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Rearrangement of *CRLF2* in B-progenitor– and Down syndrome–associated acute lymphoblastic leukemia

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Aneuploidy and translocations are hallmarks of B-progenitor acute lymphoblastic leukemia (ALL), but many individuals with this cancer lack recurring chromosomal alterations. Here we report a recurring interstitial deletion of the pseudoautosomal region 1 of chromosomes X and Y in B-progenitor ALL that juxtaposes the first, noncoding exon of *P2RY8* with the coding region of *CRLF2*. We identified the *P2RY8-CRLF2* fusion in 7% of individuals with B-progenitor ALL and 53% of individuals with ALL associated with Down syndrome. *CRLF2* alteration was associated with activating *JAK* mutations, and expression of human *P2RY8-CRLF2* together with mutated mouse *Jak2* resulted in constitutive Jak-Stat activation and cytokine-independent growth of Ba/F3 cells overexpressing interleukin-7 receptor alpha. Our findings indicate that these two genetic lesions together contribute to leukemogenesis in B-progenitor ALL.

Chromosomal alterations are a hallmark of ALL, the most common malignancy of childhood, and include aneuploidy (hyperdiploidy and hypodiploidy) and recurring chromosomal translocations such as t(12;21) (*ETV6-RUNX1*), t(1;19) (*TCF3-PBX1*), t(9;22) (*BCR-ABL1*) and rearrangement of *MLL*[1]. These alterations are important events in leukemogenesis and influence patients' response to therapy. However, up to one-quarter of individuals with childhood ALL lack a recurring chromosomal alteration, and the genetic basis for disease in these cases is poorly understood.

To identify submicroscopic genetic alterations contributing to the pathogenesis of ALL, we previously conducted high-resolution profiling of DNA copy-number alterations and loss of heterozygosity using SNP microarrays. We identified multiple recurring genetic alterations targeting key cellular pathways, including lymphoid development, cell cycle regulation and tumor suppression[2,3]. These alterations included a newly discovered deletion involving the pseudoautosomal region 1 (PAR1) of Xp22.3/Yp11.3 in 15 B-progenitor ALL cases lacking common chromosomal translocations. Notably, six of eight individuals with Down syndrome–associated ALL (DS-ALL) harbored this deletion.

To further characterize the PAR1 deletion, we expanded our analysis of DNA copy-number alterations and loss of heterozygosity to include 329 individuals with ALL, including 272 with B-progenitor ALL (22 of those with DS-ALL) and 57 with T-lineage childhood ALL (see **Supplementary Table 1** for subject characteristics and **Supplementary Table 2** for a full listing of all DNA copy-number alterations). We identified the PAR1 deletion in 19 individuals with B-progenitor ALL (7%), including 12 of 22 (54.5%) of those with DS-ALL, all of whom lacked recurring translocations commonly associated with non-DS-ALL (**Supplementary Table 3**). Notably, all ten DS-ALL–affected individuals with cytogenetic abnormalities commonly observed in DS-ALL[4–6] (gain of chromosome X in eight cases and deletion of chromosome 9p22 in two cases) had a PAR1 deletion.

The region of PAR1 deletion appeared identical in all cases (**Fig. 1a**), involved at least three genes (*P2RY8, SLC25A6* and *IL3RA*; **Fig. 1b**) and was confirmed by genomic quantitative PCR (**Supplementary Table 4**). The deletion was adjacent to the cytokine receptor genes *CSF2RA* and *CRLF2*, but owing to sparse probe coverage on the SNP array platform used (**Fig. 1b**), we could not precisely define the extent of deletion using SNP array data alone.

To map the boundaries of deletion, we conducted array-based comparative genomic hybridization on two samples using a

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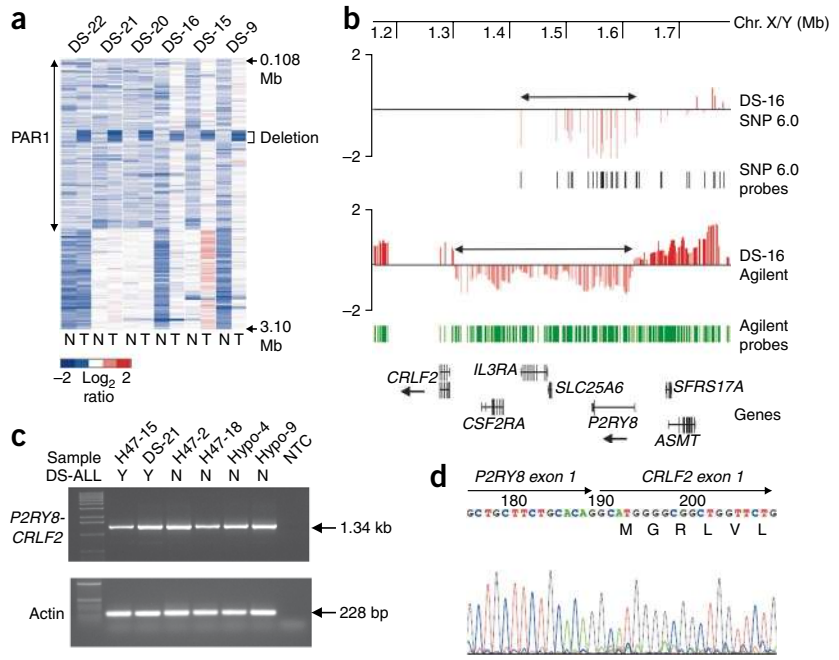

Figure 1 PAR1 deletion and *P2RY8-CRLF2* fusion in B-progenitor ALL. (**a**) Representative $\log_2$ ratio SNP 6.0 microarray DNA copy-number data of six affected individuals with PAR1 deletion. White, normal; blue, deletion; red, gain. Paired data are shown, with normal (N) and tumor (T) for each individual. (**b**) Mapping of the extent of the PAR1 deletion for a representative subject. Sparse SNP 6.0 probe coverage of the region, particularly lack of coverage of the *CRLF2-CSF2RA-IL3RA* region, is shown. Vertical black lines, locations of SNP 6.0 probes; green lines, coverage of 1 million–feature Agilent array; red lines, corresponding $\log_2$ ratio copy-number data. Horizontal arrows indicate region of deletion defined by each platform. (**c**) RT-PCR showing *P2RY8-CRLF2* fusion transcripts. NTC, no template control. (**d**) Direct sequencing of *P2RY8-CRLF2* RT-PCR product, showing that the fusion junction is identical in each *P2RY8-CRLF2*–positive individual and involves the first noncoding exon of *P2RY8* and the entire *CRLF2* ORF.

1 million–feature oligonucleotide array with dense coverage of the region. We found that the PAR1 deletion extended from immediately centromeric (upstream) of *CRLF2* exon 1 to *P2RY8* intron 1 (**Fig. 1b**). *CRLF2* encodes cytokine receptor–like factor 2 (also known as thymic stromal lymphopoietin (TSLP) receptor), a lymphoid signaling receptor molecule that forms a heterodimeric complex with interleukin-7 receptor alpha (IL7R) and binds TSLP[7,8]. *P2RY8* encodes a purinergic receptor (P2Y, G-protein coupled, 8) that is expressed at high levels in many tissues, including leukemic cells[9]. A single case of rearrangement of *P2RY8* to *SOX5* has been reported in primary splenic follicular lymphoma[10]. These observations suggested that the PAR1 deletion results in a previously undescribed rearrangement involving *P2RY8* and *CRLF2*.

RT-PCR confirmed the presence of chimeric transcripts juxtaposing the first, noncoding exon of *P2RY8* to the entire coding region of *CRLF2* in all affected individuals with PAR1 deletion who had available material for analysis, but none of the 50 affected individuals who lacked the deletion (**Fig. 1c** and **Supplementary Fig. 1**). The fusion junction was identical in each case (**Fig. 1d**). Quantitative RT-PCR analysis revealed increased *P2RY8-CRLF2* expression in those with the PAR1 deletion (**Supplementary Fig. 2**). Moreover, we detected elevated cell surface expression of CRLF2 by flow cytometric analysis of cryopreserved leukemic cells (**Supplementary Fig. 3**). A single individual with DS-ALL (DS-ALL-#14) had elevated *CRLF2* mRNA levels, as assessed by real-time PCR, but lacked the deletion, suggesting an alternative mechanism of *CRLF2* dysregulation. Rearrangements of the immunoglobulin heavy chain locus (*IGH@*) at 14q32.33 to *CRLF2* have recently been reported in B-progenitor ALL[11], and FISH analyses of interphase nuclei confirmed *IGH@-CRLF2* rearrangement in subject DS-ALL-#14 (**Supplementary Fig. 4**). Thus, 13 of the individuals with DS-ALL (60%) had genomic rearrangements resulting in dysregulated *CRLF2* expression.

We next characterized the genomic breakpoints of the PAR1 deletion by long-template PCR of genomic DNA extracted from leukemic cells (**Supplementary Figs. 5** and **6**). The deletion breakpoints were highly conserved and were located 3.4 kb upstream of *CRLF2* exon 1 and 0.3–1 kb distal to *P2RY8* exon 1 (**Supplementary Fig. 5c**). Notably, we observed partly or fully conserved heptamer recombination signal sequences immediately internal to the deletion breakpoints and a variable number of nonconsensus nucleotides between the aligning sequences in each subject (**Supplementary Figs. 5c** and **6**). These data suggest that the PAR1 deletion arises as a result of aberrant activity of the antigen receptor recombinases encoded by the RAG recombinase-activating genes, a mechanism that has been implicated in the generation of other sentinel chromosomal rearrangements and deletions in ALL[3,12].

DS-ALL is characterized by the presence of activating *JAK* mutations in up to 28% of those affected, most commonly in the JAK2 pseudokinase domain at or around Arg683 (refs. 13–16). *JAK1*, *JAK2* and *JAK3* mutations have also been identified in 10% of high-risk B-progenitor ALL–affected individuals without Down syndrome[16]. In this cohort, we identified previously described and newly discovered *JAK* mutations in 11 individuals with B-progenitor ALL (4%), including 6 (27.2%) with DS-ALL (**Supplementary Fig. 7**). These included alterations in the JAK2 pseudokinase domain (R683G, $n = 5$; R683S, $n = 2$; and IR682RG, $n = 1$), JAK2 kinase domain (T875N and G861W, $n = 1$ each) and JAK1 pseudokinase domain (V658F, the homolog of JAK2 V617F). Moreover, we observed significant association between *CRLF2* and *JAK* mutations. Nine affected individuals (45%) with *CRLF2* alterations had *JAK* mutations, compared to two (0.6%) who were lacking *CRLF2* lesions (Fisher's exact $P < 0.0001$; **Table 1** and **Supplementary Table 1**). Although we previously identified an association between outcome and the presence of *JAK* mutations in high-risk pediatric ALL[16], we observed no association between *CRLF2* and/or *JAK* mutation status and outcome in DS-ALL (data not shown).

To validate the high frequency of *CRLF2* and *JAK* mutations in DS-ALL, we examined a second cohort of 53 individuals with B-progenitor DS-ALL (**Supplementary Table 5**). Twenty-eight (52.3%) had the PAR1 deletion detected by genomic PCR (**Supplementary Fig. 8a**). In those for whom appropriate sample material was available, the deletion was associated with elevated *CRLF2* expression on microarray analysis (**Supplementary Fig. 9**) and expression of *P2RY8-CRLF2* (**Supplementary Fig. 8b**). Moreover, eight individuals (27.6%) with the PAR1 deletion had *JAK2* mutations, compared to one (4.2%) without the PAR1 deletion (Fisher's exact $P = 0.02$), again highlighting the strong association between *CRFL2* overexpression and activating *JAK2* mutations.

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Table 1 Distribution of PAR1 deletions and *JAK* mutations in pediatric ALL

Group	*n*	PAR1 deletion only	*JAK* mutation only	PAR1 deletion and *JAK* mutation
Non-DS-ALL				
High hyperdiploid	43	0	1	0
TCF3-PBX1	17	0	0	0
ETV6-RUNX1	49	0	0	0
MLL rearranged	24	0	0	0
BCR-ABL1	21	0	0	0
Hypodiploid	10	2	0	0
Other	86	2	1[a]	3
T-lineage ALL	57	0	0	0
DS-ALL				
St. Jude cohort	22	7	0	6[b]
Validation cohort	53	20	1	8

[a]JAK2 G861W. [b]Includes one individual with *IGH@-CRLF2* translocation.

The co-occurrence of *CRLF2* and *JAK* mutations suggested that these events cooperate in leukemogenesis. To examine this hypothesis, we assessed the effect of *P2RY8-CRLF2* and *Jak* mutations on the ability of the cytokine-dependent mouse B-progenitor Ba/F3 cell line to grow in the absence of exogenous cytokine. *Jak* mutations are usually insufficient on their own to transform Ba/F3 cells, but they render the cells growth factor-independent when coexpressed with erythropoietin or thrombopoietin receptors[13,15,16]. As CRLF2 normally forms a heterodimeric complex with IL7R, we expressed IL7R in Ba/F3 cells (Ba/F3-IL7R cells). Expression of *P2RY8-CRLF2* or *Jak2* mutants alone (either Jak2 R683G or the kinase domain alteration P933R[16]) in the Ba/F3-IL7R cells did not induce cytokine-independent growth. In contrast, coexpression of *P2RY8-CRLF2* and *Jak* mutants resulted in constitutive Jak-Stat activation and cytokine-independent growth in Ba/F3-IL7R cells (**Fig. 2a**,**b** and **Supplementary Figs. 10** and **11**). Moreover, this transformation was attenuated by pharmacological Jak inhibition (**Fig. 2c**) and knockdown of CRLF2 expression by short hairpin RNA (shRNA; **Fig. 2d** and **Supplementary Fig. 12**).

Together, these data describe a recurrent intrachromosomal deletion of PAR1 of Xp22.3 and Yp11.3, which results in the generation of chimeric *P2RY8-CRLF2* mRNA and markedly elevated expression of *CRLF2*. *CRLF2* overexpression from *IGH@-CRLF2* rearrangement or PAR1 deletion has also been reported in B-progenitor ALL[11]. However, *CRLF2* alteration is uncommon in B-progenitor ALL (5% of affected individuals), whereas it is present in over 55% of those with DS-ALL, in whom chromosomal rearrangements characteristic of non-DS-ALL are uncommon[4]. Moreover, *CRLF2* alteration was observed exclusively in cases lacking translocations associated with ALL, suggesting that *CRLF2* alteration is a potent leukemogenic event in the setting of trisomy 21 and may account in part for the up to 20-fold increased risk of developing ALL in children with DS[6,17]. The associations of *CRLF2* and *JAK* mutations and additional recurring cytogenetic alterations in DS-ALL (gain of chromosome X and deletion of 9p)[4] are also notable and suggest that these lesions cooperate in leukemogenesis. Notably, three of five subjects with PAR1 deletion and gain of chromosome X had evidence of two copies of the PAR1 deletion on FISH analysis (**Supplementary Fig. 4e–g**), suggesting that gain of X results in duplication and high-level expression of the *P2RY8-CRLF2* fusion. Amplification of regions of chromosomal rearrangement resulting in gene fusion has previously been noted in acute leukemia, for example the *NUP214-ABL1* translocation in T-lineage ALL[18].

CRLF2 interacts with IL7R to form a heterodimeric receptor for the cytokine TSLP. TSLP-CRLF2 signaling has important roles in T-cell and

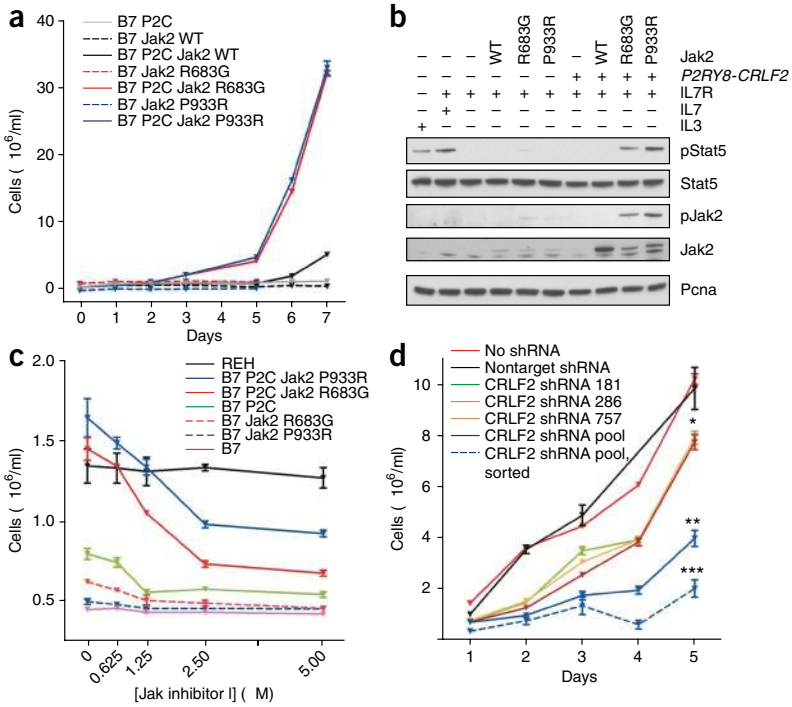

Figure 2 Transforming effects of *P2RY8-CRLF2* and *Jak* mutations. (**a**) Ba/F3 cells expressing mouse IL7R (Ba/F3-IL7R, or B7 cells) were transduced with retroviral constructs expressing *P2RY8-CRLF2* (P2C) and/or *Jak2* alleles (encoding wild-type (WT) mouse Jak2, or Jak2 R683G and P933R). Cells were washed and cultured in the absence of cytokine. Coexpression of *P2RY8-CRLF2* and *Jak* mutants, but not expression of either mutant alone, resulted in cytokine-independent growth. (**b**) Western blotting showing constitutive Jak-Stat activation in Ba/F3-IL7R cells expressing *P2RY8-CRLF2* and *Jak2* mutants. Ba/F3 cells grown in IL-3 and Ba/F3-IL7R cells grown in IL-7 (without starvation and stimulation) are included in the leftmost two lanes as positive controls. Pcna was used as a loading control. A representative blot of three independent experiments is shown. (**c**) Pharmacological Jak inhibition (with Jak inhibitor I) inhibits the growth of Ba/F3-IL7R cells transduced with *P2RY8-CRLF2* and Jak2 R683G or P933R. Cells were washed three times, plated at 0.5×10^6 cells/ml in triplicate, and counted after 48 h. The *ETV6-RUNX1* B-progenitor ALL cell line REH, which does not harbor *P2RY8-CRLF2* or *JAK* mutations, was used as a control. (**d**) Knockdown of CRLF2 expression by lentiviral shRNA attenuates cytokine-independent growth of Ba/F3-IL7R cells expressing *P2RY8-CRLF2* and Jak2 R683G. Cells were transduced with nontarget (scrambled) shRNA, each of three CRLF2-specific shRNAs (181, 286 and 757) and a pool of all three shRNAs. This resulted in substantial but incomplete attenuation of CRLF2 expression (see **Supplementary Fig. 12**) and reduced cytokine-independent growth. Cells with near-total downregulation of CRLF2 expression after shRNA knockdown (isolated by flow cytometric sorting for CRLF2) showed marked abrogation of cytokine-independent growth. *$0.05 < P < 0.10$; **$P < 0.01$; ***$P < 0.001$ by *t*-test compared to cells transduced with nontarget shRNA. All error bars show s.e.m.

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dendritic cell development, inflammation and allergic disease[7,19] and promotes B-lymphoid proliferation, but may not be required for normal B-cell development[20,21]. CRLF2 signaling results in downstream STAT5 phosphorylation[20,22] and, for the human receptor, phosphorylation of JAK2 (ref. 20). In contrast to myeloproliferative diseases, in which homozygous alteration of JAK2 Val617 is common[23], the JAK alterations in B-progenitor ALL are usually heterozygous and do not occur at JAK2 Val617 (refs. 13,15,16). The basis of the disease specificity of the different JAK alterations is unknown, but it has been suggested that the different JAK2 pseudokinase domain alterations facilitate interaction with different substrates and signaling pathways[13]. Detailed analysis of the transforming effect of mutant *Jak* alleles in Ba/F3 cells expressing *P2RY8-CRLF2* and/or IL7R indicated that most *Jak* mutations are not transforming in the absence of *CRLF2* overexpression (exceptions being the *Jak2* mutation resulting in V617F and the homologous *Jak1* mutation resulting in V658F; **Supplementary Note** and **Supplementary Fig. 11**). In contrast, the mutations most commonly observed in B-progenitor ALL (those at or near JAK2 R683) require coexpression of *P2RY8-CRLF2* for transformation in this assay. Notably, transformation (as measured by the rate of cytokine-independent cell growth) was more marked with concomitant IL7R expression (**Supplementary Fig. 11**). Moreover, coimmunoprecipitation experiments using 3×FLAG-tagged *P2RY8-CRLF2* showed direct interaction of CRLF2 and phosphorylated Jak2 (**Supplementary Fig. 13**). Thus, our results indicate that aberrant signaling through the CRLF2-IL7R receptor, mediated by *CRLF2* overexpression and *Jak* mutation, is a key event in B-lymphoid transformation. Consistent with this, in a recent study identifying *CRLF2* rearrangement by FISH in human B-progenitor ALL, overexpression of CRLF2 promoted transformation and Stat5 phosphorylation of primary mouse lymphoid progenitors[11]. This study examined *JAK2* exon 14 mutational status in a small cohort of individuals with DS-ALL ($n = 24$) and observed an association between *CRLF2* rearrangement and *JAK* mutations[11], further supporting cooperativity of these lesions in leukemogenesis.

