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Deletions of *IKZF1* and *SPRED1* are associated with poor prognosis in a population-based series of pediatric B-cell precursor acute lymphoblastic leukemia diagnosed between 1992 and 2011

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Running head: Relapsed pediatric ALL

Abstract

Despite the favorable prognosis of childhood acute lymphoblastic leukemia (ALL), a substantial subset of patients relapses. Since this occurs not only in the high risk but also in the standard/intermediate groups, the presently used risk stratification is suboptimal. The underlying mechanisms for treatment failure include presence of genetic changes causing insensitivity to the therapy administered. To identify relapse-associated aberrations we performed single nucleotide polymorphism array analyses of 307 uniformly treated, consecutive pediatric ALL cases accrued 1992-2011. Recurrent aberrations of 14 genes in patients who subsequently relapsed or had induction failure were detected. Of these, deletions/uniparental isodisomies of *ADD3, ATP10A, EBF1*, *IKZF1, PAN3, RAG1, SPRED1*, and *TBL1XR1* were significantly more common in B-cell precursor ALL patients who relapsed compared with those remaining in complete remission. In univariate analyses, age (≥10 years), WBC counts (>100 x 10^9/l), t(9;22)(q34;q11), *MLL* rearrangements, near-haploidy, and deletions of *ATP10A*, *IKZF1*, *SPRED1*, and the pseudoautosomal 1 regions on Xp/Yp were significantly associated with decreased 10-year event-free survival, with *IKZF1* abnormalities being an independent risk factor in multivariate analysis irrespective of risk group. High age and deletions of *IKZF1* and *SPRED1* were also associated with poor overall survival. Thus, analyses of these genes provide clinically important information.

Keywords: Pediatric acute lymphoblastic leukemia; single nucleotide polymorphism array analyses; relapse; *IKZF1*; *SPRED1*

Introduction

The cure rate for pediatric acute lymphoblastic leukemia (ALL) has improved dramatically during the last few decades, with disease-free survival at 5 years now exceeding 80% in most current treatment protocols.[1,2] However, the one fifth that relapses still fares poorly, with overall survival (OS) rates of only approximately 30% despite aggressive chemotherapy and stem cell transplantation, indicating that the blasts at relapse are refractory to presently available therapeutic regimes in most instances.[1,3-5] Hence, it is vital to identify "relapse-prone" clones already at the time of diagnosis in order to ensure proper risk stratification and treatment decisions. Today, several clinical and genetic factors are routinely used to stratify patients into different risk groups/treatment intensities, such as white blood cell (WBC) count, age, and immunophenotypic and genetic features.[1,2,5,6] However, since relapses occur not only in the high risk group but also in the standard and intermediate groups, these factors are suboptimal.

A number of studies aiming at elucidating the underlying mechanisms for relapse has compared genetic features in paired diagnostic and relapse samples using conventional cytogenetic,[7,8] clone-specific polymerase chain reaction (PCR),[9,10] fluorescence in situ hybridization (FISH),[11,12] and single nucleotide polymorphism (SNP) array analyses,[4,13-17] revealing that the relapsed clones can be identical to the ones seen at diagnosis, display additional changes (clonal evolution), or harbor both additional, identical as well as fewer changes (evolution from a preleukemic/ancestral clone). The two latter evolution patterns indicate outgrowth of therapy-resistant minor subclones.[4,9-12,16,17] In addition, high-resolution genomic profiling has identified genes, for example *CDKN2A*, *ETV6*, *IKZF1*, and *EBF1*, that are more frequently deleted in samples from patients who subsequently relapse than in samples from those remaining in fist complete remission (CR1).[4,13,14,18] However, whether these deletions serve as independent prognostic markers is still unclear.[13,14,18,19]

In the present study, SNP array analyses were performed on diagnostic, CR1, relapse (R), and induction failure (IF) samples from pediatric ALL patients to identify copy number aberrations and uniparental isodisomies (UPDs) associated with R/IF. In a next step, all identified recurrent abnormalities were screened for in diagnostic samples from patients without R/IF to ascertain whether they may be associated with event-free survival (EFS) and/or OS in a large patient cohort uniformly treated according to Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL protocols.

