2	0	1
ALL_patient_157	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_158	BCR-ABL1	BCR-ABL1	Plus 2.0	2	1	1	0
ALL_patient_159	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_160	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_161	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_162	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_163	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_164	Ph-like	Ph-like	Plus 2.0	1	2	0	1
ALL_patient_165	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_166	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_167	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_168	Other	Border Ph-like	Plus 2.0	1	2	0.5	0.5
ALL_patient_169	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_170	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_171	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_172	Other	Other	Plus 2.0	1	1	0.977	0.023
ALL_patient_173	Other	Border Ph-like	Plus 2.0	1	2	0.314	0.686
ALL_patient_174	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_175	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_176	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_177	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_178	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_179	Ph-like	Ph-like	Plus 2.0	1	2	0	1
ALL_patient_180	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_181	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_182	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_183	Other	Other	Plus 2.0	1	1	1	0

ALL_patient_184	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_185	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_186	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_187	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_188	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_189	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_190	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_191	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_192	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_193	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_194	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_195	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_196	Other	Other	Plus 2.0	1	1	0.999	0.001
ALL_patient_197	Ph-like	Ph-like	Plus 2.0	1	2	0	1
ALL_patient_198	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_199	Other	Other	Plus 2.0	1	1	1	0
ALL_patient_200	Ph-like	Ph-like	Plus 2.0	1	2	0	1
ALL_patient_201	Other	Other	Plus 2.0	1	1	0.875	0.125
ALL_patient_202	BCR-ABL1	BCR-ABL1	Plus 2.0	2	2	0	1
ALL_patient_203	Ph-like	Ph-like	Plus 2.0	1	2	0	1
ALL_patient_204	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_205	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_206	MLL	MLL	Plus 2.0	1	1	1	0
ALL_patient_207	Other	Other	Plus 2.0	1	1	0.997	0.003

Supplementary Table S4: Genes included in targeted amplicon sequencing

Entrez Gene ID	**Gene**	**Description**
25	ABL1	c-abl oncogene 1, non-receptor tyrosine kinase
105	ADARB2	adenosine deaminase, RNA-specific, B2
83478	ARHGAP24	Rho GTPase activating protein 24
84071	ARMC2	armadillo repeat containing 2
8623	ASMTL	acetylserotonin O-methyltransferase-like
171023	ASXL1	additional sex combs like 1 (Drosophila)
55729	ATF7IP	activating transcription factor 7 interacting protein
472	ATM	ataxia telangiectasia mutated
57194	ATP10A	ATPase, class V, type 10A
64919	BCL11B	B-cell CLL/lymphoma 11B (zinc finger protein)
54880	BCOR	BCL6 corepressor
613	BCR	breakpoint cluster region
330	BIRC3	baculoviral IAP repeat containing 3
29760	BLNK	B-cell linker
648	BMI1	BMI1 polycomb ring finger oncogene
673	BRAF	v-raf murine sarcoma viral oncogene homolog B1
867	CBL	Cas-Br-M (murine) ecotropic retroviral transforming sequence
1029	CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)

1030	CDKN2B	cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)
1050	CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha
4849	CNOT3	CCR4-NOT transcription complex, subunit 3
1387	CREBBP	CREB binding protein
64109	CRLF2	cytokine receptor-like factor 2
1436	CSF1R	colony stimulating factor 1 receptor
1441	CSF3R	colony stimulating factor 3 receptor (granulocyte)
10664	CTCF	CCCTC-binding factor (zinc finger protein)
8847	DLEU2	deleted in lymphocytic leukemia 2 (non-protein coding)
1785	DNM2	dynamin 2
1788	DNMT3A	DNA (cytosine-5-)-methyltransferase 3 alpha
55840	EAF2	ELL associated factor 2
345930	ECT2L	epithelial cell transforming 2 like
8726	EED	embryonic ectoderm development
2033	EP300	E1A binding protein p300
2045	EPHA7	EPH receptor A7
2057	EPOR	erythropoietin receptor
2078	ERG	v-ets erythroblastosis virus E26 oncogene homolog (avian)
2120	ETV6	ets variant 6
2146	EZH2	enhancer of zeste homolog 2 (Drosophila)
2195	FAT1	FAT tumor suppressor homolog 1 (Drosophila)
120114	FAT3	FAT tumor suppressor homolog 3 (Drosophila)
55294	FBXW7	F-box and WD repeat domain containing 7
2222	FDFT1	farnesyl-diphosphate farnesyltransferase 1
2322	FLT3	fms-related tyrosine kinase 3
2623	GATA1	GATA binding protein 1 (globin transcription factor 1)
2624	GATA2	GATA binding protein 2
2625	GATA3	GATA binding protein 3
2626	GATA4	GATA binding protein 4
140628	GATA5	GATA binding protein 5
2627	GATA6	GATA binding protein 6
8339	HIST1H2BG	histone cluster 1, H2bg
3265	HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog
3417	IDH1	isocitrate dehydrogenase 1 (NADP+), soluble
3418	IDH2	isocitrate dehydrogenase 2 (NADP+), mitochondrial
10320	IKZF1	IKAROS family zinc finger 1 (Ikaros)
22807	IKZF2	IKAROS family zinc finger 2 (Helios)
22806	IKZF3	IKAROS family zinc finger 3 (Aiolos)
64375	IKZF4	IKAROS family zinc finger 4 (Eos)
64376	IKZF5	IKAROS family zinc finger 5 (Pegasus)
3575	IL7R	interleukin 7 receptor
3394	IRF8	interferon regulatory factor 8
3716	JAK1	Janus kinase 1
3717	JAK2	Janus kinase 2
3718	JAK3	Janus kinase 3
84643	KIF2B	kinesin family member 2B
3815	KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog

89857	KLHL6	kelch-like 6 (Drosophila)
3845	KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
51176	LEF1	lymphoid enhancer-binding factor 1
4005	LMO2	LIM domain only 2 (rhombotin-like 1)
5594	MAPK1	mitogen-activated protein kinase 1
8085	MLL2	myeloid/lymphoid or mixed-lineage leukemia 2
124540	MSI2	musashi homolog 2 (Drosophila)
4585	MUC4	mucin 4, cell surface associated
4602	MYB	v-myb myeloblastosis viral oncogene homolog (avian)
4605	MYBL2	v-myb myeloblastosis viral oncogene homolog (avian)-like 2
4615	MYD88	myeloid differentiation primary response gene (88)
9611	NCOR1	nuclear receptor corepressor 1
4763	NF1	neurofibromin 1
4851	NOTCH1	notch 1
4869	NPM1	nucleophosmin (nucleolar phosphoprotein B23, numatrin)
2908	NR3C1	nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)
4306	NR3C2	nuclear receptor subfamily 3, group C, member 2
4893	NRAS	neuroblastoma RAS viral (v-ras) oncogene homolog
8021	NUP214	nucleoporin 214kDa
55824	PAG1	phosphoprotein associated with glycosphingolipid microdomains 1
5079	PAX5	paired box 5
5087	PBX1	pre-B-cell leukemia homeobox 1
5159	PDGFRB	platelet-derived growth factor receptor, beta polypeptide
79834	PEAK1	NKF3 kinase family member
84295	PHF6	PHD finger protein 6
57480	PLEKHG1	pleckstrin homology domain containing, family G (with RhoGef domain) member 1
25913	POT1	protection of telomeres 1 homolog (S. pombe)
5728	PTEN	phosphatase and tensin homolog
5781	PTPN11	protein tyrosine phosphatase, non-receptor type 11
5903	RANBP2	RAN binding protein 2
5922	RASA2	RAS p21 protein activator 2
5925	RB1	retinoblastoma 1
58517	RBM25	RNA binding motif protein 25
92241	RCSD1	RCSD domain containing 1
5649	RELN	reelin
6134	RPL10	ribosomal protein L10
6125	RPL5	ribosomal protein L5
861	RUNX1	runt-related transcription factor 1
26040	SETBP1	SET binding protein 1
29072	SETD2	SET domain containing 2
7536	SF1	splicing factor 1
10291	SF3A1	splicing factor 3a, subunit 1, 120kDa
23451	SF3B1	splicing factor 3b, subunit 1, 155kDa
10019	SH2B3	SH2B adaptor protein 3
293	SLC25A6	solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 6
6688	SPI1	spleen focus forming virus (SFFV) proviral integration oncogene spi1
6427	SRSF2	serine/arginine-rich splicing factor 2

6774	STAT3	signal transducer and activator of transcription 3 (acute-phase response factor)
6776	STAT5A	signal transducer and activator of transcription 5A
6777	STAT5B	signal transducer and activator of transcription 5B
57620	STIM2	stromal interaction molecule 2
29966	STRN3	striatin, calmodulin binding protein 3
23512	SUZ12	suppressor of zeste 12 homolog (Drosophila)
6886	TAL1	T-cell acute lymphocytic leukemia 1
79718	TBL1XR1	transducin (beta)-like 1 X-linked receptor 1
6938	TCF12	transcription factor 12
6925	TCF4	transcription factor 4
6934	TCF7L2	transcription factor 7-like 2 (T-cell specific, HMG-box)
63892	THADA	thyroid adenoma associated
7157	TP53	tumor protein p53
10206	TRIM13	tripartite motif containing 13
7991	TUSC3	tumor suppressor candidate 3
7441	VPREB1	pre-B lymphocyte 1
7490	WT1	Wilms tumor 1
7514	XPO1	exportin 1 (CRM1 homolog, yeast)
8233	ZRSR2	zinc finger (CCCH type), RNA-binding motif and serine/arginine rich 2