As a substantial proportion of ALL cases with *CRLF2* overexpression lack *JAK* mutations, mutational analysis of other kinases and mediators of JAK-STAT signaling is warranted. These findings also suggest that detection of increased CRLF2 expression will be a useful diagnostic strategy in ALL, and that JAK-STAT inhibition may be useful in the treatment of individuals with B-progenitor ALL with *CRLF2* and *JAK* mutations.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Accession codes. Agilent array comparative genomic hybridization (CGH) data has been deposited in the NCBI's Gene Expression Omnibus under accession no. GSE16724. The *P2RY8-CRLF2* mRNA sequence has been deposited in GenBank under accession no. GQ280263. SNP array data is available from the authors upon request.

Note: Supplementary information is available on the Nature Genetics website.

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AUTHOR CONTRIBUTIONS

C.G.M. designed and coordinated the study, designed assays, conducted experiments, analyzed data and wrote the manuscript. J.R.C.-U. generated retroviral vectors and conducted Ba/F3 assays. L.A.A.P. conducted JAK sequencing and quantitative PCR assays. M.L.L. conducted *PAR1* deletion genomic PCR. W.L. conducted statistical analysis. J.Z. analyzed sequencing data. J. Ma analyzed microarray data. E.C.-S. conducted flow cytometry and analyzed data. R.C.H. and C.L.W. developed FISH assays. J. Meyer conducted experiments and analyzed data. F.M.M., A.J.C. and N.A.H. conducted FISH assays and analyzed cytogenetic data. R.T.W. provided luciferase vectors. J.C. designed subcloning vectors. G.B., A.P., C.-H.P. and J.R.D. provided patient samples. S.C.R. conducted cytogenetic analysis. S.P.H. coordinated studies and sample collection. W.L.C. provided patient samples, conducted experiments and analyzed data. K.R.R. provided samples, conducted experiments and analyzed data.

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ONLINE METHODS

Subjects and samples. We studied 272 children with B-progenitor ALL and 57 with T-lineage ALL treated at St. Jude Children's Research Hospital, including 22 with B-progenitor DS-ALL (**Supplementary Table 1**). SNP array analysis of all except 14 of the individuals with DS-ALL has been previously reported[2,3,24,25]. PAR1 alterations were examined in a validation cohort of 53 B-progenitor DS-ALL cases treated on or according to Children's Oncology Group protocols ($n = 34$) and the Associazione Italiana Ematologia de Oncologia Pediatrica ($n = 19$). All case samples were obtained with informed consent under protocols approved by institutional review board (US) or ethics committee (Italy). The study was approved by the institutional review boards of St. Jude Children's Research Hospital, Baylor College of Medicine and New York University.

SNP microarrays and array-CGH. SNP array analysis using 250K and 50K arrays or SNP 6.0 arrays (Affymetrix) was done as previously described[2,3,24–26].

Array-based CGH. We conducted CGH using a 974,016-feature array (G4447A, Agilent) in two individuals with DS-ALL. The two-color array raw data were background-subtracted and normalized by locally weighted scatterplot smoothing using the Linear Models for Microarray Analysis[27]. The circular binary segmentation algorithm[28] was applied to normalized $\log_2$ ratio data to identify copy-number alterations.

***JAK1* and *JAK2* sequencing.** We sequenced *JAK* exons known to harbor mutations in B-progenitor ALL (*JAK1* exons 13 and 14, and *JAK2* exons 16, 20 and 21)[13–16] as previously described[16] (primers are listed in **Supplementary Table 6**). Mutations were confirmed by repeat PCR and sequencing of tumor and normal DNA. The *JAK2* mutation resulting in IR682RG (Down-SNP-#09) was confirmed by RT-PCR, cloning and sequencing of *JAK2* exon 16.

Flow cytometric measurement of CRLF2 expression. Cryopreserved leukemic cells were stained with monoclonal antibodies, including phycoerythrin-conjugated antibody to human TSLP receptor (clone 1A6; eBioscience); allophycocyanin-conjugated antibody to CD19, FITC-conjugated antibody to CD10 and peridinin chlorophyll protein–conjugated antibody to CD34 (all from BD Biosciences); and mouse IgG2a phycoerythrin-conjugated isotype control as a control for CRLF2 staining. Fc receptor binding was blocked using rabbit serum (Invitrogen). Data were acquired using a FACSCalibur flow cytometer (BD Biosciences) and analyzed with CellQuest Pro software. Blast cells were identified by Boolean gating using light-scattering properties of the blast cells (forward scatter vs. side scatter) and CD19 plus CD10 or CD34 positivity.

FISH detection of *IGH@-CRLF2* translocation and PAR1 deletion. Interphase FISH analysis was done using cells stored in Carnoy fixative. Two probe mixtures were used: an *IGH@-CRLF2* fusion probe mixture, in which BAC clones RP11-309M23 and RP11-261P4 flanking *CRLF2* were labeled with Alexa Fluor 568 (red) and clone RP11-815P21 centromeric to *IGH@* at 14q32.33 was labeled with Alexa Fluor 488 (green). In normal cells, the expected pattern is two green and two red signals (2G,2R). In cells containing the *IGH@-CRLF2* fusion, the expected pattern is one green, two red and one fusion signal (1G,2R,1F). A second *CRLF2* break-apart probe mixture was used, containing two BAC clones that flank the *CRLF2* gene (RP11-309M23 labeled with Alexa Fluor 488, and RP11-74L17 labeled with Alexa Fluor 568). The signal pattern expected in interphase cells lacking *CRLF2* rearrangement is two fusion signals (2F). In abnormal cells containing *CRLF2* disruption, the expected pattern is one green, one red and one fusion signal (1G,1R,1F). All BAC clones were labeled using a standard nick translation protocol. Slide hybridization and washes were done using standard FISH protocols. The slides were then counterstained with the nuclear dye DAPI and analyzed with an Olympus BX61 microscope and CytoVision image analysis system (Applied Imaging). We scored 25–100 interphase cells for each probe mixture.

Mapping of genomic breakpoints of the PAR1 deletion. Genomic PCR using primers tiled outward from the limits of the PAR1 deletion was done on leukemic cell DNA. PCR products were purified and sequenced, and sequences were aligned to the hg18 reference genome using BLAT implemented in the UCSC genome browser.

RT-PCR and quantitative PCR. To amplify *P2RY8-CRLF2* fusion transcripts, 0.5–1 μg of total leukemic cell RNA was reverse-transcribed and PCR-amplified using Phusion HF polymerase (New England Biolabs). Quantification of transcript levels of *CRLF2* (using TaqMan gene expression assay Hs00277134_m1 from Applied Biosystems) and *P2RY8-CRLF2* (using custom primers and probe) was done as previously described[2,3].

***P2RY8-CRLF2* cloning, retroviral construct generation and Ba/F3 assays.** Full-length *P2RY8-CRLF2* was cloned into pGEM-T-Easy (Promega) and subcloned into the MSCV-IRES-eGFP retroviral vector. *P2RY8-CRLF2* bearing a 3×FLAG tag at the C terminus of CRLF2 was PCR-amplified using primers C1459 and CRLF2 3×FLAG (**Supplementary Table 6**) and subcloned into MSCV-IRES-eGFP. Transduction of Ba/F3-IL7R cells with MSCV-P2RY8-CRLF2-3×FLAG-IRES-eGFP resulted in identical expression of CRLF2 (as assessed by quantitative PCR, western blotting and flow cytometry) to the non–FLAG-tagged construct, and comparable transformation and Jak-Stat activation after transduction with mutant Jak2.

MSCV-Jak2-IRES-luc2 vectors expressing wild-type or mutant *Jak2* alleles were generated by subcloning the firefly luciferase cassette excised from the MSCV (Babe MCS)-IRES-*luc2* retroviral vector into the previously described MSCV-Jak2-IRES-eGFP retroviral vectors[16]. The transforming effect of the MSCV-Jak2-IRES-*luc2* vectors was confirmed by transducing Ba/F3-EpoR cells as previously described[16]. Retroviral supernatants were produced using ecotropic Phoenix packaging cells. Ba/F3-IL7R cells were generated by transducing Ba/F3 cells with MSCV-mIL7R-IRES-hCD4 and then cultured in medium supplemented with 10 ng/ml recombinant mouse IL7 (PeproTech). Ba/F3-IL7R cells were sequentially transduced with retroviral supernatants expressing P2RY8-CRLF2 and/or wild-type and mutant *Jak2* alleles. Transduced cells were washed and grown in the absence of cytokine, and growth was quantified using a ViCell cell counter (Beckman Coulter). Expression of P2RY8-CRLF2 was assessed by flow cytometric measurement of GFP and CRLF2 expression. Expression of mouse IL7R was measured by flow cytometric measurement of human CD4 (using allophycocyanin-conjugated antibody to human CD4; BD PharMingen). Expression of *Jak2* alleles was measured using a Bright-Glo luciferase assay system (Promega). Western blotting was done as previously described[16].

Drug exposure assays were done as previously described[16]. Ba/F3 cells were washed three times and plated at a density of 0.5×10^6 cells/ml in increasing concentrations of Jak inhibitor I (Calbiochem) or vehicle (dimethylsulfoxide). Cells were counted after 48 h of exposure to drug.

For immunoprecipitation assays, Jak-transduced Ba/F3-IL7R cells expressing 3×FLAG tagged P2RY8-CRLF2 were washed and cultured in the absence of cytokine. Ten million cells were washed and resuspended in lysis buffer (10× PBS with 0.5 M EDTA, 10% NP-40 and 50% glycerol) with protease inhibitors (Roche) and phosphatase inhibitors (Sigma-Aldrich). Lysates were passed through 21-gauge needles five times and centrifuged at 20,817*g* for 10 min at 4 C. Supernatants were incubated with washed protein-G agarose beads (Sigma-Aldrich) for 1 h at 4 °C. An aliquot of each precleared lysate was set aside to run as input. The remaining precleared lysates were incubated with washed anti-FLAG M2-agarose beads (Sigma-Aldrich) by rotating for 90 min. Lysates were incubated with 100 μg/ml 3×FLAG peptide (Sigma-Aldrich) to elute FLAG-bound proteins. LDS sample buffer (Invitrogen) was added to eluates, which were then boiled, electrophoresed and transferred to nitrocellulose membranes (Invitrogen). Membranes were probed with antibodies to Jak2, phosphorylated Jak2, Stat5 and phosphorylated Stat5 (Cell Signaling); CRLF2 (R&D Systems); and FLAG (Sigma-Aldrich). Antibody to PCNA (Santa Cruz Biotechnology) served as a loading control.

shRNA knockdown of CRLF2 in Ba/F3 cells. Five shRNAs targeting CRLF2 in the pLKO.1-puro lentiviral vector were tested (clones NM_022148.2-524s1c1 (524), NM_022148.2-181s1c1 (181), NM_022148.2-757s1c1 (757), NM_022148.2-286s1c1 (286) and NM_022148.2-689s1c1 (689); Sigma-Aldrich). Lentiviral particles for each CRLF2-specific shRNA and nontarget (scrambled) shRNA control vector (SHC002V) were produced by transient transfection of HEK293T cells with shRNA plasmid and the packaging plasmids CAG kGP1-1R (gag-pol), CAG4 RTR2 (rev-tat) and pHDMG (vesicular stomatitis virus-G envelope)[29].

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The efficacy of knockdown was assessed by transducing transformed, cytokine-independent Ba/F3-IL7R cells (previously transduced with MSCV-*P2RY8-CRLF2*-IRES-eGFP and MSCV-Jak2-683G-IRES-*luc2*) with each shRNA, followed by puromycin selection for at least 5 d, and then measuring CRLF2 expression (by flow cytometry, western blotting and quantitative PCR for *CRLF2* and *P2RY8-CRLF2* transcripts) and Jak-Stat activation (by western blotting). Three shRNAs (181s1c1, 286s1c1 and 757s1c1) resulted in at least 70–85% knockdown of CRLF2 expression (as quantified by flow cytometry analysis of CRLF2 expression). Cytokine withdrawal assays were then done for the Ba/F3-IL7R cells expressing *P2RY8-CRLF2* and Jak2 R683G after transduction with each of the three shRNAs alone and as a pool. Assays were done in triplicate.

Statistical analysis. Associations between categorical variables were examined using the Fisher's exact test. Associations with treatment outcome (event-free survival and relapse) were done as previously described[25,30–33]. Analyses were done using Prism v 5.0 (GraphPad), R, SAS (SAS v9.1.2, SAS Institute), SPLUS 7.0 (Insightful) and StatXact v 8.0.0 (Cytel).

URLs. G.P. Nolan laboratory, http://www.stanford.edu/group/nolan/; R statistical software, http://www.r-project.org.

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SUPPLEMENTARY INFORMATION

REARRANGEMENT OF *CRLF2* IN B-PROGENITOR AND DOWN SYNDROME ASSOCIATED ACUTE LYMPHOBLASTIC LEUKEMIA

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SUPPLEMENTARY NOTE

Ba/F3 transformation assays. To examine the relative importance of expression of *P2RY8-CRLF2*, mutant Jak alleles and *P2RY8-CRLF2* in transformation, Jak transformation assays were performed in Ba/F3 cells not transduced with IL7RA or *P2RY8-CRLF2*, Ba/F3 cells transduced with either IL7RA or *P2RY8-CRLF2,* and cells transduced with both IL7RA and *P2RY8-CRLF2* (Supplementary Fig. 10). We developed the Ba/F3-IL7R cell line to test the transforming effects of *P2RY8-CRLF2* and JAK mutations, as despite Ba/F3 being nominally a pro-B cell line, Ba/F3 cells express low levels of the IL-7 receptor (IL7RA, CD127, and common gamma chain, CD132). Ba/F3 cells do not grow in the presence of supplemental IL-7, in contrast to Ba/F3-IL7R cells, which grow with supplemental IL7. In the absence of IL7RA and *P2RY8-CRLF2,* Ba/F3 cells are transformed by Jak1 V658F (the homolog of Jak2 V617F), and weakly by Jak2 V617F, but not by any of the other Jak2 mutant alleles identified in ALL (Supplementary Fig. 11a). Ba/F3 cells transduced with *P2RY8-CRLF2* (but not IL7RA) are transformed by Jak1 V658F and Jak2 R683G, and weakly by Jak2 P933R but not the other mutants. Ba/F3 cells transduced with IL7RA are transformed by Jak1 V658F and Jak2 V617F, but not the other Jak2 mutant alleles. In stark contrast, Ba/F3 cells expressing both mIL7RA and *P2RY8-CRLF2* are transformed by all mutants, and the rate of cytokine-independent growth is greater than in Ba/F3 cells expressing IL7RA or *P2RY8-CRLF2* alone. Thus, in this system, transformation by several types of Jak mutants, notably those at or near Jak2 R683, require over-expression of *P2RY8-CRLF2*. Moreover, in the absence of co-expression of mIL7RA, transformation is weak with many Jak mutations. These data suggest that interaction of Jak2 mutants, *P2RY8-CRLF2* and IL7RA is required for transformation. The transformation induced by V658F (and to a lesser extent, the homolog V617F) in the absence of *P2RY8-CRLF2* also suggests different signaling pathway interactions exerted by each mutant. Notably, however, the

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transformation induced by these mutations is more pronounced in the presence of *P2RY8-CRLF2* (which is present in the single case with V658F in this study).

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Supplementary Table 1

Details of St Jude cases examined in this study, including SNP array platform and chip identifier. "500K + 50K" refers to the use of 250k Nsp, 205k Sty, 50k Hind 240 and 50k Xba 240 mapping arrays (c. 615,000 markers). "500K" refers to the use of the two 250k arrays alone (c. 500,000 markers).

Sample	Previously studied? [1-4]	DS	*CRLF2* alteration	*JAK* mutation	SNP platform	Agilent array
Hyperdip>50-SNP-#1	Yes				500K + 50K	
Hyperdip>50-SNP-#2	Yes				500K + 50K	
Hyperdip>50-SNP-#3	Yes				500K + 50K	
Hyperdip>50-SNP-#4	Yes				500K + 50K	
Hyperdip>50-SNP-#5	Yes				500K + 50K	
Hyperdip>50-SNP-#6	Yes				500K + 50K	
Hyperdip>50-SNP-#7	Yes				500K + 50K	
Hyperdip>50-SNP-#8	Yes				500K + 50K	
Hyperdip>50-SNP-#9	Yes				500K + 50K	
Hyperdip>50-SNP-#10	Yes				500K + 50K	
Hyperdip>50-SNP-#11	Yes				500K + 50K	
Hyperdip>50-SNP-#12	Yes				500K + 50K	
Hyperdip>50-SNP-#13	Yes			R683G	500K + 50K	
Hyperdip>50-SNP-#14	Yes				500K + 50K	
Hyperdip>50-SNP-#15	Yes				500K + 50K	
Hyperdip>50-SNP-#16	Yes				500K + 50K	
Hyperdip>50-SNP-#17	Yes				500K + 50K	
Hyperdip>50-SNP-#18	Yes				500K + 50K	
Hyperdip>50-SNP-#19	Yes				500K + 50K	
Hyperdip>50-SNP-#20	Yes				500K + 50K	
Hyperdip>50-SNP-#21	Yes				500K + 50K	
Hyperdip>50-SNP-#22	Yes				500K + 50K	
Hyperdip>50-SNP-#23	Yes				500K + 50K	
Hyperdip>50-SNP-#24	Yes				500K + 50K	
Hyperdip>50-SNP-#25	Yes				500K + 50K	
Hyperdip>50-SNP-#26	Yes				500K + 50K	
Hyperdip>50-SNP-#28	Yes				500K + 50K	
Hyperdip>50-SNP-#29	Yes				500K + 50K	
Hyperdip>50-SNP-#30	Yes				500K + 50K	
Hyperdip>50-SNP-#31	Yes				500K + 50K	
Hyperdip>50-SNP-#32	Yes				500K + 50K	
Hyperdip>50-SNP-#33	Yes	Yes	PAR1 deletion	R683G	500K + 50K	
Hyperdip>50-SNP-#34	Yes				500K + 50K	
Hyperdip>50-SNP-#35	Yes				500K + 50K	
Hyperdip>50-SNP-#36	Yes				500K + 50K	
Hyperdip>50-SNP-#37	Yes				500K + 50K	
Hyperdip>50-SNP-#38	Yes				500K + 50K	
Hyperdip>50-SNP-#39	Yes				500K + 50K	
Hyperdip>50-SNP-#27	Yes				SNP 6.0	
Hyperdip50-SNP-#51	Yes				SNP 6.0	
Hyperdip50-SNP-#52	Yes				SNP 6.0	
Hyperdip50-SNP-#53	Yes				SNP 6.0	

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Sample	Previously studied? [1-4]	DS	*CRLF2* alteration	*JAK* mutation	SNP platform	Agilent array
Hyperdip50-SNP-#54	Yes				SNP 6.0	
Hyperdip50-SNP-#55	Yes				SNP 6.0	
E2A-PBX1-SNP-#1	Yes				500K + 50K	
E2A-PBX1-SNP-#2	Yes				500K + 50K	
E2A-PBX1-SNP-#3	Yes				500K + 50K	
E2A-PBX1-SNP-#4	Yes				500K + 50K	
E2A-PBX1-SNP-#5	Yes				500K + 50K	
E2A-PBX1-SNP-#6	Yes				500K + 50K	
E2A-PBX1-SNP-#7	Yes				500K + 50K	
E2A-PBX1-SNP-#8	Yes				500K + 50K	
E2A-PBX1-SNP-#9	Yes				500K + 50K	
E2A-PBX1-SNP-#10	Yes				500K + 50K	
E2A-PBX1-SNP-#11	Yes				500K + 50K	
E2A-PBX1-SNP-#13	Yes				500K + 50K	
E2A-PBX1-SNP-#14	Yes				500K + 50K	
E2A-PBX1-SNP-#15	Yes				500K + 50K	
E2A-PBX1-SNP-#16	Yes				500K + 50K	
E2A-PBX1-SNP-#17	Yes				500K + 50K	
E2A-PBX1-SNP-#12	Yes				SNP 6.0	
TEL-AML1-SNP-#1	Yes				500K + 50K	
TEL-AML1-SNP-#2	Yes				500K + 50K	
TEL-AML1-SNP-#3	Yes				500K + 50K	
TEL-AML1-SNP-#4	Yes				500K + 50K	
TEL-AML1-SNP-#5	Yes				500K + 50K	
TEL-AML1-SNP-#6	Yes				500K + 50K	
TEL-AML1-SNP-#7	Yes				500K + 50K	
TEL-AML1-SNP-#8	Yes				500K + 50K	
TEL-AML1-SNP-#9	Yes				500K + 50K	
TEL-AML1-SNP-#10	Yes				500K + 50K	
TEL-AML1-SNP-#11	Yes				500K + 50K	
TEL-AML1-SNP-#12	Yes				500K + 50K	
TEL-AML1-SNP-#13	Yes				500K + 50K	
TEL-AML1-SNP-#14	Yes				500K + 50K	
TEL-AML1-SNP-#15	Yes				500K + 50K	
TEL-AML1-SNP-#16	Yes				500K + 50K	
TEL-AML1-SNP-#17	Yes				500K + 50K	
TEL-AML1-SNP-#18	Yes				500K + 50K	
TEL-AML1-SNP-#19	Yes				500K + 50K	
TEL-AML1-SNP-#20	Yes				500K + 50K	
TEL-AML1-SNP-#21	Yes				500K + 50K	
TEL-AML1-SNP-#22	Yes				500K + 50K	
TEL-AML1-SNP-#23	Yes				500K + 50K	
TEL-AML1-SNP-#24	Yes				500K + 50K	
TEL-AML1-SNP-#25	Yes				500K + 50K	
TEL-AML1-SNP-#26	Yes				500K + 50K	
TEL-AML1-SNP-#27	Yes				500K + 50K	
TEL-AML1-SNP-#28	Yes				500K + 50K	
TEL-AML1-SNP-#29	Yes				500K + 50K	
TEL-AML1-SNP-#30	Yes				500K + 50K	
TEL-AML1-SNP-#31	Yes				500K + 50K	