Methods

Patient cohort

Between 1992 and 2011, 307 children/adolescents (<18 years) were diagnosed with ALL at the Departments of Pediatric Oncology and Hematology, Lund and Linköping University Hospitals, Sweden. The vast majority (n = 288; 94%) were treated according to the NOPHO ALL 1992 (n = 138), 2000 (n = 94), or 2008 (n = 56) protocols.[2] The median age was 4 years, the male/female ratio 1.4, and the median WBC count 10.8 x 10^9/l (range 0.8 – 802). Of the 307 patients, 269 (88%) had B-cell precursor (BCP) ALL, 33 (11%) T-ALL, four (1.3%) mature B-cell ALL, and one (0.3%) had a biphenotypic leukemia. All bone marrow (BM)/ peripheral blood (PB) samples were analyzed using conventional chromosome banding and targeted analyses (RT-PCR, FISH, or Southern blot analyses). Among the BCP ALL cases, 5.6% were positive for 11q23/*MLL* rearrangements (251 analyzed cases), 5.2% for t(1;19)(q23;p13) (*TCF3/PBX1*; n = 212), 2.7% for t(9;22)(q34;q11) (*BCR/ABL1*; n = 219), and 24% for t(12;21)(p13;q22) (*ETV6/RUNX1*; n = 230), and 70 (26%) cases were high hyperdiploid. None of the T-ALL or mature B-cell ALL cases analyzed was positive for any of these rearrangements. The single case with biphenotypic leukemia harbored an *MLL* rearrangement. Basic clinical and genetic features are provided in Supplementary Table 1.

Among the 307 patients, 60 (20%) relapsed, 44 (73%) of which were BM relapses. In addition, 17 (5.5%) had IF (defined as >5% abnormal nuclei as ascertained by locus specific FISH analyses at days 15 or 29). The median age of all 77 patients with R/IF was 3.5 years (range 0 – 17), the male/female ratio 1.7, and the median WBC count 14.1 x 10^9/l (range 0.8 – 802). Sixty-seven (87%) of the patients had BCP ALL; the remaining 10 (13%) had T-ALL (Table 1).

The genetic subgroups represented among the 67 BCP ALL samples, obtained from patients with subsequent R/IF, comprised high hyperdiploidy (HeH, 51-67 chromosomes; 25%), t(12;21) (19%), *MLL* rearrangements (13%), normal karyotype (NK; 4.5%), t(9;22) (6.0%), and near-haploidy (23-29 chromosomes; 6.0%); the remaining cases (25%) had other abnormalities or were cytogenetic failures. Among the 10 T-ALL cases, three had NK, four harbored *CDKN2A* deletions, and three carried various, non-recurrent abnormalities. The clinical and cytogenetic data on the 77 R/IF patients are given in Supplementary Table 2.

SNP array analysis

DNA was extracted using standard methods from BM or PB cells at the time of diagnosis, CR1, and at R/IF. The analyses were performed using the HumanOmni1-Quid and Human1M-Duo array systems (Illumina, San Diego, CA), covering >1,000,000 SNPs. The Genomestudio software 2011.1 (Illumina) was applied for analysis of copy number aberrations and UPDs; some samples were analyzed in build GRCh36.1, whereas the majority was analyzed in build GRCh37 (Supplementary Table 2). All recurrent aberrations detected were converted to GRCh37 coordinates (http://www.ensembl.org/Homo_sapiens /Info/Index) to find the smallest overlap. Imbalances seen in remission samples or that overlapped with copy number polymorphisms listed in the Database of Genomic Variants (http://projects.tcag.ca/variation/) were excluded from further analysis, and so were deletions

corresponding to somatic rearrangements of the T-cell receptor and immunoglobulin loci.[16] A flowchart depicting the cases analyzed by SNP arrays is shown in Supplementary Figure 1.