Supplementary Table S5: Quality metrics summary of targeted amplicon sequencing

	Median
Paired reads past filter [k]	594
Total reads	1,062,698
Individual reads past filter [k]	1,188
Raw read length [bp]	251
Raw sequence before quality trimming [Mb]	298
Reads surviving quality trim [% of raw reads]	91
Reads post trimming [k]	1,063
Mean length of trimmed reads [bp]	159
Reads aligned to hg19 with MAPQ>20 [k]	1,039
Confidently aligned [% of trimmed reads]	97
Confidently aligned sequence [Mb]	173
Confidently aligned HQ sequence (Q>30) [Mb]	168
Substitution rate [%]	0
Indel rate [%]	0
Reads aligned in pairs [% of paired reads]	100

Supplementary Table S6: Non-synonymous mutations identified by targeted amplicon sequencing

Sample	**Mutation**	**Chr**	**Position_start**	**Position_end**	**Gene**	**Type**	**Reference reads**	**Variant reads**

ALL_patient_10	p.L2304V	9	139391281	139391281	NOTCH1	nonsynonymous SNV	161	180
ALL_patient_11	p.F232C	X	1314966	1314966	CRLF2	nonsynonymous SNV	161	54
ALL_patient_11	p.R683G	9	5078360	5078360	JAK2	nonsynonymous SNV	90	13
ALL_patient_11	p.R683S	9	5078362	5078362	JAK2	nonsynonymous SNV	92	10
ALL_patient_11	p.Y299delinsX	9	36923365	36923365	PAX5	stopgain SNV	120	28
ALL_patient_195	p.G12D	1	115258747	115258747	NRAS	nonsynonymous SNV	107	55
ALL_patient_195	p.D2014delinsGKVPD	3	47125229	47125229	SETD2	nonframeshift insertion	37	17
ALL_patient_195	p.I1884R	3	47125619	47125619	SETD2	nonsynonymous SNV	127	10
ALL_patient_196	p.L724fs	20	31022685	31022685	ASXL1	frameshift insertion	260	226
ALL_patient_197	p.W898X	20	31023209	31023209	ASXL1	stopgain SNV	412	17
ALL_patient_200	p.R1453C	4	187549884	187549884	FAT1	nonsynonymous SNV	70	85
ALL_patient_200	p.R683G	9	5078360	5078360	JAK2	nonsynonymous SNV	125	44
ALL_patient_200	p.R683S	9	5078362	5078362	JAK2	nonsynonymous SNV	145	20
ALL_patient_201	p.Y195C	17	7577580	7577580	TP53	nonsynonymous SNV	1079	311
ALL_patient_203	p.T875N	9	5089726	5089726	JAK2	nonsynonymous SNV	153	132
ALL_patient_203	p.V722I	19	17945696	17945696	JAK3	nonsynonymous SNV	188	227
ALL_patient_203	p.G13D	12	25398281	25398281	KRAS	nonsynonymous SNV	80	12
ALL_patient_203	p.Q61R	1	115256529	115256529	NRAS	nonsynonymous SNV	486	12
ALL_patient_3	p.G12A	1	115258747	115258747	NRAS	nonsynonymous SNV	118	62
ALL_patient_3	p.P80R	9	37015165	37015165	PAX5	nonsynonymous SNV	11	52
ALL_patient_4	p.G12D	1	115258747	115258747	NRAS	nonsynonymous SNV	137	14
ALL_patient_4	p.K2511fs	3	47059128	47059128	SETD2	frameshift insertion	171	42
ALL_patient_45	p.C381R	11	119148921	119148921	CBL	nonsynonymous SNV	29	254
ALL_patient_45	p.R1446H	16	3788617	3788617	CREBBP	nonsynonymous SNV	63	57
ALL_patient_46	p.E2503fs	3	47059154	47059154	SETD2	frameshift insertion	196	59
ALL_patient_46	p.D2504A	3	47059150	47059150	SETD2	nonsynonymous SNV	191	60
ALL_patient_46	p.D2504N	3	47059151	47059151	SETD2	nonsynonymous SNV	199	61
ALL_patient_46	p.2505_2505del	3	47059146	47059147	SETD2	frameshift deletion	146	61
ALL_patient_47	p.R683G	9	5078360	5078360	JAK2	nonsynonymous SNV	76	96
ALL_patient_48	p.G16delinsPG	4	153332910	153332910	FBXW7	nonframeshift insertion	190	144
ALL_patient_49	p.G13D	12	25398281	25398281	KRAS	nonsynonymous SNV	58	31
ALL_patient_49	p.E571K	2	61719472	61719472	XPO1	nonsynonymous SNV	169	21
ALL_patient_5	p.A322fs	9	36882049	36882049	PAX5	frameshift insertion	297	261
ALL_patient_50	p.V108fs	17	7578491	7578491	TP53	frameshift deletion	274	17
ALL_patient_52	p.G158S	7	50450288	50450288	IKZF1	nonsynonymous SNV	12	81