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Sample	Previously studied? [1-4]	DS	*CRLF2* alteration	*JAK* mutation	SNP platform	Agilent array
TEL-AML1-SNP-#32	Yes				500K + 50K	
TEL-AML1-SNP-#33	Yes				500K + 50K	
TEL-AML1-SNP-#34	Yes				500K + 50K	
TEL-AML1-SNP-#35	Yes				500K + 50K	
TEL-AML1-SNP-#36	Yes				500K + 50K	
TEL-AML1-SNP-#37	Yes				500K + 50K	
TEL-AML1-SNP-#38	Yes				500K + 50K	
TEL-AML1-SNP-#39	Yes				500K + 50K	
TEL-AML1-SNP-#40	Yes				500K + 50K	
TEL-AML1-SNP-#41	Yes				500K + 50K	
TEL-AML1-SNP-#42	Yes				500K + 50K	
TEL-AML1-SNP-#43	Yes	Yes			500K + 50K	
TEL-AML1-SNP-#44	Yes				500K + 50K	
TEL-AML1-SNP-#45	Yes				500K + 50K	
TEL-AML1-SNP-#46	Yes				500K + 50K	
TEL-AML1-SNP-#47	Yes				500K + 50K	
TEL-AML1-SNP-#48	Yes				SNP 6.0	
TEL-AML1-SNP-#49	Yes				SNP 6.0	
TEL-AML1-SNP-#50	Yes				SNP 6.0	
MLL-SNP-#12	Yes				500K	
MLL-SNP-#13	Yes				500K	
MLL-SNP-#15	Yes				500K	
MLL-SNP-#1	Yes				500K	
MLL-SNP-#2	Yes				500K	
MLL-SNP-#3	Yes				500K + 50K	
MLL-SNP-#4	Yes				500K	
MLL-SNP-#16	Yes				500K	
MLL-SNP-#17	Yes				500K	
MLL-SNP-#18	Yes				500K	
MLL-SNP-#19	Yes				500K	
MLL-SNP-#5	Yes				500K	
MLL-SNP-#6	Yes				500K + 50K	
MLL-SNP-#7	Yes				500K	
MLL-SNP-#20	Yes				500K	
MLL-SNP-#8	Yes				500K	
MLL-SNP-#9	Yes				500K + 50K	
MLL-SNP-#10	Yes				500K	
MLL-SNP-#21	Yes				500K	
MLL-SNP-#22	Yes				500K	
MLL-SNP-#11	Yes				500K + 50K	
MLL-SNP-#23	Yes				SNP 6.0	
MLL-SNP-#24	Yes				SNP 6.0	
MLL-SNP-#25	Yes				SNP 6.0	
BCR-ABL-SNP-#1	Yes				500K + 50K	
BCR-ABL-SNP-#2	Yes				500K + 50K	
BCR-ABL-SNP-#3	Yes				500K + 50K	
BCR-ABL-SNP-#4	Yes				500K + 50K	
BCR-ABL-SNP-#5	Yes				500K + 50K	
BCR-ABL-SNP-#6	Yes				500K + 50K	
BCR-ABL-SNP-#7	Yes				500K + 50K	

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Sample	Previously studied? [1-4]	DS	*CRLF2* alteration	*JAK* mutation	SNP platform	Agilent array
BCR-ABL-SNP-#10	Yes				500K	
BCR-ABL-SNP-#12	Yes				500K	
BCR-ABL-SNP-#13	Yes				500K	
BCR-ABL-SNP-#14	Yes				500K	
BCR-ABL-SNP-#16	Yes				500K	
BCR-ABL-SNP-#17	Yes				500K	
BCR-ABL-SNP-#8	Yes				500K + 50K	
BCR-ABL-SNP-#19	Yes				500K	
BCR-ABL-SNP-#20	Yes				500K	
BCR-ABL-SNP-#9	Yes				500K + 50K	
BCR-ABL-SNP-#21	Yes				500K	
BCR-ABL-SNP-#11	Yes				SNP 6.0	
BCR-ABL-SNP-#15	Yes				SNP 6.0	
BCR-ABL-SNP-#18	Yes				SNP 6.0	
Hypodip-SNP-#1	Yes				500K + 50K	
Hypodip-SNP-#26	Yes				500K + 50K	
Hypodip-SNP-#3	Yes				500K + 50K	
Hypodip-SNP-#4	Yes	No	PAR1 deletion		500K + 50K	
Hypodip-SNP-#5	Yes				500K + 50K	
Hypodip-SNP-#6	Yes				500K + 50K	
Hypodip-SNP-#7	Yes				500K + 50K	
Hypodip-SNP-#8	Yes				500K + 50K	
Hypodip-SNP-#9	Yes	No	PAR1 deletion		500K + 50K	
Hypodip-SNP-#10	Yes				500K + 50K	
Hyperdip47-50-SNP-#1	Yes				500K + 50K	
Hyperdip47-50-SNP-#2	Yes	No	PAR1 deletion	R683S	500K + 50K	
Hyperdip47-50-SNP-#3	Yes				500K + 50K	
Hyperdip47-50-SNP-#5	Yes				500K + 50K	
Hyperdip47-50-SNP-#6	Yes				500K + 50K	
Hyperdip47-50-SNP-#7	Yes				500K + 50K	
Hyperdip47-50-SNP-#8	Yes	Yes	PAR1 deletion		500K + 50K	
Hyperdip47-50-SNP-#9	Yes				500K + 50K	
Hyperdip47-50-SNP-#10	Yes				500K + 50K	
Hyperdip47-50-SNP-#11	Yes				500K + 50K	
Hyperdip47-50-SNP-#12	Yes	Yes	PAR1 deletion	R683G	500K + 50K	
Hyperdip47-50-SNP-#13	Yes				500K + 50K	
Hyperdip47-50-SNP-#14	Yes	Yes	PAR1 deletion		500K + 50K	
Hyperdip47-50-SNP-#15	Yes	Yes	PAR1 deletion		500K + 50K	
Hyperdip47-50-SNP-#16	Yes				500K + 50K	
Hyperdip47-50-SNP-#17	Yes				500K + 50K	
Hyperdip47-50-SNP-#18	Yes	No	PAR1 deletion	R683G	500K + 50K	
Hyperdip47-50-SNP-#19	Yes	Yes			500K + 50K	
Hyperdip47-50-SNP-#20	Yes				500K + 50K	
Hyperdip47-50-SNP-#21	Yes				500K + 50K	
Hyperdip47-50-SNP-#22	Yes	No	PAR1 deletion	T875N	500K + 50K	
Hyperdip47-50-SNP-#23	Yes				500K + 50K	
Pseudodip-SNP-#1	Yes				500K + 50K	
Other-SNP-#1	Yes				500K + 50K	
Pseudodip-SNP-#2	Yes				500K + 50K	
Pseudodip-SNP-#3	Yes				500K + 50K	

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Sample	Previously studied? [1-4]	DS	*CRLF2* alteration	*JAK* mutation	SNP platform	Agilent array
Pseudodip-SNP-#4	Yes				500K + 50K	
Pseudodip-SNP-#22	Yes				500K + 50K	
Pseudodip-SNP-#5	Yes				500K + 50K	
Pseudodip-SNP-#6	Yes				500K + 50K	
Pseudodip-SNP-#7	Yes				500K + 50K	
Other-SNP-#2	Yes				500K + 50K	
Other-SNP-#3	Yes				500K + 50K	
Other-SNP-#4	Yes				500K + 50K	
Other-SNP-#5	Yes				500K + 50K	
Pseudodip-SNP-#8	Yes				500K + 50K	
Pseudodip-SNP-#9	Yes				500K + 50K	
Pseudodip-SNP-#10	Yes				500K + 50K	
Pseudodip-SNP-#11	Yes				500K + 50K	
Other-SNP-#6	Yes				500K + 50K	
Pseudodip-SNP-#12	Yes				500K + 50K	
Other-SNP-#7	Yes				500K + 50K	
Pseudodip-SNP-#23	Yes				500K	
Pseudodip-SNP-#24	Yes			G861W	500K	
Other-SNP-#17	Yes				500K	
Hyperdip47-50-SNP-#24	Yes				500K	
Other-SNP-#8	Yes				500K + 50K	
Other-SNP-#9	Yes				500K + 50K	
Pseudodip-SNP-#13	Yes				500K + 50K	
Pseudodip-SNP-#14	Yes				500K + 50K	
Pseudodip-SNP-#15	Yes				500K + 50K	
Other-SNP-#18	Yes				500K	
Pseudodip-SNP-#16	Yes				500K + 50K	
Other-SNP-#11	Yes				500K + 50K	
Pseudodip-SNP-#21	Yes				500K	
Other-SNP-#12	Yes				500K + 50K	
Hyperdip>50-SNP-#40	Yes				500K + 50K	
Other-SNP-#19	Yes				500K + 50K	
Other-SNP-#13	Yes		PAR1 deletion		500K + 50K	
Pseudodip-SNP-#17	Yes				500K + 50K	
Other-SNP-#14	Yes				500K + 50K	
Pseudodip-SNP-#19	Yes				500K + 50K	
Pseudodip-SNP-#20	Yes				500K + 50K	
Other-SNP-#15	Yes				500K + 50K	
Other-SNP-#20	Yes				500K + 50K	
Other-SNP-#16	Yes				500K + 50K	
Other-SNP-#22	Yes				500K	
Other-SNP-#23	Yes				500K	
Other-SNP-#24	Yes				500K	
Other-SNP-#25	Yes				500K	
Other-SNP-#26	Yes				500K	
Pseudodip-SNP-#18	Yes				SNP 6.0	
Other-SNP-#21	Yes				SNP 6.0	
Hyperdip47-50-SNP-#4	Yes				SNP 6.0	
Other-SNP-#27	Yes				SNP 6.0	
Other-SNP-#28	Yes				SNP 6.0	

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Sample	Previously studied? [1-4]	DS	*CRLF2* alteration	*JAK* mutation	SNP platform	Agilent array
Other-SNP-#29	Yes				SNP 6.0	
Other-SNP-#30	Yes				SNP 6.0	
Other-SNP-#31	Yes				SNP 6.0	
Other-SNP-#32	Yes	No	PAR1 deletion		SNP 6.0	
Other-SNP-#33	Yes	Yes	PAR1 deletion		SNP 6.0	
Other-SNP-#34	Yes				SNP 6.0	
Other-SNP-#35	Yes				SNP 6.0	
Other-SNP-#36	Yes				SNP 6.0	
Other-SNP-#37	Yes				SNP 6.0	
Other-SNP-#38	Yes				SNP 6.0	
Other-SNP-#39	Yes				SNP 6.0	
Other-SNP-#40	Yes				SNP 6.0	
Other-SNP-#41	Yes				SNP 6.0	
Other-SNP-#42	Yes				SNP 6.0	
Other-SNP-#43	Yes				SNP 6.0	
Other-SNP-#10	Yes				500K + 50K	
Down-SNP-#09	No	Yes	PAR1 deletion	IR682RG	SNP 6.0	
Down-SNP-#10	No	Yes			SNP 6.0	
Down-SNP-#11	No	Yes			SNP 6.0	
Down-SNP-#12	No	Yes			SNP 6.0	
Down-SNP-#13	No	Yes			SNP 6.0	
Down-SNP-#14	No	Yes	IGH@-CRLF2	R683S	SNP 6.0	
Down-SNP-#15	No	Yes	PAR1 deletion	R683G	SNP 6.0	
Down-SNP-#16	No	Yes	PAR1 deletion		SNP 6.0	Yes
Down-SNP-#17	No	Yes			SNP 6.0	
Down-SNP-#18	No	Yes			SNP 6.0	
Down-SNP-#19	No	Yes			SNP 6.0	
Down-SNP-#20	No	Yes	PAR1 deletion		SNP 6.0	Yes
Down-SNP-#21	No	Yes	PAR1 deletion	JAK1 V658F	SNP 6.0	
Down-SNP-#22	No	Yes	PAR1 deletion		SNP 6.0	
T-ALL-SNP-#1	Yes				500K + 50K	
T-ALL-SNP-#2	Yes				500K + 50K	
T-ALL-SNP-#3	Yes				500K + 50K	
T-ALL-SNP-#4	Yes				500K + 50K	
T-ALL-SNP-#5	Yes				500K + 50K	
T-ALL-SNP-#6	Yes				500K + 50K	
T-ALL-SNP-#7	Yes				500K + 50K	
T-ALL-SNP-#8	Yes				500K + 50K	
T-ALL-SNP-#9	Yes				500K + 50K	
T-ALL-SNP-#10	Yes				500K + 50K	
T-ALL-SNP-#11	Yes				500K + 50K	
T-ALL-SNP-#12	Yes				500K + 50K	
T-ALL-SNP-#13	Yes				500K + 50K	
T-ALL-SNP-#14	Yes				500K + 50K	
T-ALL-SNP-#15	Yes				500K + 50K	
T-ALL-SNP-#16	Yes				500K + 50K	
T-ALL-SNP-#17	Yes				500K + 50K	
T-ALL-SNP-#18	Yes				500K + 50K	
T-ALL-SNP-#19	Yes				500K + 50K	

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Sample	Previously studied? [1-4]	DS	*CRLF2* alteration	*JAK* mutation	SNP platform	Agilent array
T-ALL-SNP-#20	Yes				500K + 50K	
T-ALL-SNP-#21	Yes				500K + 50K	
T-ALL-SNP-#22	Yes				500K + 50K	
T-ALL-SNP-#23	Yes				500K + 50K	
T-ALL-SNP-#24	Yes				500K + 50K	
T-ALL-SNP-#25	Yes				500K + 50K	
T-ALL-SNP-#26	Yes				500K + 50K	
T-ALL-SNP-#27	Yes				500K + 50K	
T-ALL-SNP-#28	Yes				500K + 50K	
T-ALL-SNP-#29	Yes				500K + 50K	
T-ALL-SNP-#30	Yes				500K + 50K	
T-ALL-SNP-#31	Yes				500K + 50K	
T-ALL-SNP-#32	Yes				500K + 50K	
T-ALL-SNP-#33	Yes				500K + 50K	
T-ALL-SNP-#34	Yes				500K + 50K	
T-ALL-SNP-#35	Yes				500K + 50K	
T-ALL-SNP-#37	Yes				500K + 50K	
T-ALL-SNP-#38	Yes				500K + 50K	
T-ALL-SNP-#39	Yes				500K + 50K	
T-ALL-SNP-#40	Yes				500K + 50K	
T-ALL-SNP-#41	Yes				500K + 50K	
T-ALL-SNP-#42	Yes				500K + 50K	
T-ALL-SNP-#44	Yes				500K	
T-ALL-SNP-#45	Yes				500K + 50K	
T-ALL-SNP-#47	Yes				500K + 50K	
T-ALL-SNP-#48	Yes				500K + 50K	
T-ALL-SNP-#49	Yes				500K + 50K	
T-ALL-SNP-#50	Yes				500K + 50K	
T-ALL-SNP-#36	Yes				SNP 6.0	
T-ALL-SNP-#43	Yes				SNP 6.0	
T-ALL-SNP-#46	Yes				SNP 6.0	
T-ALL-SNP-#51	Yes				SNP 6.0	
T-ALL-SNP-#52	Yes				SNP 6.0	
T-ALL-SNP-#53	Yes				SNP 6.0	
T-ALL-SNP-#54	Yes				SNP 6.0	
T-ALL-SNP-#55	Yes				SNP 6.0	
T-ALL-SNP-#57	Yes				SNP 6.0	
T-ALL-SNP-#58	Yes				SNP 6.0	

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Supplementary Table 2

Listing of all segments (regions) of tumor-acquired copy number alteration in all St Jude DS-ALL cases, and non DS-ALL cases with PAR1 deletions. The table excludes constitutional trisomy 21, and deletions associated with antigen receptor gene rearrangements.

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Supplementary Table 2

	Chr	cytoband	Start (Mb)	End (Mb)	Copy number	Segment size/c	Number of	Comment	first 10 genes in segment
DS-ALL cases									
Hyperdip>50-SNP-#33	4	p16.3-q35.2	0.019	191.306	2.7			Trisomy 4	
Hyperdip>50-SNP-#33	9	p21.3	21.880	21.982	0.9	101.426	1		/CDKN2A
Hyperdip>50-SNP-#33	14	q11.2-q32.33	19.273	106.356	2.83			Trisomy 14	
Hyperdip>50-SNP-#33	15	q11.2-q26.3	19.916	100.211	2.69			Trisomy 15	
Hyperdip>50-SNP-#33	17	p13.3-q25.3	0.007	31.461	2.66			Trisomy 17	
Hyperdip>50-SNP-#33	21	p11.2-q22.3	9.888	46.925	4.19		241	+21c, and gain of additional chr 21 in tumor	
Hyperdip>50-SNP-#33	X	p22.33	0.034	0.993	2.42	958.531	4		/PLCXD1/GTPBP6/PPP2R3B/SHOX
Hyperdip>50-SNP-#33	**X**	**p22.33**	**1.017**	**1.759**	**1.05**	**742.144**	**8**	**PAR1**	**/CSF2RA/IL3RA/SLC25A6/CXYorf2/ASMTL/P2RY8/RP13-297E16.1/ASMT**
Hyperdip>50-SNP-#33	X	p22.33-q28	1.792	154.480	2.8	152665.104	737		/ASMT/ZBED1/CD99/XG/GYG2/ARSD/ARSE/ARSH/ARSF/MXRA5
TEL-AML1-SNP-#43	3	p22.3	35.615	35.615	0.89	306.309	0		
TEL-AML1-SNP-#43	8	q12.1	60.206	60.261	0.77	55.416	0		
TEL-AML1-SNP-#43	9	p21.3	21.920	21.949	0.74	28.858	0		
TEL-AML1-SNP-#43	9	p21.3	21.959	21.995	0.2	36.618	2		/CDKN2A/CDKN2B
TEL-AML1-SNP-#43	9	p21.1	28.584	28.752	0.18	167.978	1		/LRRN6C
TEL-AML1-SNP-#43	X	q26.2-q28	130.475	154.480	4.32	24005.146	176		/RP6-213H19.1/RP6-213H19.2/RAP2C/MBNL3/HS6ST2/USP26/TFDP3/GPC4/GPC3/PHF6
Hyperdip47-50-SNP-#19	2	q33.3	208.13056	208.281566	1.17	151.006	2		/CREB1/FAM119A
Hyperdip47-50-SNP-#19	3	q27.3;q28	188.921216	190.495267	0.37	1574.051	3		/BCL6/LPP/TPRG1
Hyperdip47-50-SNP-#19	9	p24.3-p21.3	0.03091	21.904576	1.1	21873.666	84		/FOXD4/CBWD1/C9orf66/DOCK8/KANK1/DMRT1/DMRT3/DMRT2/SMARCA2/VLDLR
Hyperdip47-50-SNP-#19	9	p21.3	21.908568	22.109128	0.2	200.56	2		/CDKN2A/CDKN2B
Hyperdip47-50-SNP-#19	9	p21.3-q13	22.111621	70.133638	1.13	48022.017	129		/DMRTA1
Hyperdip47-50-SNP-#19	9	q13-q34.3	70.139836	140.211203	2.9	70071.367	520		/PGM5/C9orf71/PIP5K1B/FAM122A/PRKACG/FXN/TJP2/C9orf61/APBA1
Hyperdip47-50-SNP-#19	10	q22.1	72.804151	73.008286	1.12	204.135	1		/CDH23
Hyperdip47-50-SNP-#19	11	q24.1	122.045364	122.119993	1.07	74.629	1		/UBASH3B
Hyperdip47-50-SNP-#19	12	q21.33;q22	90.802579	91.351732	1.1	549.153	3		/BTG1/CLLU1OS/CLLU1
Hyperdip47-50-SNP-#19	13	q22.3;q31.1	77.006747	78.921307	1.16	1914.56	6		/SCEL/SLAIN1/EDNRB/POU4F1/RNF219/RBM26
Hyperdip47-50-SNP-#8	1	q31.1	186.25171	186.341243	1	89.533	0		
Hyperdip47-50-SNP-#8	3	p12.3	75.509785	75.629408	1.1	119.623	0		
Hyperdip47-50-SNP-#8	3	q13.2	113.535936	113.700796	1.06	164.86	2		/CD200/BTLA
Hyperdip47-50-SNP-#8	6	p22.1	26.25277	26.35578	1.07	103.01	14		ST1H2AD/HIST1H2BF/HIST1H4E/HIST1H2BG/HIST1H2AE
Hyperdip47-50-SNP-#8	7	p12.3	47.095404	47.099867	0.74	4.463	0		
Hyperdip47-50-SNP-#8	7	q11.21	61.624717	61.794045	3.09	169.328	0		
Hyperdip47-50-SNP-#8	7	q21.12;q21.13	87.988734	88.175329	2.9	186.595	0		
Hyperdip47-50-SNP-#8	7	q21.13	88.178084	88.464008	4.14	285.924	2		/ZNF804B/MGC26647
Hyperdip47-50-SNP-#8	7	q21.13	88.46497	90.004781	2.78	1539.811	4		/ZNF804B/STEAP1/STEAP2/FLJ21062
Hyperdip47-50-SNP-#8	7	q22.1	100.752321	100.922118	2.93	169.797	1		/EMID2
Hyperdip47-50-SNP-#8	9	p13.2	36.578714	37.021876	1.1	443.162	2		/MELK/PAX5
Hyperdip47-50-SNP-#8	11	p15.2	13.096023	13.144599	1	48.576	0		
Hyperdip47-50-SNP-#8	**X**	**p22.33**	**1.4158**	**1.600371**	**1.17**	**184.571**	**4**	**PAR1**	**/IL3RA/SLC25A6/ASMTL/P2RY8**
Hyperdip47-50-SNP-#12	1	q32.3-q42.12	208.896	222.727	1.41	13830.806	67		/PPP2R5A/C1orf75/NENF/ATF3/FAM71A/SNFT/C1orf48/LOC149643/FLVCR/VASH2
Hyperdip47-50-SNP-#12	1	q42.12-q44	222.752	245.378	1.08	22625.924	163		/LIN9/PARP1/C1orf95/ITPKB/PSEN2/CABC1/CDC42BPA/ZNF678/JMJD4/C1orf142
Hyperdip47-50-SNP-#12	10	q21.3	64.530	65.488	2.57	957.861	3		/NRBF2/JMJD1C/REEP3
Hyperdip47-50-SNP-#12	14	q11.2-q32.33	19.495	105.717	2.47	Trisomy 14			

Supplementary Table 2

	Chr	cytoband	Start (Mb)	End (Mb)	Copy number	Segment size/d	Number of	Comment	first 10 genes in segment
Hyperdip47-50-SNP-#12	17	q21.31	38.250	41.569	2.72	3318.892	69		/AOC2/AOC3/FLJ31222/G6PC/AARSD1/RUNDC1/RPL27/IFI35/VAT1/RND2
Hyperdip47-50-SNP-#12	17	q21.31-q25.3	41.708	78.605	3.61	36865.185	405		/LRRC37A/LOC474170/ARL17P1/NSF/NSF/WNT3/WNT9B/GOSR2/RPRML/CDC27/MYL4/ITGB3/C17orf57/NPEPPS
Hyperdip47-50-SNP-#12	X	p22.33	0.034	0.993	3.33	958.531	4		/PLCXD1/GTPBP6/PPP2R3B/SHOX
Hyperdip47-50-SNP-#12	**X**	**p22.33**	**1.017**	**1.683**	**0.96**	**666.722**	**6**	**PAR1**	**/CSF2RA/IL3RA/SLC25A6/CXYorf2/ASMTL/P2RY8**
Hyperdip47-50-SNP-#12	X	p22.33	1.709	2.688	3.3	979.008	5		/RP13-297E16.1/ASMT/ZBED1/CD99/XG
Hyperdip47-50-SNP-#12	X	p22.33-q28	2.697	154.480	4.58	151782.927	733		/XG/GYG2/ARSD/ARSE/ARSH/ARSF/MXRA5/PRKX/NLGN4X/VCX3A
Hyperdip47-50-SNP-#14	X	p22.33	0.034	0.914	3.06	879.749	4		/PLCXD1/GTPBP6/PPP2R3B/SHOX
Hyperdip47-50-SNP-#14	**X**	**p22.33**	**1.499**	**1.683**	**0.94**	**183.82**	**5**	**PAR1**	**/IL3RA/SLC25A6/CXYorf2/ASMTL/P2RY8**
Hyperdip47-50-SNP-#14	X	p22.33	1.709	2.683	2.47	974.343	5		/RP13-297E16.1/ASMT/ZBED1/CD99/XG
Hyperdip47-50-SNP-#14	X	p22.33-q28	2.684	154.480	3.16	151724.639	734		/XG/GYG2/ARSD/ARSE/ARSH/ARSF/MXRA5/PRKX/NLGN4X/VCX3A
Hyperdip47-50-SNP-#15	X	p22.33	0.034	1.017	3.16	982.145	4		/PLCXD1/GTPBP6/PPP2R3B/SHOX
Hyperdip47-50-SNP-#15	**X**	**p22.33**	**1.499**	**1.683**	**1.23**	**183.82**	**5**	**PAR1**	**/IL3RA/SLC25A6/CXYorf2/ASMTL/P2RY8**
Hyperdip47-50-SNP-#15	X	p22.33-q28	1.709	154.480	2.89	152771.086	737		/RP13-297E16.1/ASMT/ZBED1/CD99/XG/GYG2/ARSD/ARSE/ARSH/ARSF
Other-SNP-#33	2	q21.2	134.746111	134.816827	1.18	70.716	0		
Other-SNP-#33	3	p14.1	69.591297	69.607008	1.01	15.711	0		
Other-SNP-#33	3	q13.33	123.002773	123.032854	1.06	30.081	1		/IQCB1
Other-SNP-#33	6	p22.2;p22.1	26.264565	26.400414	0.37	135.849	19		/HIST1H1E/HIST1H2BD/HIST1H2BE/HIST1H4D/HIST1H3D/HIST1H2AD/HIST1H2BF/HIST1H4E/HIST1H2BG/HIST1H2AE
Other-SNP-#33	7	p12.2	50.381206	50.476072	1.04	94.866	2		/DDC/GRB10
Other-SNP-#33	9	p23-p21.3	12.624026	21.958712	1.71	9334.686	46		/TYRP1/C9orf150/MPDZ/NFIB/ZDHHC21/CER1/FREM1/C9orf52/SNAPC3/PSIP1
Other-SNP-#33	9	p21.3	21.966858	21.995382	0.75	28.524	2		/CDKN2A/CDKN2B
Other-SNP-#33	9	p21.3	21.99996	22.283804	1.6	283.844	0		
Other-SNP-#33	9	p21.3;p21.2;p21.1	22.290326	31.282989	1.73	8992.663	13		/DMRTA1/ELAVL2/TUSC1/C9orf82/PLAA/IFT74/LRRC19/TEK/C9orf11/MOBKL2B
Other-SNP-#33	9	p21.1-p13.1	31.28388	38.656106	1.67	7372.226	88		/ACO1/DDX58/TOPORS/NDUFB6/TAF1L/LOC401498/APTX/DNAJA1/SMU1/B4GALT1
Other-SNP-#33	12	p13.2	11.905252	11.931648	3.02	26.396	1		/ETV6
Other-SNP-#33	**X**	**p22.33**	**1.4158**	**1.600371**	**1.11**	**184.571**	**4**	**PAR1**	**/IL3RA/SLC25A6/CXYorf2/ASMTL**
Down-SNP-#09	9	p21.3	21.904576	21.948524	1.16	43.948	0		
Down-SNP-#09	9	p21.3	21.948554	21.995382	0.4	46.828	2		/CDKN2A/CDKN2B
Down-SNP-#09	15	q22.31	63.805343	63.86605	0.97	60.707	1		/DENND4A
Down-SNP-#09	X	p22.33	0.108465	1.146863	3.08	1038.398	4		/PLCXD1/GTPBP6/PPP2R3B/SHOX
Down-SNP-#09	**X**	**p22.33**	**1.4158**	**1.600371**	**0.94**	**184.571**	**4**	**PAR1**	**/IL3RA/SLC25A6/ASMTL/P2RY8**
Down-SNP-#09	X	p22.33	1.618943	2.724459	3.15	1105.516	6		/SFRS17A/ASMT/DHRSX/ZBED1/CD99/XG
Down-SNP-#09	X	p22.33-q28	2.724756	154.907376	4.05	152182.62	787		/XG/GYG2/ARSD/ARSE/ARSH/ARSF/MXRA5/PRKX/NLGN4X/VCX3A
Down-SNP-#10	3	p14.2	60.164389	60.210116	0.98	45.727	1		/FHIT
Down-SNP-#10	7	p22.3-p12.2	0.052899	50.379256	0.99	50326.357		with	A1/COX19/CYP2W1/C7orf50
Down-SNP-#10	7	p12.2	50.381206	50.424682	0.22	43.476	1		/IKZF1
Down-SNP-#10	7	p12.2-q34	50.433798	158.819753	0.99	108385.955			/IKZF1/FIGNL1/DDC/GRB10/COBL
Down-SNP-#10	9	p24.3-p11.2	0.03091	65.356954	1	65326.044		9p-	RT2/SMARCA2/VLDLR
Down-SNP-#10	9	q12-q34.3	65.370754	140.211203	2.9	74840.449		9q+	
Down-SNP-#10	11	q14.3	89.068615	89.114467	0.96	45.852	1		/PSMAL
Down-SNP-#10	11	q23.1	110.669668	110.676856	0.77	7.188	1		/FLJ45803
Down-SNP-#10	15	q11.2	20.224751	20.968714	3.19	743.963	5		/LOC283767/TUBGCP5/CYFIP1/NIPA2/NIPA1

Supplementary Table 2

	Chr	cytoband	Start (Mb)	End (Mb)	Copy number	Segment size/c	Number of	Comment	first 10 genes in segment
Down-SNP-#11	6	p22.1	26.29202	26.35958	1.16	67.56	13		/HIST1H2BE/HIST1H4D/HIST1H3D/HIST1H2AD/HIST1H2BF/HIST1H4E/HIST1H2BG/HIST1H2AE/HIST1H3E/HIST1H1D
Down-SNP-#11	7	p22.2	4.326589	4.498403	1.03	171.814	0		
Down-SNP-#11	7	p21.3	8.793683	8.832382	1.01	38.699	0		
Down-SNP-#11	7	p12.1	53.433507	53.558229	1.03	124.722			
Down-SNP-#11	7	q21.11	80.094739	80.118116	0.97	23.377	1		/CD36
Down-SNP-#11	12	p11.21	31.893551	31.959157	2.96	65.606	0		
Down-SNP-#11	15	q11.2	22.225832	22.269677	1.07	43.845	0		
Down-SNP-#12	No lesions								
Down-SNP-#13	3	p22.3	35.397885	35.658108	1.17	260.223	0		Adjacent to ARPP21
Down-SNP-#13	5	q33.3	157.223774	157.3035	1.16	79.726	0		Distal to EBF1
Down-SNP-#13	5	q33.3	158.373438	158.457083	1.17	83.645	1		/EBF1
Down-SNP-#13	12	p13.2	11.698451	11.842382	1.21	143.931	1		/ETV6
Down-SNP-#13	15	q21.2	48.436232	48.70673	1.14	270.498	3		/USP8/USP50/TRPM7
Down-SNP-#14	3	p22.1	39.714103	39.748539	0.89	34.436	0		
Down-SNP-#14	3	p14.2	60.04165	60.357868	1.17	316.218	1		/FHIT
Down-SNP-#14	3	q25.2	153.829772	153.839161	1.09	9.389	0		Adjacent MBNL1
Down-SNP-#14	5	q33.3	157.877758	158.453167	1.28	575.409	1		/EBF1
Down-SNP-#14	7	p12.2	50.382544	50.433798	1.02	51.254	1		/IKZF1
Down-SNP-#14	9	q21.32	84.871848	84.911971	0.79	40.123	0		
Down-SNP-#14	11	q24.1	120.815774	120.87446	1.19	58.686	1		/SORL1
Down-SNP-#14	12	p13.2	11.674778	11.695111	1.21	20.333	1		/ETV6
Down-SNP-#14	14	q32.2	98.581642	98.612433	0.93	30.791	0		
Down-SNP-#14	15	q26.3	99.782644	99.883303	2.98	100.659	1		/PCSK6
Down-SNP-#14	16	p13.3	3.482409	3.59946	1.27	117.051	4		/LOC646174/CLUAP1/NLRC3/BTBD12
Down-SNP-#15	4	q12	53.932189	53.982078	0.93	49.889	1		/FIP1L1
Down-SNP-#15	6	p22.1	26.245402	26.369985	0.24	124.583	16		/HIST1H1E/HIST1H2BD/HIST1H2BE/HIST1H4D/HIST1H3D/HIST1H2AD/HIST1H2BF/HIST1H4E/HIST1H2BG/HIST1H2AE
Down-SNP-#15	6	p22.1	27.90637	27.990246	0.85	83.876	11		/HIST1H4K/HIST1H2AK/HIST1H2BN/HIST1H2AL/HIST1H1B/HIST1H3I/HIST1H4L/HIST1H3J/HIST1H2AM/HIST1H2BO
Down-SNP-#15	7	p15.1-p11.1	29.253457	58.0239	1.14	28770.443	85		/CHN2/PRR15/WIPF3/SCRN1/FKBP14/PLEKHA8/C7orf41/ZNRF2/NOD1/C7orf24
Down-SNP-#15	8	q22.1	96.350967	96.49908	1.04	148.113	0		
Down-SNP-#15	X	p22.33	0.108465	0.941508	3.12	833.043	4		/PLCXD1/GTPBP6/PPP2R3B/SHOX
Down-SNP-#15	**X**	**p22.33**	**1.131508**	**1.600371**	**1.26**	**468.863**	**6**	**PAR1**	**/CRLF2/CSF2RA/IL3RA/SLC25A6/ASMTL/P2RY8**
Down-SNP-#15	X	p22.33-q28	1.618943	154.907376	3.03	153288.433	794		/SFRS17A/ASMT/DHRSX/ZBED1/CD99/XG/GYG2/ARSD/ARSE/ARSH
Down-SNP-#16	4	q35.2	190.776255	190.819835	1.34	43.58	0		
Down-SNP-#16	8	q12.1	60.20333	60.40437	1.17	201.04	0		/TOX
Down-SNP-#16	9	p21.3	21.81811	21.958712	1.21	140.602	2		/MTAP/CDKN2A
Down-SNP-#16	9	p21.3	21.966858	21.995382	0.45	28.524	2		/CDKN2A/CDKN2B
Down-SNP-#16	11	q24.2	126.705741	126.709006	1.27	3.265	0		
Down-SNP-#16	12	q13.13	51.770621	51.777276	0.99	6.655	0		
Down-SNP-#16	X	p22.33	0.108465	1.146863	2.93	1038.398	4		/PLCXD1/GTPBP6/PPP2R3B/SHOX
Down-SNP-#16	**X**	**p22.33**	**1.4158**	**1.600371**	**1.17**	**184.571**	**4**	**PAR1**	**/IL3RA/SLC25A6/ASMTL/P2RY8**
Down-SNP-#16	X	p22.33-q28	1.618943	154.711269	3.51	22043.569	796		/SFRS17A/ASMT/DHRSX/ZBED1/CD99/XG/GYG2/ARSD/ARSE/ARSH
Down-SNP-#17	5	q34	165.779329	165.779738	4.34	0.409	0		
Down-SNP-#17	9	p24.3-p21.3	0.03091	21.958712	1.67	21916.588	86		/CBWD1/C9orf66/DOCK8/KANK1/DMRT1/DMRT3/DMRT2/SMARCA2/VLDLR/KCNV2
Down-SNP-#17	9	p21.3	21.966858	21.995382	0.59	28.524	2		/CDKN2A/CDKN2B

Supplementary Table 2

	Chr	cytoband	Start (Mb)	End (Mb)	Copy number	Segment size/c	Number of	Comment	first 10 genes in segment
Down-SNP-#17	9	p21.3-p12	21.99996	42.055254	1.19	20055.294	110		/DMRTA1/ELAVL2/TUSC1/C9orf82/PLAA/IFT74/LRRC19/TEK/C9orf11/MOBKL2B/IFNK
Down-SNP-#17	9	q12-q34.3	69.267815	140.211203	2.87	70943.388	537		/FOXD4L5/FOXD4L4/FOXD4L2/CBWD3/CBWD5/FOXD4L3/PGM5/C9orf71/PIP5K1B/FAM122A
Down-SNP-#17	17	p13.3	0.394414	0.407266	1.16	12.852	1		/VPS53
Down-SNP-#18	none								
Down-SNP-#19	1	p31.3	65.178977	65.18465	0.9	5.673	1		/JAK1
Down-SNP-#19	3	q26.32	178.299328	178.395593	1.07	96.265	1		/TBL1XR1
Down-SNP-#19	6	p25.3-p22.1	0.094649	28.018718	2.3	27924.069	184		/DUSP22/IRF4/EXOC2/HUS1B/FOXQ1/FOXF2/FOXC1/GMDS/C6orf195/MYLK4
Down-SNP-#19	6	p22.1	28.023292	28.110942	1.24	87.65	1		/OR2B6
Down-SNP-#19	6	p22.1	28.110943	35	2.3	6889.057			manual
Down-SNP-#19	9	q32	114.29217	114.513389	1.06	221.219	2		/KIAA1958/C9orf80
Down-SNP-#19	11	p12	36.578171	36.595168	0.94	16.997	1		/C11orf74
Down-SNP-#19	15	q14;q15.1;q15.2	35.098273	40.994899	1.2	5896.626	68		/MEIS2/TMCO5/SPRED1/FAM98B/RASGRP1/C15orf53/C15orf54/THBS1/FSIP1/GPR176
Down-SNP-#19	15	q21.1	44.974225	45.295558	2.97	321.333	0		
Down-SNP-#19	15	q24.1-q26.3	70.658668	100.286551	1.21	29627.883	203		/ARIH1/GOLGA6B/BBS4/ADPGK/NEO1/HCN4/LOC283677/NPTN/CD276/LOC388135
Down-SNP-#19	20	q11.22	32.856631	32.874454	0.94	17.823	1		/NCOA6
Down-SNP-#19	21	q22.2	38.661535	38.78387	1.38	122.335	1		/ERG
Down-SNP-#19	**X**	**p22.33**	**0.108465**	**2.70424**	**1.07**	**2595.775**	**16**	**PAR1**	**/PLCXD1/GTPBP6/PPP2R3B/SHOX/CRLF2/CSF2RA/IL3RA/SLC25A6/ASMTL/P2RY8**
Down-SNP-#19	X	q12-q28	65.468629	154.58268	3.42	89114.051	370		/EDA2R/AR/OPHN1/YIPF6/STARD8/EFNB1/PJA1/FAM155B/EDA/DGAT2L4
Down-SNP-#19	Y	p11.32-q12	0.169542	57.427794	0.43	57258.252	79		/GTPBP6/PPP2R3B/SHOX/CRLF2/CSF2RA/IL3RA/SLC25A6/ASMTL/P2RY8/SFRS17A
Down-SNP-#20	3	p14.2	60.04165	60.256157	1	214.507	1		/FHIT
Down-SNP-#20	4	p16.3	2.700454	2.744738	2.99	44.284	2		/C4orf8/TNIP2
Down-SNP-#20	4	p16.2	3.849404	4.23695	2.64	387.546	0		
Down-SNP-#20	5	q31.1	130.99968	131.14389	0.98	144.21	1		/FNIP1
Down-SNP-#20	7	p12.2	50.307349	50.3369	0.98	29.551	1		/IKZF1
Down-SNP-#20	12	p13.2	11.743762	11.946702	1.08	202.94	1		/ETV6
Down-SNP-#20	**X**	**p22.33**	**1.4158**	**1.600371**	**1.08**	**184.571**	**4**	**PAR1**	**/IL3RA/SLC25A6/ASMTL/P2RY8**
Down-SNP-#21	2	q14.1	113.881867	113.903417	0.87	21.55	0		
Down-SNP-#21	3	q13.2	113.538286	113.700796	1.11	162.51	2		/CD200/BTLA
Down-SNP-#21	4	q31.21	144.387613	144.475288	0.96	87.675	0		
Down-SNP-#21	5	q33.3	157.733901	158.457083	0.95	723.182	1		/EBF1
Down-SNP-#21	7	p14.3-p12.1	35.583523	51.415691	1.22	15832.168	79		/HERPUD2/SEPT7/LOC641961/EEPD1/KIAA0895/ANLN/AOAH/ELMO1/GPR141/TXNDC3
Down-SNP-#21	15	q12	23.604291	23.654278	0.95	49.987	1		/ATP10A
Down-SNP-#21	15	q26.1	91.179546	91.258898	1.15	79.352	1		/CHD2
Down-SNP-#21	16	p13.3	3.814783	3.9507	0.98	135.917	1		/CREBBP
Down-SNP-#21	16	q21	65.156974	65.189613	0.94	32.639	3		/CKLF/CMTM1/CMTM2
Down-SNP-#21	20	p12.2	10.365404	10.370231	0.65	4.827	1		/C20orf94
Down-SNP-#21	20	p12.2	10.370353	10.399978	1.07	29.625	1		/C20orf94
Down-SNP-#21	20	q11.22	32.856631	32.889861	1.22	33.23	1		/NCOA6
Down-SNP-#21	**X**	**p22.33**	**1.146863**	**1.600371**	**0.96**	**453.508**	**6**	**PAR1**	**/CRLF2/CSF2RA/IL3RA/SLC25A6/ASMTL/P2RY8**
Down-SNP-#21	X	p11.4	40.743819	40.84975	0.87	105.931	1		/USP9X
Down-SNP-#22	5	q22.1	110.329336	110.375277	1.29	45.941	0		
Down-SNP-#22	5	q33.1	150.125632	150.131715	1.04	6.083	0		
Down-SNP-#22	6	p22.1	26.236425	26.358233	0.94	121.808	14		/HIST1H1E/HIST1H2BD/HIST1H2BE/HIST1H4D/HIST1H3D/HIST1H2AD/HIST1H2BF/HIST1H4E/HIST1H2BG/HIST1H2AE
Down-SNP-#22	7	q22.3	106.43767	106.466603	0.75	28.933	0		