ALL_patient_52	p.G13D	12	25398281	25398281	KRAS	nonsynonymous SNV	83	11
ALL_patient_52	p.A146T	12	25378562	25378562	KRAS	nonsynonymous SNV	143	48
ALL_patient_52	p.R507X	17	16029511	16029511	NCOR1	stopgain SNV	57	54
ALL_patient_52	p.S413F	21	36164637	36164637	RUNX1	nonsynonymous SNV	658	269
ALL_patient_54	p.H588Q	19	17947960	17947960	JAK3	nonsynonymous SNV	177	80
ALL_patient_54	p.E571K	2	61719472	61719472	XPO1	nonsynonymous SNV	168	46
ALL_patient_55	p.R683G	9	5078360	5078360	JAK2	nonsynonymous SNV	97	92
ALL_patient_59	p.G12D	1	115258747	115258747	NRAS	nonsynonymous SNV	108	71
ALL_patient_59	p.2445_2446del	3	47079169	47079171	SETD2	nonframeshift deletion	50	52
ALL_patient_61	p.F232C	X	1314966	1314966	CRLF2	nonsynonymous SNV	165	108
ALL_patient_61	p.R100H	19	11492734	11492734	EPOR*	nonsynonymous SNV	192	190
ALL_patient_62	p.R234H	17	7577120	7577120	TP53	nonsynonymous SNV	14	32
ALL_patient_64	p.G12D	12	25398284	25398284	KRAS	nonsynonymous SNV	66	20
ALL_patient_64	p.G12D	1	115258747	115258747	NRAS	nonsynonymous SNV	182	18
ALL_patient_64	p.P80R	9	37015165	37015165	PAX5	nonsynonymous SNV	24	69
ALL_patient_64	p.A72T	12	112888198	112888198	PTPN11	nonsynonymous SNV	164	121
ALL_patient_64	p.E322fs	3	47165160	47165160	SETD2	frameshift insertion	108	57
ALL_patient_64	p.S321X	3	47165164	47165164	SETD2	stopgain SNV	109	58
ALL_patient_67	p.D894G	9	5089783	5089783	JAK2	nonsynonymous SNV	84	36
ALL_patient_68	p.K91N	7	50444343	50444343	IKZF1	nonsynonymous SNV	28	95
ALL_patient_68	p.K91fs	7	50444341	50444341	IKZF1	frameshift insertion	27	94
ALL_patient_68	p.R683G	9	5078360	5078360	JAK2	nonsynonymous SNV	62	49
ALL_patient_68	p.1829_1829del	3	47125783	47125785	SETD2	nonframeshift deletion	48	37
ALL_patient_68	p.K1831_T1832delinsPX	3	47125779	47125779	SETD2	stopgain SNV	146	38
ALL_patient_69	p.F232C	X	1314966	1314966	CRLF2	nonsynonymous SNV	182	141
ALL_patient_70	p.R45W	19	11493891	11493891	EPOR*	nonsynonymous SNV	51	43
ALL_patient_70	p.G12S	1	115258748	115258748	NRAS	nonsynonymous SNV	244	39
ALL_patient_8	p.D835Y	13	28592642	28592642	FLT3	nonsynonymous SNV	563	93
ALL_patient_8	p.G12D	1	115258747	115258747	NRAS	nonsynonymous SNV	203	10
Mutations of unknown significance								
ALL_patient_10	p.P384L	21	36164724	36164724	RUNX1	nonsynonymous SNV	380	10
ALL_patient_10	p.G187W	3	176768267	176768267	TBL1XR1	nonsynonymous SNV	9	67
ALL_patient_11	p.P300fs	9	36923363	36923363	PAX5	frameshift insertion	164	27
ALL_patient_195	p.E61fs	11	47381553	47381553	SPI1	frameshift insertion	88	24
ALL_patient_195	p.E61fs	11	47381553	47381553	SPI1	frameshift insertion	81	24