Supplementary Table 2

	Chr	cytoband	Start (Mb)	End (Mb)	Copy number	Segment size/d	Number of	Comment	first 10 genes in segment
Down-SNP-#22	8	q24.21	130.624762	130.708986	3.31	84.224	0		
Down-SNP-#22	9	p22.2-p21.3	17.803501	21.809465	1.17	4005.964	21		/MLLT3/KIAA1797/PTPLAD2/IFNB1/IFNW1/IFNA21/IFNA4/IFNA7/IFNA10/IFNA16
Down-SNP-#22	9	p21.3	21.81811	21.995382	0.29	177.272	3		/MTAP/CDKN2A/CDKN2B
Down-SNP-#22	9	p21.3	21.99996	23.575469	1.06	1575.509	1		/DMRTA1
Down-SNP-#22	10	q25.1;q25.2	111.756579	111.858222	0.97	101.643	1		/ADD3
Down-SNP-#22	13	q14.11	42.855073	42.871462	1.03	16.389	1		/ENOX1
Down-SNP-#22	19	q13.12	41.697459	41.709636	0.92	12.177	1		/ZNF260
Down-SNP-#22	**X**	**p22.33**	**1.4158**	**1.600371**	**1.03**	**184.571**	**4**	**PAR1**	**/IL3RA/SLC25A6/ASMTL/P2RY8**
Down-SNP-#22	X	p21.1	33.37474	33.71865	0.46	343.91	0		Adjacent to DMD
Down-SNP-#22	X	q23	115.139163	115.17702	3.98	37.857	0		
Down-SNP-#22	X	q24	118.693816	119.129688	3.51	435.872	11		/SEPT6/ANKRD58/RPL39/UPF3B/RNF113A/NDUFA1/AKAP14/NKAP/RHOXF2B/RHOXF2
Non DS-ALL cases with PAR1 deletions									
Hyperdip47-50-SNP-#18	3	p26.2	3.076	3.337	3.24	261.189	3		/IL5RA/TRNT1/CRBN
Hyperdip47-50-SNP-#18	9	p22.2;p22.1	17.500	19.214	0.99	1714.728	7		/SH3GL2/ADAMTSL1/C9orf94/C9orf138/RRAGA/FAM29A/ADFP
Hyperdip47-50-SNP-#18	9	p22.1;p21.3	19.464	21.169	1.03	1704.905	7		/SLC24A2/MLLT3/KIAA1797/PTPLAD2/IFNB1/IFNW1/IFNA21
Hyperdip47-50-SNP-#18	9	p21.3	21.171	22.375	0.3	1203.735	17		/IFNA4/IFNA14/IFNA7/IFNA10/IFNA16/IFNA17/IFNA5/KLHL9/IFNA6/IFNA13
Hyperdip47-50-SNP-#18	9	p21.3	22.376	23.615	1.03	1239.181	1		/DMRTA1
Hyperdip47-50-SNP-#18	21	p11.2-q22.3	9.888	46.925	3.05	37036.776	241		/TPTE/BAGE5/BAGE3/BAGE4/BAGE2/BAGE/C21orf99/ANKRD21/LOC441956/C21orf81
Hyperdip47-50-SNP-#18	**X**	**p22.33**	**1.549**	**1.709**	**0.84**	**159.268**	**4**	**PAR1**	**/SLC25A6/CXYorf2/ASMTL/P2RY8**
Hyperdip47-50-SNP-#22	9	p21.3	21.169	24.819	0.16	3650.134	19		/IFNA4/IFNA14/IFNA7/IFNA10/IFNA16/IFNA17/IFNA5/KLHL9/IFNA6/IFNA13
Hyperdip47-50-SNP-#22	20	p12.2	10.376	10.405	0.78	28.63	1		/C20orf94
Hyperdip47-50-SNP-#22	22	q11.22	21.054	21.547	0.9	492.964	5		/SUHW2/SUHW1/PRAME/LOC440821/GGTL4
Hyperdip47-50-SNP-#22	X	p22.33	0.034	1.017	3.55	982.145	4		/PLCXD1/GTPBP6/PPP2R3B/SHOX
Hyperdip47-50-SNP-#22	**X**	**p22.33**	**1.499**	**1.683**	**1.01**	**183.82**	**5**	**PAR1**	**/IL3RA/SLC25A6/CXYorf2/ASMTL/P2RY8**
Hyperdip47-50-SNP-#22	X	p22.33	1.709	2.681	3.49	972.09	5		/RP13-297E16.1/ASMT/ZBED1/CD99/XG
Hyperdip47-50-SNP-#22	X	p22.33-q28	2.682	154.480	4.62	151753.126	734		/XG/GYG2/ARSD/ARSE/ARSH/ARSF/MXRA5/PRKX/NLGN4X/VCX3A
Hypodip-SNP-#4	3	p22.3	35.658	35.692	0.87	34.032	1		/ARPP-21
Hypodip-SNP-#4	8	p23.3-p21.2	0.181	27.322	1.23	27141.029	135		/ZNF596/FBXO25/C8orf42/LOC389607/ERICH1/DLGAP2/CLN8/ARHGEF10/KBTBD11/MYOM2
Hypodip-SNP-#4	9	p24.3-p21.3	0.177	21.884	0.87	21707.696	82		/C9orf66/DOCK8/ANKRD15/DMRT1/DMRT3/DMRT2/SMARCA2/VLDLR/KCNV2/KIAA0020
Hypodip-SNP-#4	9	p21.3	21.884	21.995	0.16	110.835	2		/CDKN2A/CDKN2B
Hypodip-SNP-#4	9	p21.3-p13.1	22.000	40.073	0.88	18073.235	103		/DMRTA1/ELAVL2/TUSC1/C9orf82/PLAA/IFT74/LRRC19/TEK/C9orf11/MOBKL2B
Hypodip-SNP-#4	20	q11.22-q13.33	31.727	62.377	0.89	30650.337	301		/E2F1/PXMP4/ZNF341/CHMP4B/RALY/EIF2S2/ASIP/AHCY/ITCH/DYNLRB1
Hypodip-SNP-#4	X	q25-q28	122.894	154.480	2.84	31585.645	202		/STAG2/SH2D1A/ODZ1/WDR40C/WDR40B/ACTRT1/SMARCA1/OCRL/APLN/XPNPEP2
Hypodip-SNP-#4	**X**	**p22.33**	**1.499**	**1.642**	**0.95**	**142.11**	**5**	**PAR1**	**/IL3RA/SLC25A6/CXYorf2/ASMTL/P2RY8**
Hypodip-SNP-#9	7	q21.2	91.933	92.109	0.91	175.77	1		/CDK6
Hypodip-SNP-#9	9	p21.3	21.097	21.884	0.94	787.169	17		/IFNW1/IFNA21/IFNA4/IFNA14/IFNA7/IFNA10/IFNA16/IFNA17/IFNA5/KLHL9
Hypodip-SNP-#9	9	p21.3	21.899	21.995	0.18	96.33	2		/CDKN2A/CDKN2B
Hypodip-SNP-#9	9	p21.3-p13.1	22.000	40.073	0.92	18073.235	103		/DMRTA1/ELAVL2/TUSC1/C9orf82/PLAA/IFT74/LRRC19/TEK/C9orf11/MOBKL2B
Hypodip-SNP-#9	12	q14.1	61.320	61.373	0.8	52.455	0		

Supplementary Table 2

	Chr	cytoband	Start (Mb)	End (Mb)	Copy number	Segment size/c	Number of	Comment	first 10 genes in segment
Hypodip-SNP-#9	14	q32.2-q32.33	100.249	106.356	0.92	5810.355	54		/DLK1/FLJ41170/DIO3/PPP2R5C/DYNC1H1/HSP90AA1/WDR20/RAGE/C14orf131/CINP
Hypodip-SNP-#9	20	q11.22;q13.33	32.687	62.377	0.93	29676.494	291		/CDC91L1/TP53INP2/NCOA6/GGTL3/ACSS2/GSS/MYH7B/TRPC4AP/EDEM2/PROCR
Hypodip-SNP-#9	22	q11.22	20.711	20.741	0.51	30.23	0		
Hypodip-SNP-#9	**X**	**p22.33**	**1.499**	**1.642**	**0.95**	**142.11**	**5**		**/IL3RA/SLC25A6/CXYorf2/ASMTL/P2RY8**
Hyperdip47-50-SNP-#2	3	q13.2	113.342	113.404	4.37	62.7	1		/SLC9A10
Hyperdip47-50-SNP-#2	6	p22.2	26.246	26.398	1.06	151.999	19		/HIST1H1E/HIST1H2BD/HIST1H2BE/HIST1H4D/HIST1H3D/HIST1H2AD/HIST1H2BF/HIST1H4E/HIST1H2BG/HIST1H2AE
Hyperdip47-50-SNP-#2	9	p21.3	21.920	21.949	0.92	28.858	0		
Hyperdip47-50-SNP-#2	9	p21.3	21.959	21.995	0.33	36.618	2		/CDKN2A/CDKN2B
Hyperdip47-50-SNP-#2	9	p21.3	22.000	23.204	1.23	1204.4	1		/DMRTA1
Hyperdip47-50-SNP-#2	21	p11.2-q21.2	9.888	24.291	2.34	14403.122	26		/TPTE/BAGE4/BAGE3/BAGE2/BAGE5/BAGE/C21orf99/ANKRD21/LOC441956/C21orf81
Hyperdip47-50-SNP-#2	21	q21.2-q22.3	24.292	46.925	3.2	22562.063	217		/FLJ42200
Hyperdip47-50-SNP-#2	X	p22.33	0.034	0.993	3.04	958.531	4		/PLCXD1/GTPBP6/PPP2R3B/SHOX
Hyperdip47-50-SNP-#2	**X**	**p22.33**	**1.017**	**1.644**	**1.58**	**627.098**	**6**	**PAR1**	**/CSF2RA/IL3RA/SLC25A6/CXYorf2/ASMTL/P2RY8**
Hyperdip47-50-SNP-#2	X	p22.33-q28	138.434	2.729	4.32	152768.185	740		/P2RY8/RP13-297E16.1/ASMT/ZBED1/CD99/XG
Other-SNP-#13	**X**	**p22.33**	**1.499**	**1.644**	**1.08**	**144.196**	**5**	**PAR1**	**/IL3RA/SLC25A6/CXYorf2/ASMTL/P2RY8**
Other-SNP-#32	1	q21.3	148.607422	148.687165	1.17	79.743	3		/RORC/THEM5/THEM4
Other-SNP-#32	8	p23.3	0.021242	32.488584	1.39	32467.342	2		/OR4F21/OR4F29
Other-SNP-#32	8	p12	32.488768	38.144504	2.56	5655.736	20		/NRG1/FUT10/RBM13/C8orf41/RNF122/DUSP26/UNC5D/FKSG2/ZNF703/SPFH2
Other-SNP-#32	8	p12	38.147352	38.235854	4.19	88.502	3		/LSM1/BAG4/DDHD2
Other-SNP-#32	8	p12	38.236926	38.287512	5.22	50.586	3		/DDHD2/PPAPDC1B/WHSC1L1
Other-SNP-#32	8	p12	38.289666	38.440573	16.13	150.907	3		/WHSC1L1/LETM2/FGFR1
Other-SNP-#32	8	p12;p11.23	38.440583	38.82225	9.27	381.667	3		/FGFR1/FLJ43582/TACC1
Other-SNP-#32	10	p15.3;p15.2	0.094186	39.110664	2.89	3095.969	13		/ZMYND11/DIP2C/C10orf108/LARP5/GTPBP4/IDI2/C10orf110/IDI1/WDR37/LOC399706
Other-SNP-#32	10	q11.1;q11.21	41.753746	55.254916	1.24	2236.936	10		/MGC16291/BMS1L/RET/GALNACT-2/RASGEF1A/FXYD4/HNRPF/ZNF239/ZNF485/ZNF32
Other-SNP-#32	10	q21.1	55.458808	57.837471	1.32	2378.663	2		/PCDH15/ZWINT
Other-SNP-#32	11	q12.1-q13.3	58.815689	80.593158	2.73	10168.554	272		/OR5AN1/OR5A2/OR5A1/OR4D6/OR4D10/OR4D11/OR4D9/OSBP/FLJ36874/OR10V1
Other-SNP-#32	11	q14.1;q14.2	84.791643	86.510654	4.17	1719.011	14		/TMEM126B/TMEM126A/ZF/CCDC89/SYTL2/CCDC83/PICALM/EED/C11orf73/CCDC81
Other-SNP-#32	11	q14.2	86.720887	87.438288	1.28	717.401	0		
Other-SNP-#32	11	q14.2;q14.3	87.440907	87.829795	4.08	388.888	2		/RAB38/CTSC
Other-SNP-#32	11	q14.3	87.830085	87.888766	6.64	58.681	1		/GRM5
Other-SNP-#32	11	q14.3	87.890522	89.588148	2.74	1697.626	7		/GRM5/TYR/NOX4/PSMAL/TRIM49/NAALAD2/CHORDC1
Other-SNP-#32	11	q14.3	89.588745	89.661434	4.15	72.689	1		/CHORDC1
Other-SNP-#32	11	q14.3	89.661644	90.317354	2.93	655.71	0		
Other-SNP-#32	11	q14.3	90.317539	90.44351	3.54	125.971	0		
Other-SNP-#32	11	q14.3	90.446278	90.977112	2.89	530.834	0		
Other-SNP-#32	11	q14.3	90.985235	91.86897	6.5	883.735	1		/FAT3
Other-SNP-#32	11	q14.3;q21	91.869121	93.982215	7.64	2113.094	14		/FAT3/MTNR1B/SLC36A4/CCDC67/C11orf75/JOSD3/C11orf54/CRSP6/PANX1/GPR83
Other-SNP-#32	11	q21	93.982386	93.994962	5.04	12.576	1		/PIWIL4
Other-SNP-#32	11	q21	93.994986	94.860626	6.91	865.64	5		/AMOTL1/HSPC148/JMJD2D/SFRS2B/SESN3
Other-SNP-#32	11	q21	94.862022	94.875384	3.97	13.362	0		
Other-SNP-#32	11	q21	94.875739	96.244581	7.22	1368.842	6		/FAM76B/CEP57/MTMR2/MAML2/CCDC82/JRKL
Other-SNP-#32	11	q21	96.24726	96.319422	5.01	72.162	0		
Other-SNP-#32	11	q21;q22.1	96.31993	97.747591	3.57	1427.661	0		
Other-SNP-#32	11	q22.1	97.748441	97.766841	5.49	18.4	0		
Other-SNP-#32	11	q22.1	97.767331	97.856295	3.66	88.964	0		
Other-SNP-#32	11	q22.1	97.857768	98.824357	2.79	966.589	1		/CNTN5

Supplementary Table 2

	Chr	cytoband	Start (Mb)	End (Mb)	Copy number	Segment size/c	Number of	Comment	first 10 genes in segment
Other-SNP-#32	11	q22.1	98.826592	98.864482	3.77	37.89	1		/CNTN5
Other-SNP-#32	11	q22.1	98.864909	99.122339	5.07	257.43	1		/CNTN5
Other-SNP-#32	11	q22.1	99.12685	100.400665	2.82	1273.815	2		/CNTN5/TMEM133
Other-SNP-#32	11	q22.1	100.408204	100.47693	5.16	68.726	1		/PGR
Other-SNP-#32	11	q22.1	100.478901	101.12266	3.52	643.759	2		/PGR/TRPC6
Other-SNP-#32	11	q22.1;q22.2	101.130121	102.078038	5.72	947.917	10		/ANGPTL5/KIAA1377/C11orf70/YAP1/BIRC3/BIRC2/TMEM123/MMP7/MMP20/MMP27
Other-SNP-#32	11	q22.2;q22.3	102.078527	103.894288	3.63	1815.761	10		/MMP27/MMP8/MMP10/MMP1/MMP3/MMP12/MMP13/DCUN1D5/PDGFD/DDI1
Other-SNP-#32	11	q22.3-q23.3	103.89707	120.050081	1.26	16153.011	140		/CASP4/CASP5/CASP1/COP1/INCA/ICEBERG/GRIA4/KIAA1826/KBTBD3/AASDHPPT
Other-SNP-#32	11	q23.3	120.051021	120.088304	0.89	37.283	1		/GRIK4
Other-SNP-#32	11	q23.3-q25	120.089019	134.449982	1.27	14360.963	103		/GRIK4/LRRC35/TECTA/SC5DL/SORL1/BRCC2/STS-1/CRTAM/C11orf63/HSPA8
Other-SNP-#32	12	p12.1	24.989577	25.95285	2.31	143.05	2		/BCAT1/LRMP
Other-SNP-#32	12	q21.33	90.798986	91.057747	1.23	258.761	1		/BTG1
Other-SNP-#32	13	q12.13	24.401836	24.628496	2.34	226.66	1		/PABPC3
Other-SNP-#32	13	q12.13	24.634281	24.682233	3.76	47.952	1		/FAM123A
Other-SNP-#32	13	q12.13	24.682362	24.75588	5.05	73.518	1		/MTMR6
Other-SNP-#32	13	q12.13	24.763063	24.773094	3.21	10.031	0		
Other-SNP-#32	13	q12.13	24.774011	25.090118	2.4	316.107	3		/NUPL1/FLJ37464/ATP8A2
Other-SNP-#32	13	q12.13	25.090407	25.952066	2.89	861.659	4		/ATP8A2/TMEM46/RNF6/CDK8
Other-SNP-#32	13	q12.13	25.952102	26.201847	4.21	249.745	1		/WASF3
Other-SNP-#32	13	q12.13	26.201907	26.501264	5.19	299.357	1		/GPR12
Other-SNP-#32	13	q12.13;q12.2	26.501371	27.786786	7	1285.415	13		/USP12/RPL21/RASL11A/GTF3A/MTIF3/LNX2/POLR1D/GSH1/IPF1/CDX2
Other-SNP-#32	13	q12.2;q12.3	27.787089	27.8954	2.75	108.311	1		/FLT1
Other-SNP-#32	13	q12.3	29.18191	114.126487	1.36	657.895	3		/UBL3/LOC440131/KATNAL1
Other-SNP-#32	14	q32.12-q32.33	92.248093	106.356482	1.27	13245.226	116		/LGMN/GOLGA5/CHGA/ITPK1/MOAP1/C14orf142/C14orf130/BTBD7/KIAA1409/COX8C
Other-SNP-#32	15	q14	31.887896	32.139214	1.26	251.318	3		/RYR3/AVEN/CHRM5
Other-SNP-#32	15	q21.1	46.716087	47.305471	5.38	589.384	7		/FBN1/CEP152/SHC4/CRI1/KIAA0256/COPS2/GALK2
Other-SNP-#32	15	q21.1;q21.2	47.308906	48.456009	2.65	1147.103	8		/GALK2/C15orf33/FGF7/DTWD1/ATP8B4/SLC27A2/HDC/GABPB2
Other-SNP-#32	15	q21.2	48.464801	48.573316	7.82	108.515	1		/USP8
Other-SNP-#32	15	q21.2	48.575332	48.900363	5.67	325.031	4		/USP8/USP50/TRPM7/SPPL2A
Other-SNP-#32	15	q21.2;q21.3	48.900364	52.202732	7.74	3302.368	19		/AP4E1/TNFAIP8L3/CYP19A1/GLDN/DMXL2/SCG3/LYSMD2/TMOD2/TMOD3/LEO1
Other-SNP-#32	15	q21.3	52.20348	52.817899	5.83	614.419	0		
Other-SNP-#32	15	q21.3	52.826687	53.174035	4.15	347.348	0		
Other-SNP-#32	15	q21.3	53.174884	55.815528	1.24	2640.644	15		/C15orf15/RAB27A/PIGB/CCPG1/DYX1C1/PYGO1/NEDD4/RFXDC2/TEX9/MNS1
Other-SNP-#32	15	q21.3	55.815617	55.898043	2.75	82.426	0		
Other-SNP-#32	15	q21.3	55.89999	56.2663	0.57	366.31	2		/ALDH1A2/AQP9
Other-SNP-#32	15	q21.3;q22.1;q22.2	56.534122	60.047371	3.48	3513.249	17		/LIPC/ADAM10/FAM63B/SLTM/RNF111/CCNB2/MYO1E/LDHAL6B/FAM81A/GCNT3
Other-SNP-#32	15	q22.2;q22.31	60.144866	64.029559	4.22	3884.693	43		/NLF1/NLF2/FLJ38723/TLN2/TPM1/LACTB/RPS27L/RAB8B/APH1B/CA12
Other-SNP-#32	15	q22.31	64.030747	64.6954	3.39	664.653	8		/MEGF11/MGC4562/TIPIN/MAP2K1/SNAPC5/RPL4/ZWILCH/LCTL
Other-SNP-#32	15	q22.31	64.696178	64.714182	5.84	18.004	0		
Other-SNP-#32	15	q22.31	64.715523	64.746565	3.87	31.042	0		
Other-SNP-#32	15	q22.31;q22.32;q22.33	64.747506	65.003881	5.29	256.375	1		/SMAD6
Other-SNP-#32	15	q22.33;q23	65.004948	67.441701	5.68	2436.753	16		/SMAD3/FLJ11506/IQCH/MAP2K5/PIAS1/CALML4/CLN6/FEM1B/ITGA11/CORO2B
Other-SNP-#32	15	q23	67.442085	70.019286	3.57	2577.201	11		/PAQR5/KIF23/RPLP1/TLE3/UACA/LARP6/THAP10/LRRC49/THSD4/NR2E3
Other-SNP-#32	15	q23;q24.1	70.019574	72.099847	1.22	2080.273	20		/MYO9A/SENP8/GRAMD2/PKM2/PARP6/BRUNOL6/HEXA/ARIH1/GOLGA/HIGD2BP
Other-SNP-#32	15	q24.1	72.101014	72.101501	2.3	0.487	1		/PML

Supplementary Table 2

	Chr	cytoband	Start (Mb)	End (Mb)	Copy number	Segment size/d	Number of	Comment	first 10 genes in segment
Other-SNP-#32	15	q24.1;q24.2;q24.3	72.101689	80.133553	1.22	2563.728	41		/PML/ISLR2/ISLR/STRA6/CCDC33/CYP11A1/SEMA7A/UBL7/ARID3B/CLK3
Other-SNP-#32	15	q25.2	80.138907	80.368482	3.39	229.575	2		/EFTUD1/DKFZp666G057
Other-SNP-#32	15	q25.2;q25.3	80.369473	84.208312	2.67	3838.839	29		/FLJ22795/FLJ40113/RPS17/CPEB1/AP3B2/FSD2/HOMER2/FAM103A1/C15orf40/BTBD1
Other-SNP-#32	15	q25.3-q26.3	84.214887	98.631363	1.26	14416.476	65		/FLJ32310/TMEM83/NTRK3/MRPL46/MRPS11/DET1/ISG20L1/ISG20/AGC1/HAPLN3
Other-SNP-#32	15	q26.3	98.634908	100.246564	2.79	1611.656	16		/ADAMTS17/FLJ42289/LASS3/LINS1/ASB7/LOC440313/ALDH1A3/LRRK1/CHSY1/SELS
Other-SNP-#32	21	q21.1	18.372738	18.854924	4.52	482.186	2	Complex iAmp 21	/CHODL/PRSS7
Other-SNP-#32	21	q21.1	19.034311	19.106129	2.94	71.818	0		
Other-SNP-#32	21	q21.1	19.130602	19.201491	2.92	70.889	0		
Other-SNP-#32	21	q21.1	19.230876	19.29514	4.81	64.264	0		
Other-SNP-#32	21	q21.1	19.295812	19.84108	6.71	545.268	0		
Other-SNP-#32	21	q21.1	19.847751	20.030757	4.17	183.006	0		
Other-SNP-#32	21	q21.1	20.172123	20.58487	4.49	412.747	0		
Other-SNP-#32	21	q21.1	20.585415	20.895675	6.17	310.26	0		
Other-SNP-#32	21	q21.1	20.898984	21.044364	4.39	145.38	0		
Other-SNP-#32	21	q21.1	21.197367	21.830427	5.22	633.06	1		/NCAM2
Other-SNP-#32	21	q21.1	21.832254	22.371716	2.87	539.462	1		/NCAM2
Other-SNP-#32	21	q21.1;q21.2	22.371856	22.921577	3.69	549.721	0		
Other-SNP-#32	21	q21.2	22.924311	23.000812	5.07	76.501	0		
Other-SNP-#32	21	q21.2	23.003425	23.040608	3.61	37.183	0		
Other-SNP-#32	21	q21.2	23.042731	23.288037	2.94	245.306	0		
Other-SNP-#32	21	q21.2	23.294962	24.919149	3.86	1624.187	1		/FLJ42200
Other-SNP-#32	21	q21.2;q21.3	24.922861	26.477119	2.85	1554.258	6		/C21orf42/MRPL39/JAM2/ATP5J/GABPA/APP
Other-SNP-#32	21	q21.3	26.479695	26.930037	3.59	450.342	1		/CYYR1
Other-SNP-#32	21	q21.3	26.932654	27.18724	2.82	254.586	1		/ADAMTS1
Other-SNP-#32	21	q21.3	27.187712	27.248474	3.75	60.762	1		/ADAMTS5
Other-SNP-#32	21	q21.3	27.252427	28.290404	2.78	1037.977	1		/ADAMTS5
Other-SNP-#32	21	q21.3	28.293594	28.355208	4.16	61.614	1		/C21orf94
Other-SNP-#32	21	q21.3	28.355425	28.640244	5.09	284.819	0		
Other-SNP-#32	21	q21.3	28.640819	29.480084	5.76	839.265	7		/C21orf100/HEMK2/ZNF294/C21orf6/USP16/CCT8/C21orf7
Other-SNP-#32	21	q21.3	29.482364	30.401723	5.11	919.359	2		/BACH1/GRIK1
Other-SNP-#32	21	q21.3;q22.11	30.403947	30.52019	4.06	116.243	2		/CLDN17/CLDN8
Other-SNP-#32	21	q22.11	30.521327	30.557323	5.12	35.996	0		
Other-SNP-#32	21	q22.11	30.557833	31.065594	7.31	507.761	22		/KRTAP26-1/KRTAP23-1/KRTAP13-2/KRTAP13-1/KRTAP13-3/KRTAP13-4/KRTAP15-1/KRTAP19-1/KRTAP19-2/KRTAP19-3
Other-SNP-#32	21	q22.11	31.0702	31.149893	6.74	79.693	1		/KRTAP8-1
Other-SNP-#32	21	q22.11	31.1522	31.225104	4.24	72.904	1		/KRTAP11-1
Other-SNP-#32	21	q22.11	31.228572	31.343712	5.96	115.14	1		/TIAM1
Other-SNP-#32	21	q22.11	31.345343	31.354033	10.58	8.69	1		/TIAM1
Other-SNP-#32	21	q22.11	31.354121	31.847052	6.74	492.931	1		/TIAM1
Other-SNP-#32	21	q22.11	31.849901	31.877856	9.27	27.955	1		/TIAM1
Other-SNP-#32	21	q22.11;q22.12	31.879105	34.832151	6.17	2953.046	35		/SOD1/SFRS15/HUNK/C21orf45/MRAP/C21orf119/C21orf63/C21orf77/TCP10L/C21orf59
Other-SNP-#32	21	q22.12	34.836944	34.846753	3.49	9.809	1		/DSCR1
Other-SNP-#32	21	q22.12;q22.13;q22.2	34.848309	39.104047	6.38	4255.738	26		/DSCR1/CLIC6/RUNX1/SETD4/CBR1/CBR3/DOPEY2/MORC3/CHAF1B/CLDN14
Other-SNP-#32	21	q22.2	39.112379	39.887215	6.11	774.836	8		/ETS2/FLJ45139/DSCR2/BRWD1/HMGN1/WRB/C21orf13/SH3BGR
Other-SNP-#32	21	q22.2	39.8876	40.481842	8.3	594.242	4		/C21orf88/B3GALT5/PCP4/DSCAM
Other-SNP-#32	21	q22.2	40.482235	40.588759	5.75	106.524	1		/DSCAM
Other-SNP-#32	21	q22.2	40.589924	40.750359	3.53	160.435	1		/DSCAM
Other-SNP-#32	21	q22.2	40.751661	41.172018	1.35	420.357	1		/DSCAM
Other-SNP-#32	21	q22.2;q22.3	41.173131	41.456318	2.94	283.187	0		

Supplementary Table 2

	Chr	cytoband	Start (Mb)	End (Mb)	Copy number	Segment size/c	Number of	Comment	first 10 genes in segment
Other-SNP-#32	21	q22.3	41.457718	46.921373	3.54	5463.655	97		/BACE2/PLAC4/FAM3B/MX2/MX1/TMPRSS2/C21orf129/RIPK4/PRDM15/C21orf25
Other-SNP-#32	**X**	**p22.33**	**1.146863**	**1.600371**	**1.26**	**453.508**	**5**	**PAR1**	**/CSF2RA/IL3RA/SLC25A6/CXYorf2/ASMTL**
Other-SNP-#32	X	q26.3-q28	137.114639	154.729057	2.65	17614.418	138		/FGF13/F9/MCF2/ATP11C/RP11-35F15.2/SOX3/CDR1/SPANXB2/SPANXB1/LDOC1

Supplementary Table 3

Results for PAR1 deletion status (by SNP array analysis and genomic PCR mapping), *P2RY8-CRLF2* RT-PCR, JAK mutation status and karyotype for all St Jude DS-ALL cases, and non-DS St Jude cases with PAR1 deletion. FISH, fluorescence *in situ* hybridization; NA, no material available for testing; Neg, negative; Pos, positive.

Sample	Down syndrome	JAK mutation	PAR1 deletion	Mapping PCR	P2RY8-CRLF2 RT-PCR	*IGH@-CRLF2* translocation (FISH)	Karyotype
Hyperdip>50-SNP-#33	Yes	R683G	Yes	Pos	Pos	NA	53,XX,+X,+4,+14,+15,+17,+21,+21c[15]/47,XX,+21c[5]
TEL-AML1-SNP-#43	Yes	None	No	Neg	Neg	NA	47,XY,+21c. ish t(12;21)(p13;q22)(wcp21+;wcp12+)
Hyperdip47-50-SNP-#19	Yes	None	No	Neg	Neg	Neg	47,XY,add(9)(p13),+21c[10]/47,XY,+21c[15]
Hyperdip47-50-SNP-#8	Yes	None	Yes	Pos	Pos	NA	47,XY,+21c[12]
Hyperdip47-50-SNP-#12	Yes	R683G	Yes	Pos	Pos	Neg	48,XY,+X,+21c[11]/47,XY,+21c[9]
Hyperdip47-50-SNP-#14	Yes	None	Yes	Pos	Pos	NA	48,XY,+X,add(1)(q44),+21c[9]/47,XY,+21c[11]
Hyperdip47-50-SNP-#15	Yes	None	Yes	Pos	Pos	Neg	48,XX,+X,+21c[7]/48,idem,i(17)(q10)[4]/47,XX,+21c[9]
Other-SNP-#33	Yes	None	Yes	Pos	Pos	NA	47,XX,del(9)(p22),+21c[8]/47,XX,add(9)(p23),+21c[5]/47,XX,+21c[7]
Down-SNP-#09	Yes	IR682RG	Yes	Pos	Pos	Neg	48,XY,+X,+21c[20]
Down-SNP-#10	Yes	None	No	Neg	Neg	Neg	46,XX,-7,i(9)(q10),+21c[9]/46,idem,-3,der(12)t(3;12)(p13;p13),+mar[4]
Down-SNP-#11	Yes	None	No	Neg	Neg	NA	47,XY,+21c[8]
Down-SNP-#12	Yes	None	No	Neg	Neg	NA	48,XY,+6,del(6)(q15q21),del(13)(q22q32),+21c[5]/47,XY,+21c[15]
Down-SNP-#13	Yes	None	No	Neg	Neg	Neg	47,XX,+21c[35]
Down-SNP-#14	Yes	R683S	No	Neg	Neg	Pos	46,XY,der(21;21)(q10;q10)c[24]
Down-SNP-#15	Yes	R683G	Yes	Pos	Pos	Neg	48,XX,+X,t(7;8)(p15;p23),+21c[3]/47,XX,+21c[11]
Down-SNP-#16	Yes	None	Yes	Pos	Pos	Neg	48,XY,+X,+21c[20]
Down-SNP-#17	Yes	None	No	Neg	Neg	Neg	46,XX,i(9)(q10),i(21)(q10)c[6]/46,XX,i(21)(q10)c[14]
Down-SNP-#18	Yes	None	No	Neg	Neg	Neg	47,XX,t(14;19)(q32;q13.1),+21c[24]. nuc ish (IGHx2)(5'IGH con 3'IGHx1)
Down-SNP-#19	Yes	None	No	Neg	Neg	Neg	48,XY,+21,+21c[2]/47,XY,+21c[11]
Down-SNP-#20	Yes	None	Yes	Pos	Pos	Neg	47,XX,+21c[20]
Down-SNP-#21	Yes	None	Yes	Pos	Pos	Neg	47,XX,del(7)(p13p15),+21c[20]
Down-SNP-#22	Yes	None	Yes	Pos	Pos	Neg	47,XY,del(9)(p13p22),+21c[12]/47,XY,+21c[12]

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Sample	Down syndrome	JAK mutation	PAR1 deletion	Mapping PCR	P2RY8-CRLF2 RT-PCR	*IGH@-CRLF2* translocation (FISH)	Karyotype
Hyperdip47-50-SNP-#18	No	R683G	Yes	Pos	Pos	NA	47,XY,+21[8]/46,XY[17]
Hyperdip47-50-SNP-#22	No	T875N	Yes	Pos	Pos	NA	47,XY,+X[14]/46,XY[11]
Hypodip-SNP-#4	No	None	Yes	NA	NA	Neg	45,XX,dic(9;20)(p11;q11.2)[15]
Hypodip-SNP-#9	No	None	Yes	Pos	Pos	Neg	45,XX,dic(9;20)(p11;q11.2),add(11)(q24),der(14)t(11;14)(q23-24;q32)[15]/46,XX[1]
Hyperdip47-50-SNP-#2	No	R683S	Yes	Pos	Pos	NA	47,XY,idic(21)(q22),+mar[10]/46,XY[5]
Other-SNP-#13D	No	None	Yes	Pos	Pos	NA	46,XY[20]
Other-SNP-#32	No	None	Yes	Pos	Pos	Neg	46,XX,-8,-10,add(11)(q23),del(13)(q?22),add(14)(q32),-15,-15,add(21)(q22),-22,-22,+6mar[6]/46,XX[1]

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Supplementary Table 4

Genomic quantitative PCR of genes in and flanking the PAR1 deletion. *CSF2RA* and *IL3RA* lie within the region of deletion; *CRLF2* and *SHOX* lie outside (telomeric) of the region of deletion. The assays and analysis were performed as previously described[3]. These results confirm the presence of the deletions and indicate that *CRLF2* lies outside the region of deletion. Values represent ratios of test to control (RNAse P). Values of less than 0.70 (bold) represent hemizygous deletion.

Case	***SHOX***	***CRLF2***	***CSF2RA***	***IL3RA***	**Comment**
Other-#33	1.11	0.99	**0.36**	**0.47**	PAR1 deletion
H47-#12	1.83	1.57	**0.43**	**0.67**	PAR1 deletion
H47-#14	1.85	1.67	**0.43**	**0.45**	PAR1 deletion with flanking +X
Down-#09	2.59	1.96	**0.50**	**0.48**	PAR1 deletion with flanking +X
Down-#10	0.88	0.93	1.06	0.94	No deletion
Down-#11	1.23	0.85	0.76	0.96	No deletion

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Supplementary Table 5

B-progenitor DS-ALL cases studied in the validation cohort. PAR1 deletion status was defined by genomic PCR and sequencing. *CRLF2* expression is log_2ratio gene expression from Affymetrix U133 PLus 2.0 microarrays. *t(1;19) *[TCF3-PBX1]*

Case	PAR1 deletion	P2RY8-CRLF2 RT-PCR	JAK2 mutation	*CRLF2* expression	Karyotype comment
01	yes		No		47,XY, i(17), +21c
02	yes		No		unavailable
03	no		No		47,XX,+21c
04	no		No		47,XY,t(8;14)(q11.2,q32),add(9)(p13),+21c[6]/47,XY,+21c[4]
05	yes		No		47,XX,+21c
06	no		No		48,XX,+X,+21c[11]/47,XX,+21c[4]
07	yes		No		unavailable
08	no		No		47,XX,+21c[15]
09	yes		R683G		47,XX,+21[8]/46,XX[6]
10	yes		No		47,XX,i(9)(q10),add(21)(p11.2),+21c[cp6]/47,XX,+21c[19]
11	yes		No		unavailable
12	no		No	4.17	47,XX,der(14)t(2;14)(q21;q32),+21c[4]/48,idem,+X[4]/47,XX,+21c[14]
13	no		R683G		unavailable
14	no		No	3.26	47,XX,+21c[20]
15	no		No		unavailable
16	yes	positive	R683G	7.99	47,XY,+21c[20]
17	yes		R683S		48,XX,+del(X)(q24),+21c[12]/47,XX,+21c[10]
18	yes	positive	R683S	7.69	47,XY,add(15)(q26),+21c[3]/47,XY,+21c[17]
19	no		No	4.41	unavailable
20	no		No	3.44	47,XY,+21c[20]
21	no		No	3.62	unavailable
22	no		No	3.55	48,XY,-13,+20,+21c,+21[7]/47,XY,+21c[4]
23	no		No	3.65	56,XY,+X,+4,+6,+8,+10,+14,+17,+18,+21c,+21[2]/47,XY,+21c[16]
24	no		No	3.59	47,XX,+21c[20]
25	no		No		47,XY,+21c[16]
26	no		No	3.18	48,XX,+X,t(8;14)(q11.2;q32),+21[17]
27	no		No	3.29	unavailable
28	no		No	3.61	56,XX,+X,+4,+10,+14,+14,+17,del(17)(p12),+18,+21c,+21,+21[9]/47,XX,+21c[6]
29	yes	positive	R683S		unavailable

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Case	PAR1 deletion	P2RY8-CRLF2 RT-PCR	JAK2 mutation	*CRLF2* expression	Karyotype comment
30	yes	positive	No	7.70	unavailable
31	yes		No		47,XY,+21c[20]
32	yes	positive	No	7.26	unavailable
33*	no		No	2.96	46,XX,t(1;19)(q23;p13.3),rob(14;21)(q10;q10)c,+21c[3]/46,idem,add(9)(p12),del(13)(q21 q34)[4]/46,XX,rob(14;21)(q10;q10)c,+21c[15]
34	yes	positive	No	7.22	47XY,+21c
35	no		No		unavailable
36	yes		No		unavailable
37	yes		No		unavailable
38	yes		No		unavailable
39	no		No		unavailable
40	yes		R683G		unavailable
41	yes		No		unavailable
42	yes		R683T		unavailable
43	no		No		47XX,t(7;11)(p22;q23),+21c
44	no		No	3.45	47XX,t(8;14)(p11.2;q32),+21c/47,XX,+21c
45	no	negative	No		47XY,+21c
46	yes	negative	No	9.11	unavailable
47	yes	positive	No	7.07	48XY,+X,+21c[5]/47,XY,+21c[13]
48	yes		No		unavailable
49	yes	positive	R683K	7.24	unavailable
50	no		No		unavailable
51	yes	positive	No	6.05	unavailable
52	yes		No		unavailable
53	yes	positive	No	7.06	48,XX,r(10)(p15q26),+21c,+21[11]/47,XX,+21c[9]

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Supplementary Table 6

Sequences of primers used for JAK sequencing, amplification of *P2RY8-CRLF2,* real-time PCR of *P2RY8-CRLF2* and PAR1 deletion mapping. Genomic DNA for JAK1 exons 13 and JAK2 exons 16, 20 and 21 was PCR amplified using the Advantage 2 PCR Kit (Clontech, Mountain View, CA). Thermal cycling conditions were 5 cycles of 94°C for 30 sec and 72°C 3 min, followed by 5 cycles of 94°C for 30 sec, 70°C for 30 sec and 72°C 3 min, followed by 25 cycles of 94°C for 30 sec, 68°C for 30 sec and 72°C 3 min. *Genomic DNA for JAK1 exon 14 was PCR amplified using Phusion High-Fidelity DNA polymerase (New England Biolabs, Ipswich, MA) using the following thermal cycling conditions: 98°C for 30 sec, followed by 35 cycles of 98°C for 15 sec, 66°C for 15 sec and 72°C for 1 min, followed by a final extension step of 72°C for 10 min. **Underlined sequence introduces an *Xho*I site, italicised sequence is specific for CRLF2. FAM, 6-carboxyfluorescein; MGB, minor groove binder. ***Primers C1423 and C1445 were used for genomic PCR, and C1450 for direct sequencing of PCR products.