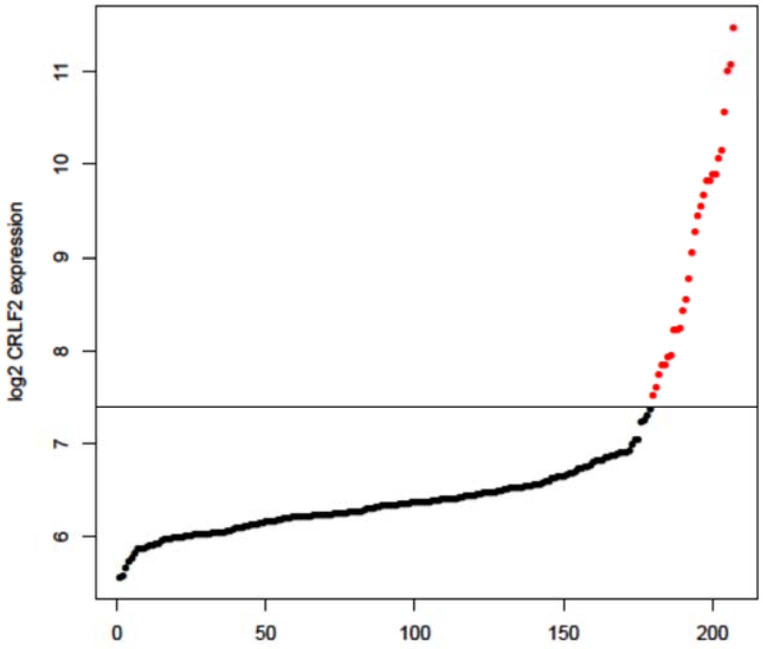
ALL_patient_196	p.R748W	X	39932357	39932357	BCOR	nonsynonymous SNV	182	108
ALL_patient_196	p.G249E	10	97969594	97969594	BLNK	nonsynonymous SNV	239	166
ALL_patient_196	p.K178N	17	16068377	16068377	NCOR1	nonsynonymous SNV	143	33
ALL_patient_196	p.R872W	9	134038451	134038451	NUP214	nonsynonymous SNV	50	44
ALL_patient_199	p.S49C	11	108098576	108098576	ATM	nonsynonymous SNV	26	30
ALL_patient_199	p.A1599G	9	134073677	134073677	NUP214	nonsynonymous SNV	145	139
ALL_patient_2	p.1263_1264del	9	134072669	134072671	NUP214	nonframeshift deletion	74	28
ALL_patient_200	p.V1433A	11	92507309	92507309	FAT3	nonsynonymous SNV	100	111
ALL_patient_201	p.N71T	6	151055029	151055029	PLEKHG1	nonsynonymous SNV	862	18
ALL_patient_203	p.F594C	13	28608275	28608275	FLT3	nonsynonymous SNV	567	24
ALL_patient_203	p.G468E	17	51901797	51901797	KIF2B	nonsynonymous SNV	105	96
ALL_patient_203	p.I473M	3	183210427	183210427	KLHL6	nonsynonymous SNV	218	208
ALL_patient_203	p.2193_2194del	17	29664535	29664538	NF1	frameshift deletion	226	16
ALL_patient_46	p.E329G	11	102198815	102198815	BIRC3	nonsynonymous SNV	72	56
ALL_patient_46	p.K382R	21	39755641	39755641	ERG	nonsynonymous SNV	127	51
ALL_patient_47	p.S452L	6	139186196	139186196	ECT2L	nonsynonymous SNV	199	196
ALL_patient_47	c.857_966GAGACCGCACC	22	22127146	22127571	MAPK1	nonframeshift substitution	367	25
ALL_patient_48	p.Q382P	5	142662164	142662164	NR3C1	nonsynonymous SNV	112	50
ALL_patient_5	p.R1130fs	17	29559793	29559793	NF1	frameshift insertion	14	140
ALL_patient_5	p.C64F	9	37020654	37020654	PAX5	nonsynonymous SNV	405	194
ALL_patient_50	p.A346V	8	11614483	11614483	GATA4	nonsynonymous SNV	212	291
ALL_patient_50	p.N295S	4	27004629	27004629	STIM2	nonsynonymous SNV	45	44
ALL_patient_52	p.S554L	14	99641512	99641512	BCL11B	nonsynonymous SNV	42	31
ALL_patient_52	p.I2958T	2	109398696	109398696	RANBP2	nonsynonymous SNV	70	72
ALL_patient_53	p.P2133A	9	139391794	139391794	NOTCH1	nonsynonymous SNV	290	10
ALL_patient_53	p.L698Q	22	30733028	30733028	SF3A1	nonsynonymous SNV	404	132
ALL_patient_54	p.W1502C	16	3786705	3786705	CREBBP	nonsynonymous SNV	285	105
ALL_patient_54	p.V306G	20	42328650	42328650	MYBL2	nonsynonymous SNV	260	327
ALL_patient_56	p.V347M	16	85953765	85953765	IRF8	nonsynonymous SNV	99	84
ALL_patient_59	p.1247_1248del	15	25925390	25925394	ATP10A	frameshift deletion	74	41
ALL_patient_59	p.I1247F	15	25925395	25925395	ATP10A	nonsynonymous SNV	72	37
ALL_patient_59	p.844_862del	12	49444881	49444934	KMT2D	nonframeshift deletion	49	46
ALL_patient_60	p.P756S	15	25958899	25958899	ATP10A	nonsynonymous SNV	344	397
ALL_patient_61	p.S130N	8	81897498	81897498	PAG1	nonsynonymous SNV	192	155
ALL_patient_61	p.E112K	5	149515148	149515148	PDGFRB	nonsynonymous SNV	162	148