Primer	Sequence (5' to 3')	Gene	Exon	Chr	Position
Primers used for genomic JAK sequencing					
C1357	catgttcccattgaggacccattcc	JAK1	13	1	65086007-65086031
C1358	tgaaaaccactgggccacaagaagg			1	65085694-65085718
C1475*	ctcaacagagcccctggggagca	JAK1	14	1	65085057-65085079
C1476*	agggtgggaagagcctccaccatct			1	65084836-65084860
C1200	ctcatgtgaaatggcattgg	JAK2	16	9	5068059-5068078
C1201	cctcacagtccatggttatatgc			9	5068628-5068650
C1202	gacagtctgctaattccagcta	JAK2	20	9	5079566-5079587
C1203	ctctgggcattggcataagt			9	5079952-5079971
C1251	tctcatcagtttattttggtttgcctga	JAK2	21	9	5080190-5080217
C1252	tcaacacggttgcttcatctacagc			9	5080593-5080617
Primer sequences for amplification of P2RY8-CRLF2 transcripts					
Primer	**Sequence (5' to 3')**	**Gene**	**Exon**	**Accession**	**Position**
C1459	gcggccgcctttgcaaggttgc	P2RY8	1	NM_178129	1-22
C1349	gtgtccatcacaacgccacgtagga	CRLF2	7	NM_022148	1115-1139 (antisense)
C1447	ttgcaaggttgctggacagatggaa	P2RY8	1	NM_178129	11-35
C1446	gtctaggaggcaccccgaagtgtga	CRLF2	3	NM_022148	253-277 (antisense)
CRLF2-3xFLAG**	<u>ctcgag</u>tcacttgtcatcgtcatccttgtaatcgatgtcatgatctttataatcaccgtcatggtctttgtagtc*caacgccacgtaggag*	CRLF2	7		

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Primers used for real time quantitative PCR of P2RY8-CRLF2 transcripts.					
Primer	**Sequence (5' to 3')**	**Gene**	**Exon**	**Accession**	**Position**
C1454	cctctgagctctcacctgctact	P2RY8	1	NM_178129	181-203 (sense)
C1455	tactccttctgctgctcctcctt	CRLF2	1-2	NM_022148	294-316 (antisense)
C1456	FAM-ctgccgctgcttc-MGB	P2RY8	1	NM_178129	205-217 (probe)
Primers used for mapping of PAR1 deletion breakpoints* **					
C1423	cggtttggggactttcagagcacaa			X/Y	1294242-1294266
C1445	tcacctgctacttctgccgctgctt			X/Y	1615822-1615846
C1450	ggcatgagccaccgcgccccgcccaatgc			X/Y	1294984-1295012

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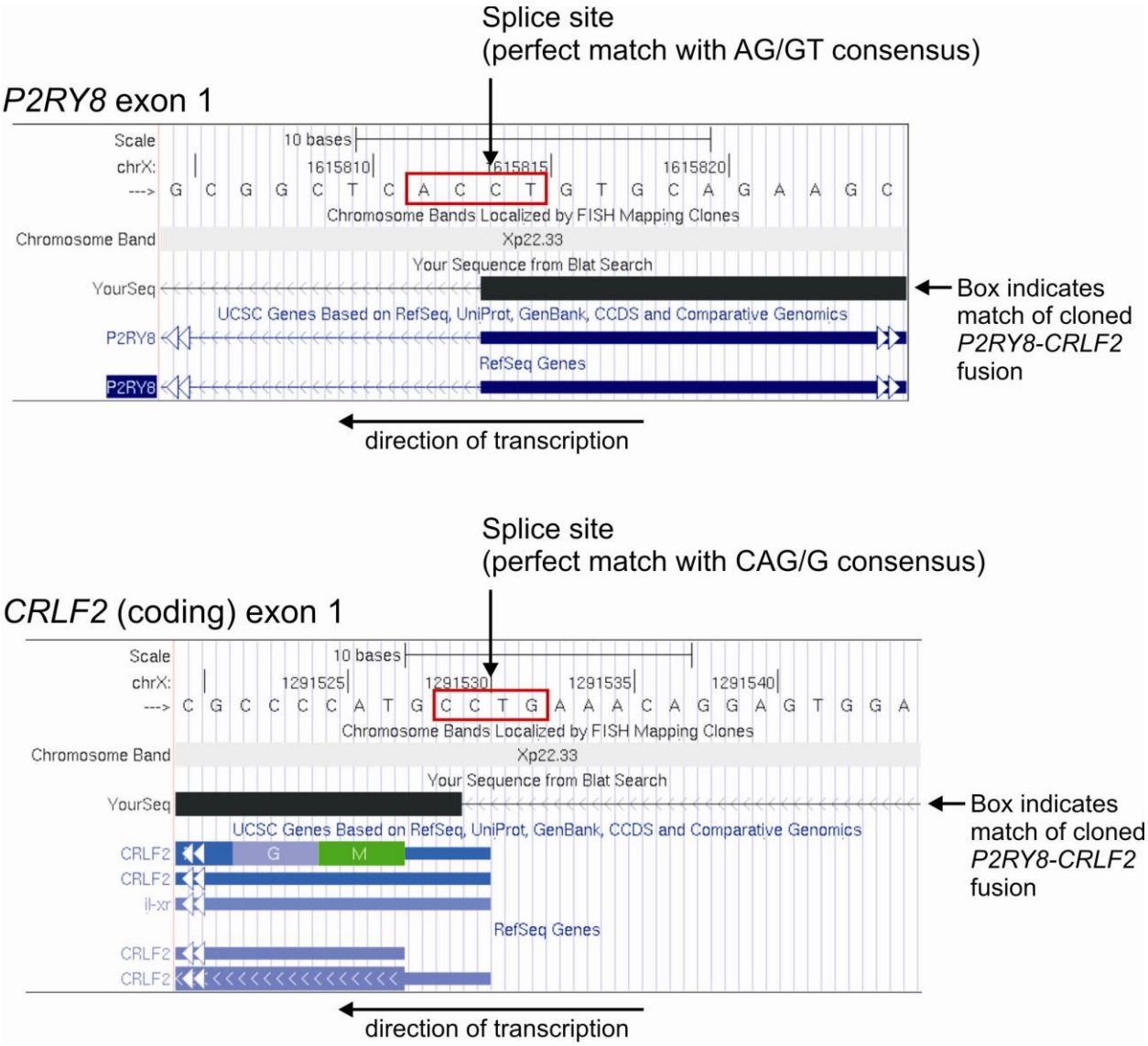
Supplementary Figure 1

Splicing of *P2RY8* exon 1 to *CRLF2* coding exon 1 in cases with *P2RY8-CRLF2* fusion. In the current reference genome (hg18), the 4-bp at *P2RY8* exon 1 intron-exon boundary are "AG/GT", which provide the donor splice site for the fusion junction. The first 14 nucleotides of the *CRLF2* mRNA do not align to the current reference genome. This region can thus be considered either the 5' untranslated region of exon 1, or an additional exon that is currently not in the reference genome assembly. Regardless, there is an acceptor-splice junction (perfectly matching the CAG/G consensus) immediately 5' of the CRLF1 coding exon 1.



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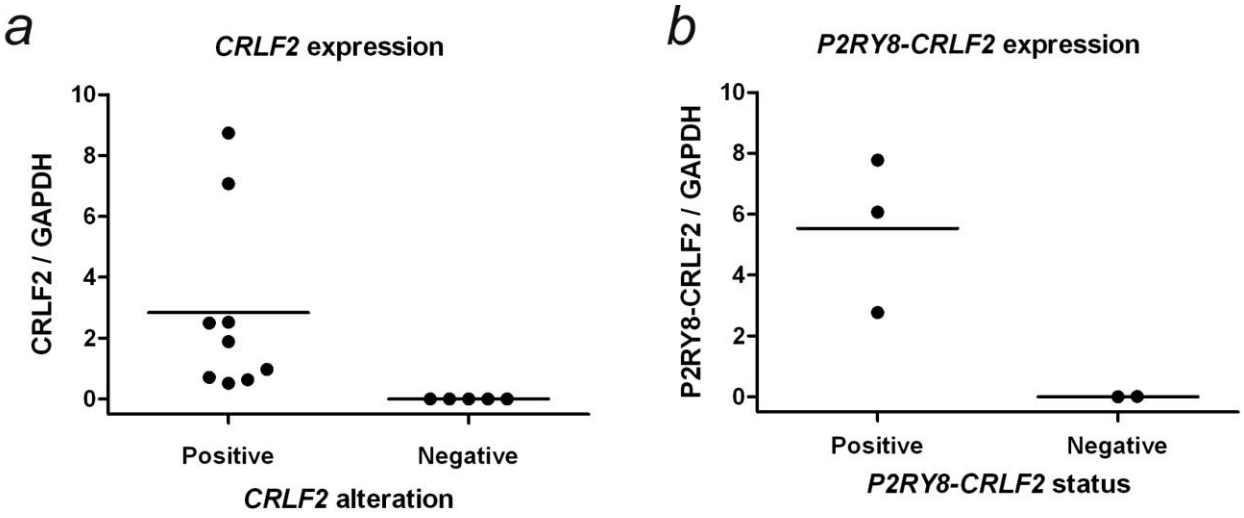
Supplementary Figure 2

Quantitation of *CRLF2* and *P2RY8-CRLF2* expression. ***a***, elevated *CRLF2* expression was observed in cases with PAR1 deletion (N=8) or *IGH@-CRLF2* translocation (N=1). ***b***, a custom Taqman assay was used to quantitate *P2RY8-CRLF2* expression. The assay used a *P2RY8* exon 1 (sense) primer, a *CRLF2* exon 1/2 (antisense) primer, and an MGB labeled probe in *P2RY8* exon 1. Expression of fusion transcripts was detected in all cases tested with available material, but never in cases lacking the PAR1 deletion.



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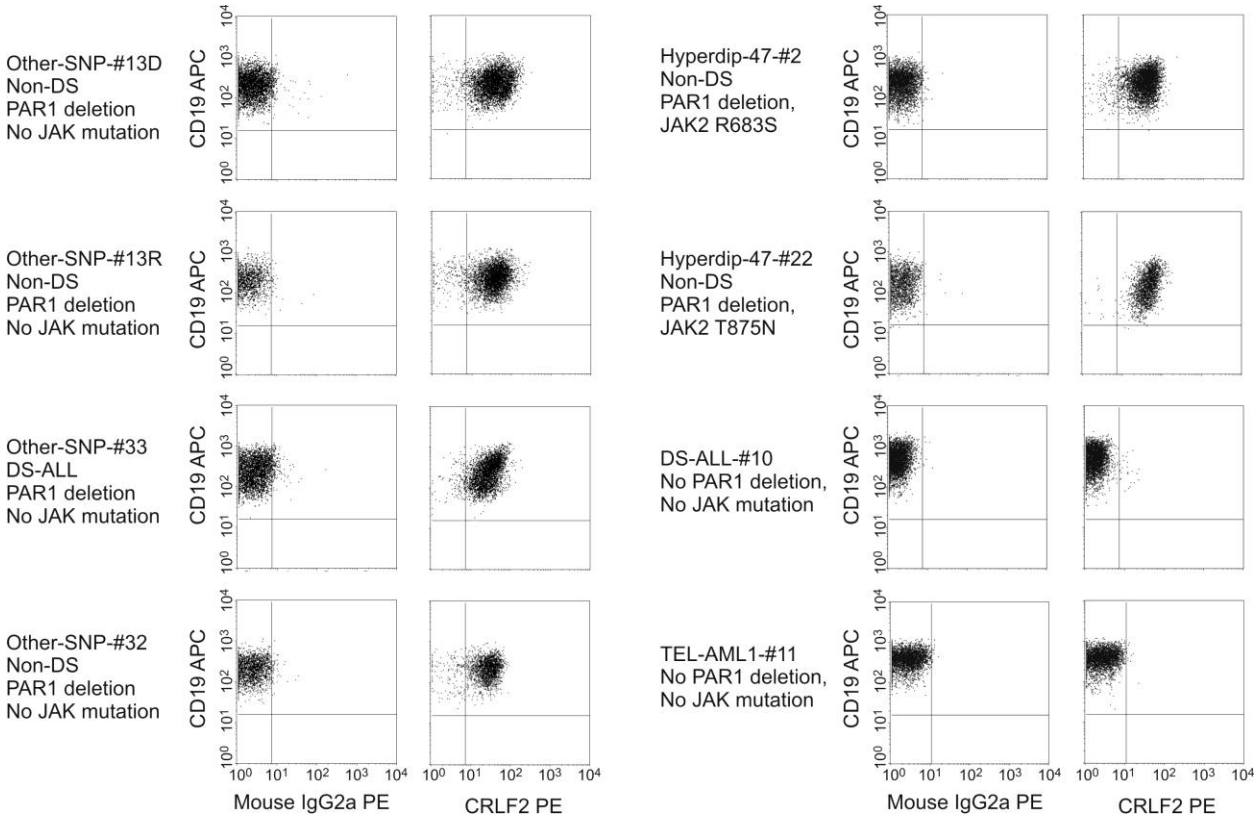
Supplementary Figure 3

Flow cytometric analysis of cell surface expression of CRLF2 for eight representative samples. Corresponding diagnosis (#13D) and relapse (#13R) samples were tested for case Other-SNP-#13. Co-staining for CD19 demonstrates positivity in the leukemic cell population in all cases. Cases lacking the PAR1 deletion or *IGH@-CRLF2* translocation were negative.



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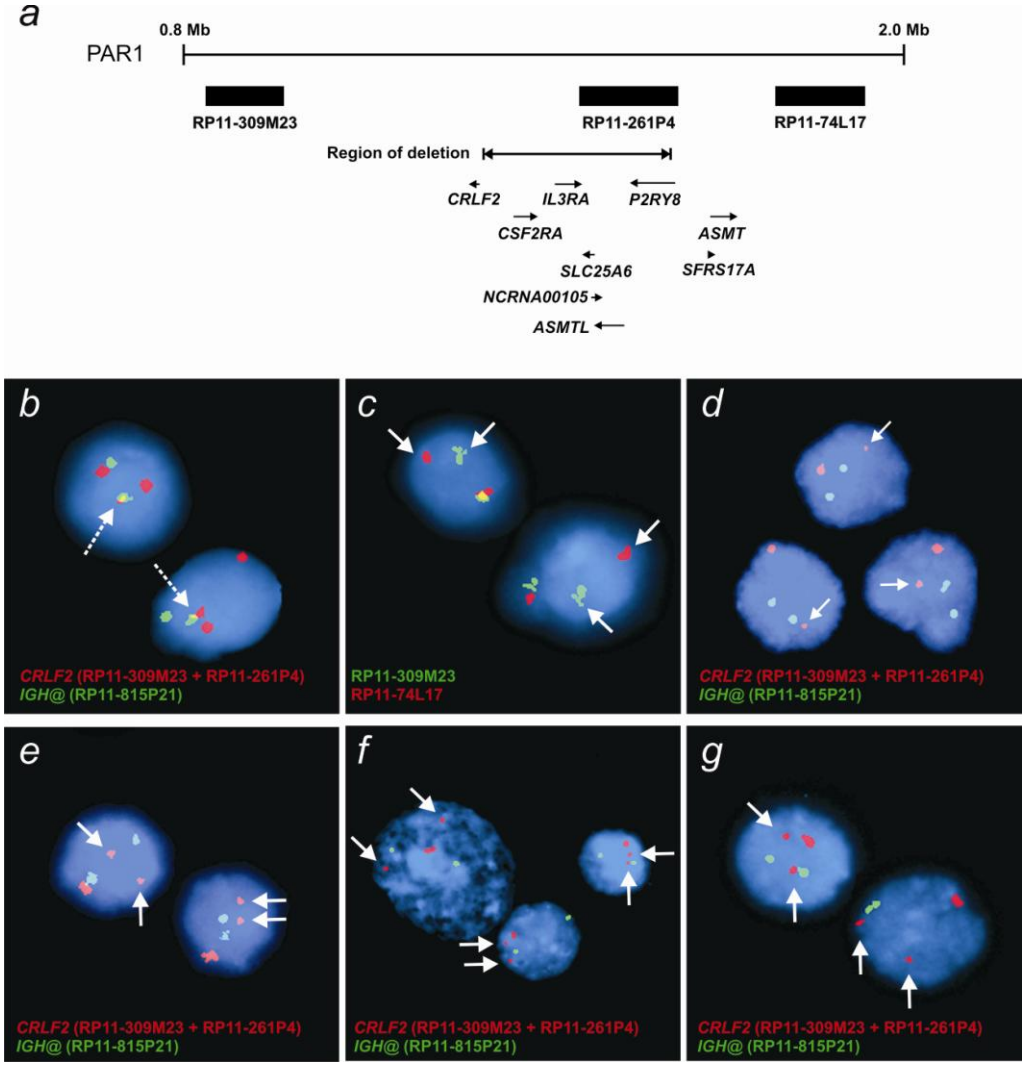
Supplementary Figure 4

Fluorescence *in situ* hybridization (FISH) analyses demonstrating deletions and translocations involving *CRLF2*. *a*, genomic location of the PAR1 deletion and probes used for FISH analyses. ***b***, fusion of *IGH@* and *CRLF2* in case Down-SNP-#14, resulting in co-localization of the *IGH@* probe (green) and *CRLF2* probe (red), generating a yellow fusion signal (dashed arrows). ***c***, FISH of the same case using a green probe telomeric to *CRLF2*, and a red probe centromeric to *CRLF2*. The separation of the green and red signals (arrows) demonstrates disruption of the locus. ***d***, FISH of a representative case with PAR1 deletion (Other-SNP-#33), showing a diminished red signal (arrows) due to deletion of the RP11-261P4 probe, which lies largely within the region of deletion. ***e-g***, FISH of three cases with PAR1 deletion and gain of chromosome X (***e***, Down-SNP-#09; ***f***, Hyperdip47-50-SNP-#15; ***g***, Down-SNP-#16) showing two diminished signals (arrows) for the *CRLF2/PAR1* probe in each case, indicating duplication of the PAR1 deletion with gain of chromosome X.



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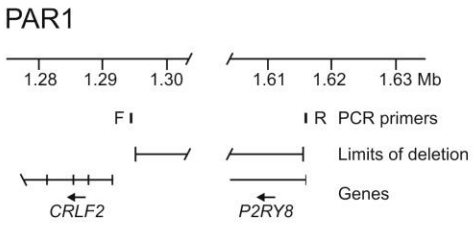
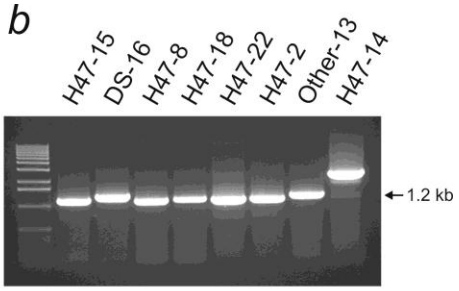
Supplementary Figure 5

Genomic mapping of the PAR1 deletion. ***a*** shows the genomic position of *CRLF2* and *P2RY8*, the limits of deletion defined by long range PCR, and the location of PCR primers used to screen for deletion by genomic PCR. ***b***, PCR products of eight representative cases with PAR1 deletion. Case H47-14 has an insertion of 640bp from the first intron of *SFRS15* gene at 21q22.11 between the *CRLF2* and *P2RY8* deletion breakpoints. ***c***, genomic sequence across the deletion breakpoints is shown for eight representative cases. All cases show a highly conserved telomeric breakpoint 3.4kb upstream of *CRLF2* exon 1, and one of three conserved breakpoints 316-1081 bases distal to *P2RY8* exon 3. The exact positions of the genomic breakpoints are numbered according to the italicized nucleotides shown in the reference sequences. Putative heptamer RSSs are shown in bold and underlined.

a



b



c

Sample	Alignment at *CRLF2*	Non-consensus nt
H47-15	catggaagagataaaataatcc	cgcccgag
DS-16	catggaagagataaaataatccaaataatg	gattcccaa
H47-8	catggaagagata	taggaccg
H47-18	catggaagagataaaataatccaaata	ccctccga
H47-22	catggaagagataaaataatccaaa	acccctcata
H47-2	catggaagagataaaataatccaaa	caa
Other-13	catggaagagataaaataatccaaataa	agggactac
H47-14	catggaagagataaaataatccaaataatga	Chr 21 insertion

Ref: catggaagaga***t***aaaataatccaaataatga**cacagtg**tgaaaggttagatgac
Position: Chr X/Y 1295059, 3432 bp 5′ of *CRLF2* exon 1

Sample	Alignment at *P2RY8*
H47-15	aggatggtctcgaact
DS-16	tagccaggatggtctcgaact
H47-8	gatggtctcgaact
H47-18	ttagccaggatggtctcgaact
H47-22	gatggtctcgaact
H47-2	ttagccaggatggtctcgaact

Ref: tttagtagagacggggttt**cac**c**gtg**ttagccag***g***atggtctcgaact
Position: X/Y 1615501 (316bp 3′ of *P2RY8* exon 1)

Other-13 gatggtctcgaactcct
Ref: agtagagacggggttt**cac**c**gtg**ttagccag***g***atggtctcgaactcct
Position: X/Y 1615366 (451bp 3′ of *P2RY8* exon 1)

H47-14 tggcctgaaattcccag
Ref: cctaaagcgccacagcaggccttgt**tgtg**tg***t***ggcctgaaattcccag
Position: X/Y 1614736 (1081bp 3′ of *P2RY8* exon 1)

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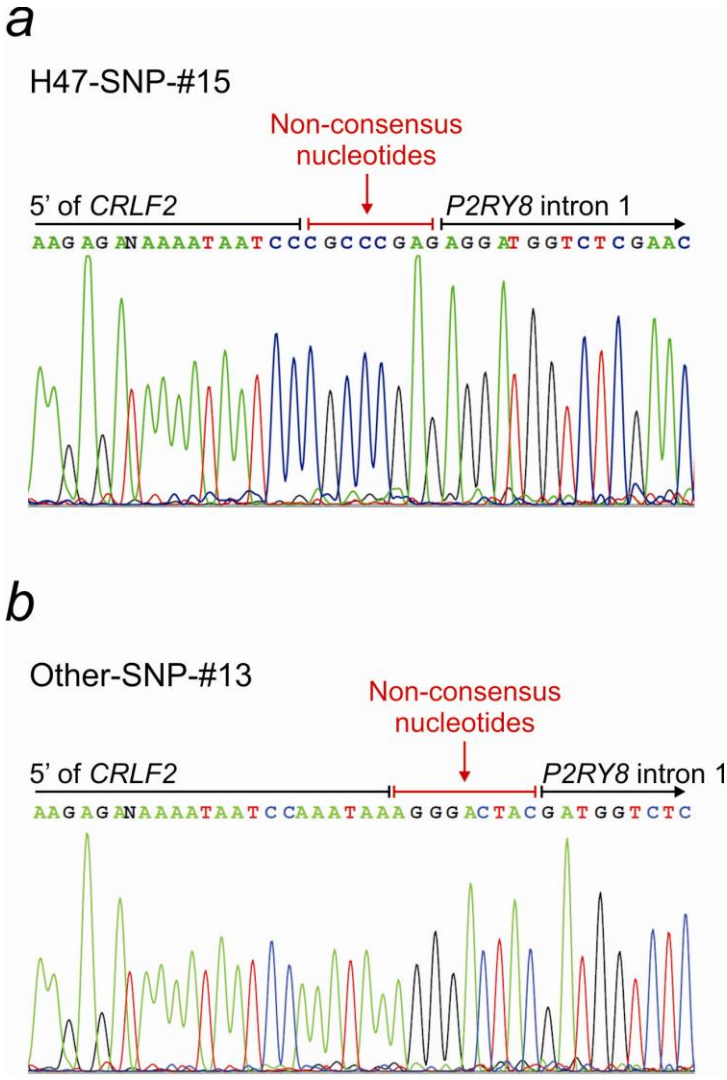
Supplementary Figure 6

Mapping of the breakpoints of the PAR1 deletion. PCR products from long template PCR were purified and sequenced directly. Each deletion involved highly conserved breakpoints 3.4kb upstream of *CRLF2* exon 1, and three closely spaced breakpoints in *P2RY8* intron 1. ***a,*** the (centromeric) *P2RY8* breakpoint is 316 bp distal to *P2RY8* exon 1. ***b***, the breakpoint is 451 nucleotides distal to exon 1. In all cases, sequences corresponding to the *CRLF2* and *P2RY8* breakpoints were separated by non-consensus nucleotides, compatible with the action of terminal deoxynucleotidyl transferase (TdT).



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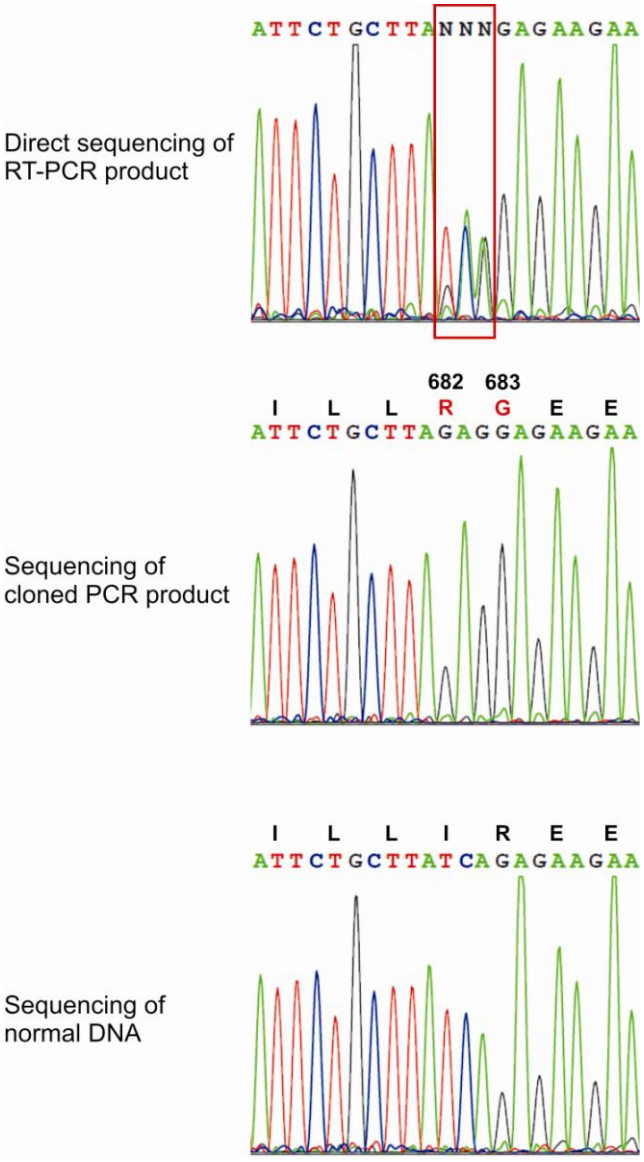
Supplementary Figure 7

Identification of a novel mutation at JAK2 IR682-3. A TCA>GAG substitution was identified on sequencing of *JAK2* exon 16 in leukemic DNA. To determine whether this represented a single mutation, or multiple compound heterozygous mutations occurring in the same sample, RT-PCR was performed and PCR products sequenced directly, and after cloning into pGEM-T-Easy (Promega). This confirmed the presence of a single mutation resulting in IR682RG.



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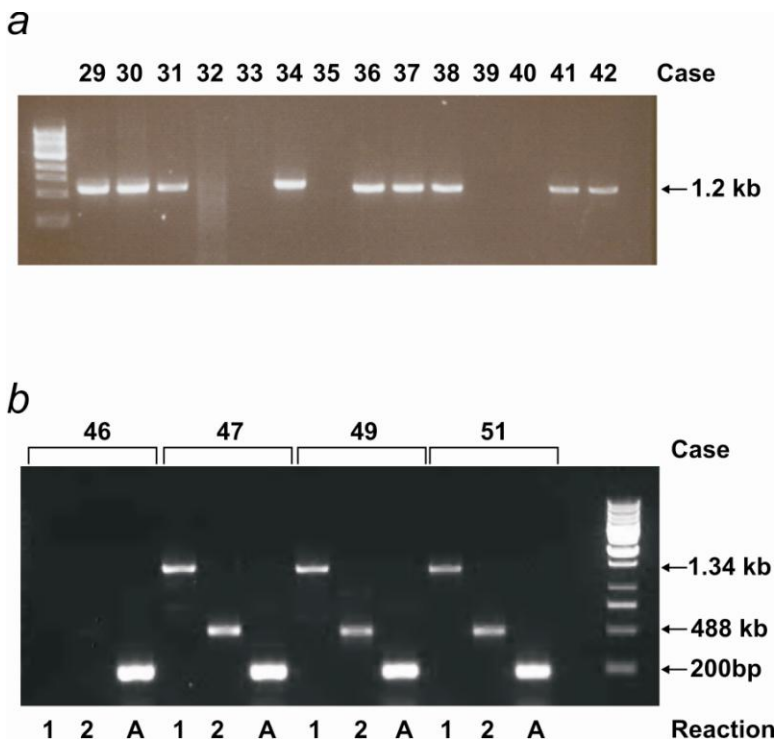
Supplementary Figure 8

Confirmation of PAR1 deletion and *P2RY8-CRLF2* fusion in the validation cohort. ***a***, genomic PCR of 14 representative cases identifying nine cases with PAR1 deletion. ***b***, *P2RY8-CRLF2* RT-PCR. Reaction 1 detects full-length *P2RY8-CRLF2*; reaction 2 detects the fusion using primers annealing in *P2RY8* exon 1 and *CRLF2* exon 3; A, actin control primers.



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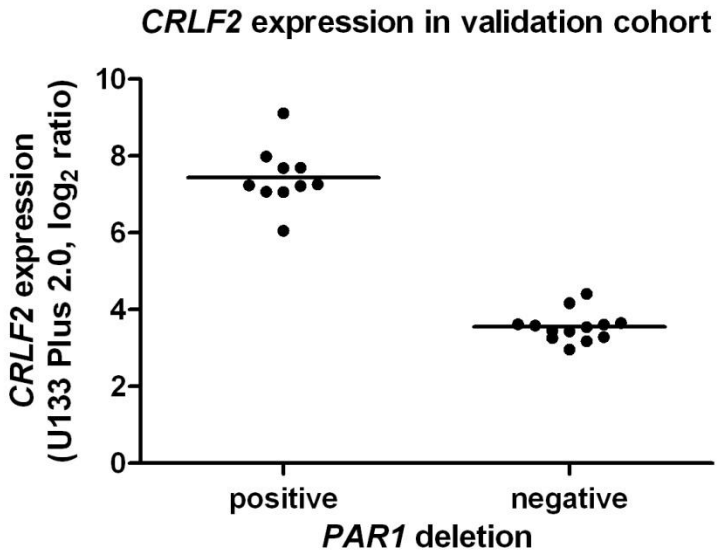
Supplementary Figure 9

Elevated *CRLF2* expression in the validation cohort was exclusively observed in cases with the PAR1 deletion (unpaired Student t test P<0.001).



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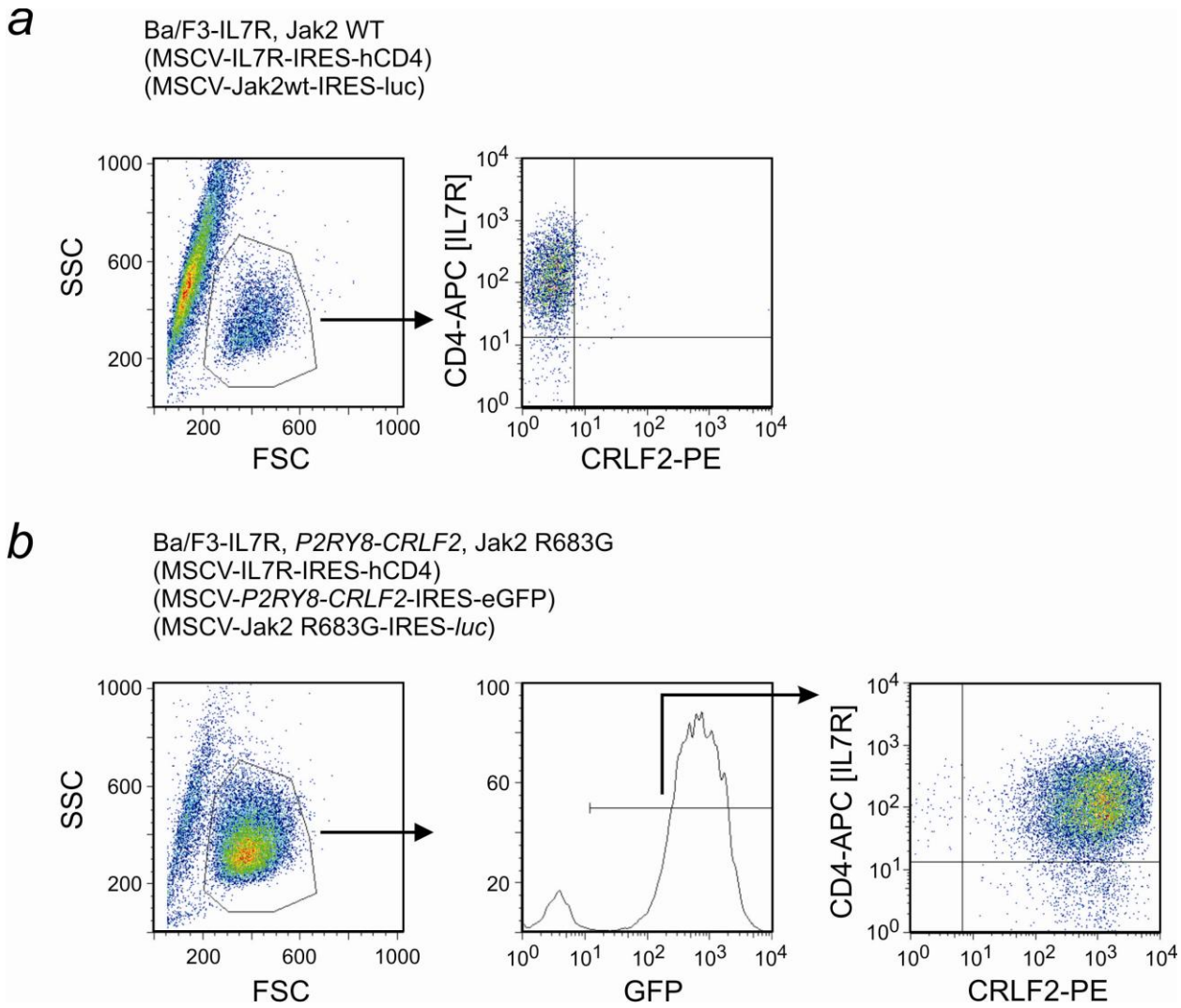
Supplementary Figure 10

Flow cytometric analysis of Ba/F3-IL7R cells confirming expression of IL7R and CRLF2. ***a***, lack of CRLF2 expression in control cells transduced with wild type Jak2, and ***b***, expression of CRLF2 in cells transduced with *P2RY8-CRLF2* and Jak2 R683G.



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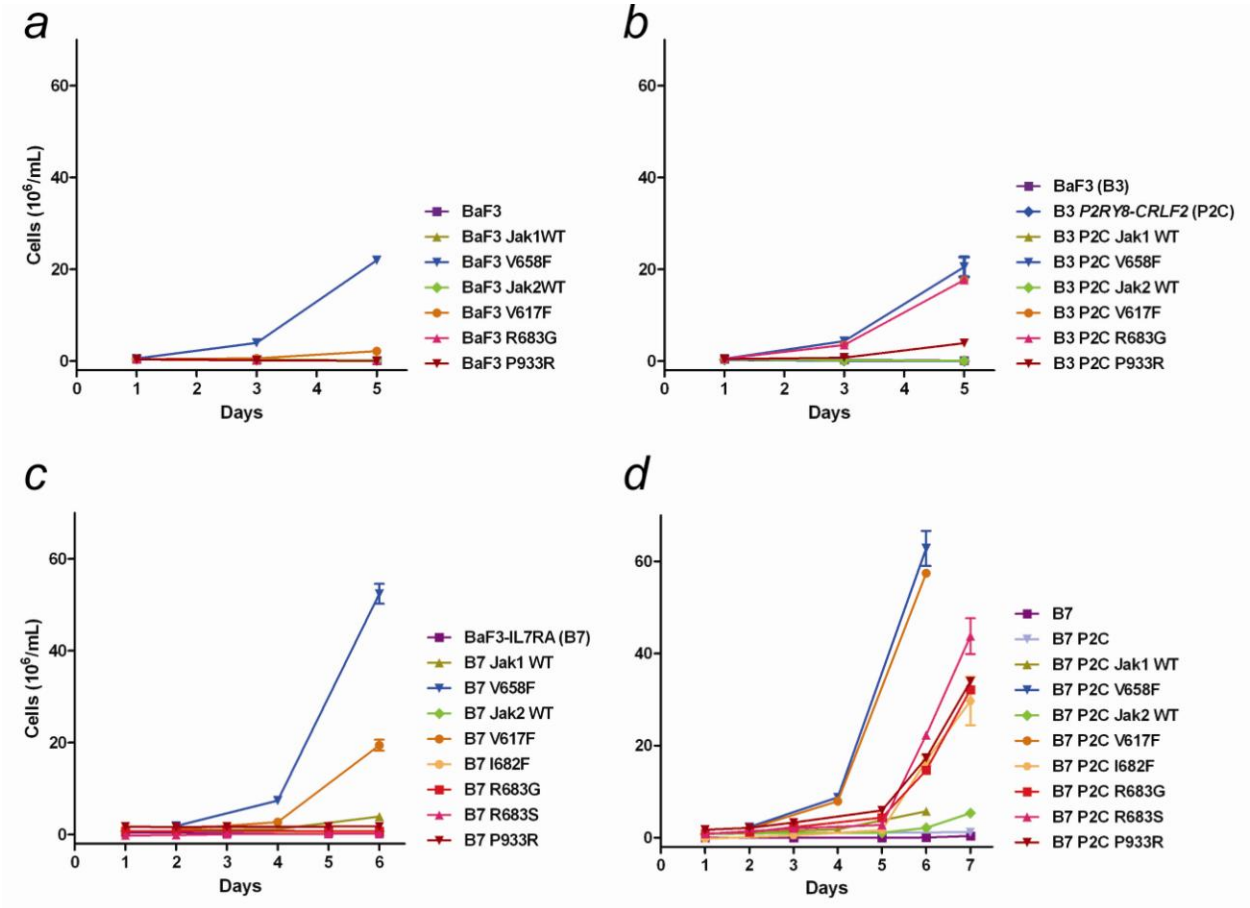
Supplementary Figure 11

Assays examining the interaction of *P2RY8-CRLF2*, *Jak1* and *Jak2* mutants, and expression of the murine IL-7 receptor alpha chain in conferring cytokine-independent growth in Ba/F3 cells. ***a***, Ba/F3 cells were transduced with MSCV-Jak1/2-IRES-*luc2* expressing wild type or mutant Jak alleles. Jak1 V658F, the ortholog of Jak2 V617F, is transforming; Jak2 V617F is only weakly transforming. Jak2 R683G and P933R are not transforming. ***b***, Ba/F3 cells expressing *P2RY8-CRLF2* were transduced with wild type or mutant Jak alleles. Jak1 V658F and Jak2 R683G are transforming, and Jak2 P933R weakly transforming. ***c***, Ba/F3 cells expressing the murine IL-7 receptor alpha chain (B7 cells) are transformed by Jak1 V658F and Jak2 V617F, but not by Jak2 682/683/933 mutant alleles. ***d,*** Ba/F3 cells coexpressing IL7RA and *P2RY8-CRLF2* (B7 P2C cells) are transformed by all Jak1 and Jak2 mutant alleles. Notably, the proliferation rate of Ba/F3 cells transduced with all three constructs (IL7RA, *P2RY8*-CRLF2, and Jak mutants) was greater than B7 cells transduced with the Jak mutants, but not *P2RY8-CRLF2* (panel ***c***); or Ba/F3 cells transduced with *P2RY8-CRLF2* but not IL7RA (panel ***b***).



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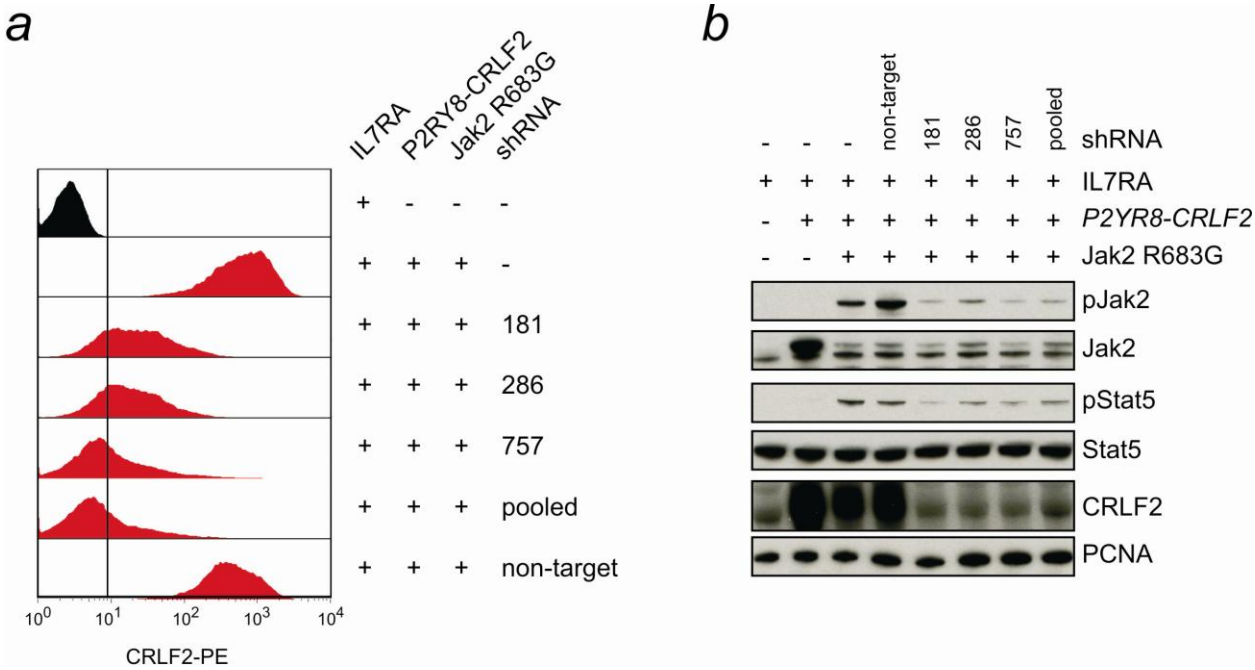
Supplementary Figure 12

Validation of lentiviral shRNA knockdown of CRLF2 in Ba/F3-IL7R cells transduced with *P2RY8-CRLF2* and Jak2 R683G. ***a***, flow cytometry for CRLF2 expression before and after CRLF2 knockdown. Cells were transduced with non-target (scrambled) shRNA, each of three CRLF2-specific shRNAs individually, and a pool of all three shRNAs. ***b***, western blotting for Jak-Stat activation and CRLF2 after knockdown.



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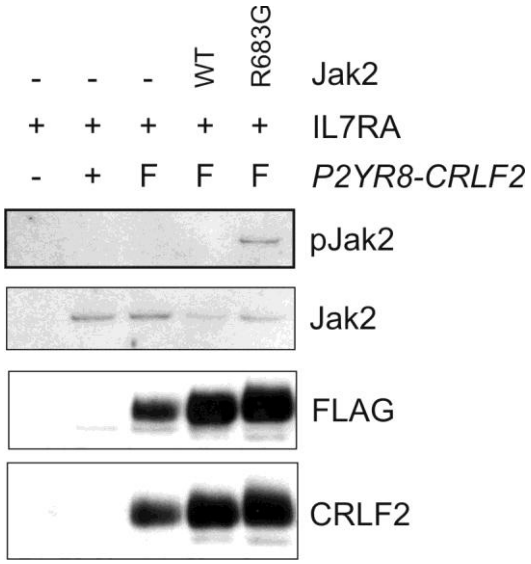
Supplementary Figure 13

Co-immunoprecipitation of CRLF2 and phosphorylated Jak2. Ba/F3-IL7R cells were transduced with either *P2RY8-CRLF2* ("+"), 3xFLAG-tagged *P2RY8-CRLF2* ("F"), and/or wild-type Jak2 ("WT") or Jak2 R683G. Immunoprecipitation with anti-FLAG antibody followed by western blotting for phospho-Jak2, Jak2, FLAG and CRLF2 were performed. This demonstrated interaction of *P2RY8-CRLF2* with phosphorylated Jak2 in Ba/F3-IL7R cells transduced with both *P2RY8-CRLF2* and Jak2 R683G, but not cells transduced with *P2RY8-CRLF2*-3xFLAG alone, or with wild type Jak2.



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