ALL_patient_62	p.Q4242K	11	92616346	92616346	FAT3	nonsynonymous SNV	211	171
ALL_patient_62	p.P1054L	12	49444210	49444210	KMT2D	nonsynonymous SNV	336	326
ALL_patient_65	p.M801R	2	25462005	25462005	DNMT3A	nonsynonymous SNV	227	14
ALL_patient_66	p.A719T	X	39932444	39932444	BCOR	nonsynonymous SNV	91	74
ALL_patient_66	p.K178N	17	16068377	16068377	NCOR1	nonsynonymous SNV	75	18
ALL_patient_69	p.E437K	4	187629673	187629673	FAT1	nonsynonymous SNV	156	166
ALL_patient_70	p.S806L	13	28597488	28597488	FLT3	nonsynonymous SNV	242	79
ALL_patient_70	p.V197fs	3	141272761	141272761	RASA2	frameshift insertion	177	10
ALL_patient_70	p.G201delinsGK	3	141272774	141272774	RASA2	nonframeshift insertion	170	11
ALL_patient_70	p.198_201del	3	141272764	141272773	RASA2	frameshift deletion	177	11
ALL_patient_8	p.H2457fs	17	29677250	29677250	NF1	frameshift insertion	257	107
ALL_patient_8	p.T1184fs	17	29560074	29560074	NF1	frameshift insertion	356	124

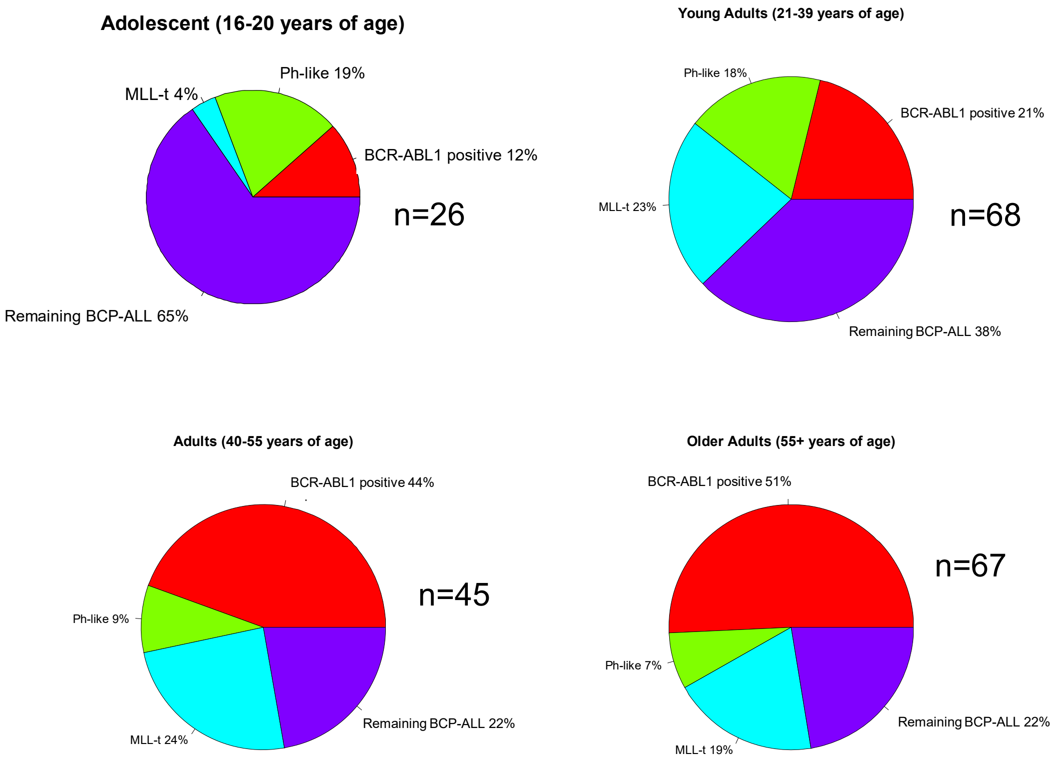
* The mutations in *EPOR* (p.R45W and p.R100H, Table S6) were both not reported before in the COSMIC data base and are located in the erythropoietin ligand binding site. There is currently to our knowledge no experimental data available that these mutations are activating. However, since both mutations were not reported to be germline polymorphisms and variants in the Catalogue Of Somatic Mutations In Cancer (COSMIC, version 67), the NCBI Short Genetic Variations database (dbSNP, version 138) and ClinVar database of variants and phenotypes, and the 1000 Genomes project and had an allelic frequency of ~50% in both cases, we would classify both alterations as putative leukemia driver mutations. Unfortunately, no remission or germline material was available to prove if these mutations were somatic.

Supplementary Figures

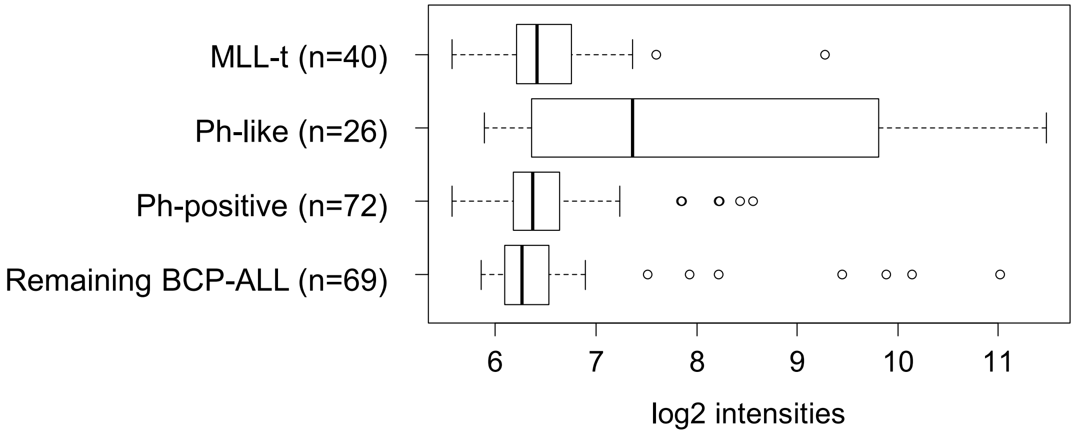
Supplementary Figure 1: Distribution of *CRLF2* expression in the microarray data set and visualization of the cut off defining high expression



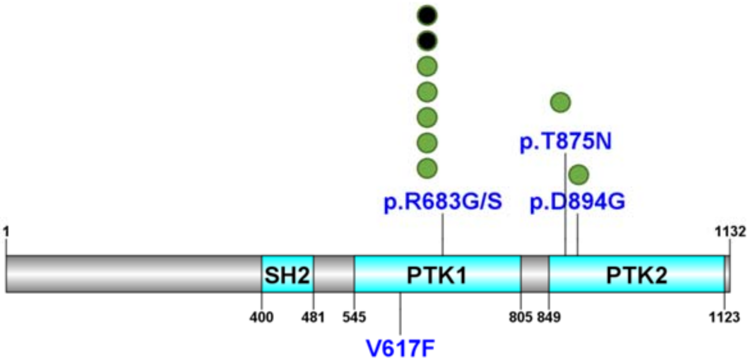
Supplementary Figure 2: Age dependent distribution of major molecular subtypes in B-cell precursor ALL



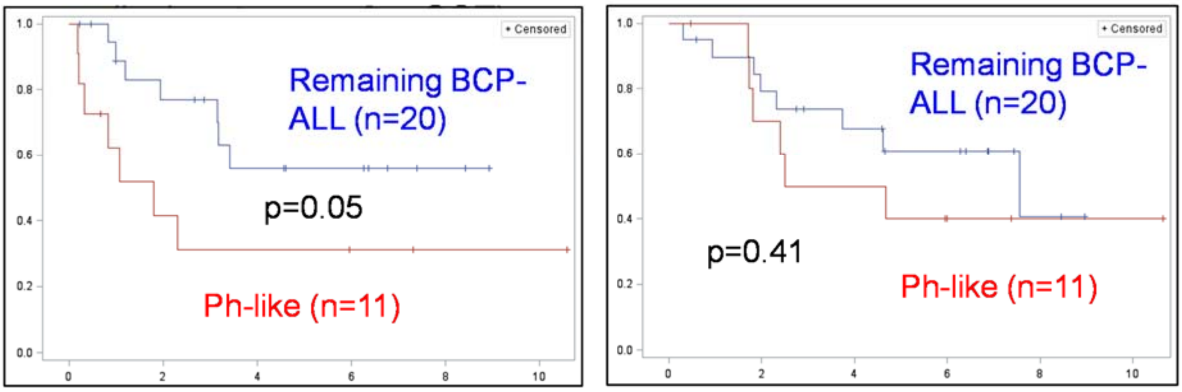
Supplementary Figure 3: Expression of *CRLF2* in B-precursor ALL



Supplementary Figure 4: Distribution of mutations in *JAK2* in Ph-like ALL

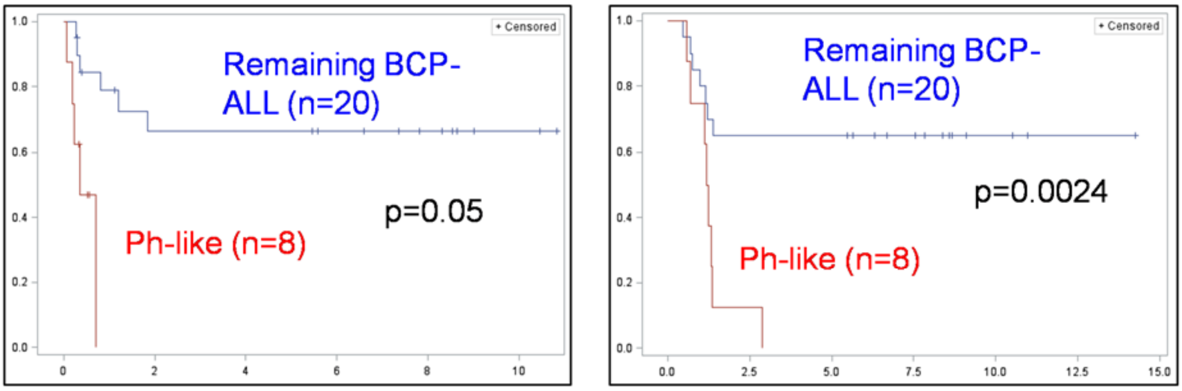


Supplementary Figure 5: Remission duration and overall survival of Ph-like and remaining BCP-ALL in patients in several subgroups



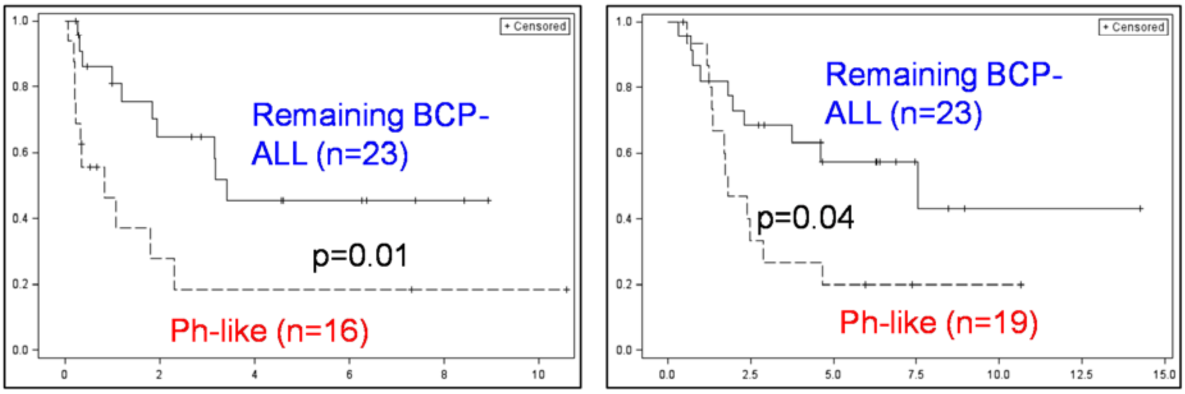
A **Remission Duration** standard risk

B **Overall Survival** standard risk



C **Remission Duration** high risk (incl. outcome after SCT)

D **Overall Survival** high risk



E **Remission Duration** (pts without SCT in CR1)

F **Overall Survival** (pts without SCT in CR1)

Supplementary Figure 6: IGH-CRLF2 and/or JAK2 mutations identify a subset of Ph-like ALL with high specificity