Identification of recurrent gene targets and genomic imbalances

Gene targets (in all instances deletions) and genomic imbalances, the latter comprising partial gains and losses not involving single genes, identified in diagnostic samples from at least two patients with subsequent R/IF were considered recurrent. To be denoted a gene target at least one of the samples had to display a focal deletion involving only the specified gene. All recurrent aberrations were subsequently ascertained in the entire patient cohort without R/IF successfully analyzed by SNP arrays (n=170).

Statistical analyses

The PASW Statistics 20 software for Windows (SPSS Inc., Chicago, IL) was used for all analyses. The significance limit for two-sided *P*-values was set to <0.05. The frequencies of gene targets/genomic imbalances in diagnostic and R/IF samples were compared using the Wilcoxon signed-rank and two-tailed Fisher's exact probability tests. The 10-year (yr) probabilities of EFS (pEFS) and OS (pOS) in relation to clinical (sex, age, risk group, and WBC count) and genetic features (modal chromosome number, cytogenetic subgroup, and gene targets/genomic imbalances) were calculated using the Kaplan-Meier method on patients treated only according to the NOPHO ALL 1992 and 2000 protocols since these protocols were virtually identical as regards risk group assignment and therapy (the study cohorts are shown in Supplementary Figure 2). Multivariate analysis using a Cox regression model was performed to identify genetic/clinical factors that had an independent impact on pEFS. The median observation time for patients in CR1 was 128 months (range 43-227 months). The investigation was approved by the Research Ethics Committee of Lund University and informed consent was provided according to the Declaration of Helsinki.

Results

SNP array findings in the paired diagnostic and R/IF samples

Among the 77 patients with subsequent R/IF (Table 1), 58 diagnostic and 21 R/IF samples could be successfully analyzed. The remaining samples could not be investigated due to lack of samples (12 diagnostic and 46 R/IF), failed SNP arrays (6 diagnostic and 5 R/IF), or presence of only non-malignant cells in the stored samples (1 diagnostic and 5 R/IF). In total, 17 paired diagnostic and R/IF samples (#1-17; Supplementary Table 2), 41 diagnostic samples without R/IF samples (#18-58), and four R samples without diagnostic samples (#59-62) were analyzed in this study.

At diagnosis, the median number of genomic imbalances per case was 7 (range 0-24), with 3 (range 0-11) duplications, 2 (range 0-12) losses (hemi-/homozygous deletions as well as monosomies), 0 (range 0-20) whole chromosome UPDs, 0 (range 0-2) partial UPDs (pUPDs), and 3 (range 0-20) structural changes, including pUPDs. The corresponding frequencies for the R/IF samples were 8 (range 0-27), 3 (range 0-11), 2 (range 0-17), 0 (range 0-20), 0 (range 0-2), and 3 (range 0-27). There were no significant differences in total number of imbalances, duplications, whole chromosome UPDs, pUPDs, and structural changes between the paired samples, whereas losses were slightly more common at R/IF ($P = 0.048$).

Genetic evolution patterns in the paired diagnostic and R/IF samples

Seven (41%) of the 17 paired cases had identical genetic changes or harbored no genomic imbalances at diagnosis and R/IF. Six (35%) cases displayed additional changes at R/IF, indicating clonal evolution from the major diagnostic clone. An additional two (12%) cases showed clonal evolution, but in these cases the SNP array findings clearly showed that they evolved from a minor clone (subclone), and not from the major clone, seen at diagnosis. The remaining two cases (12%) lacked some of the imbalances present at diagnosis and also exhibited novel aberrations at the time of relapse, suggesting the presence of ancestral clones from which the relapses evolved (Supplementary Tables 3 and 4).

Recurrent gene targets/genomic imbalances in diagnostic samples from patients who subsequently had R/IF

Fifty-eight diagnostic samples were informative in the SNP array analyses (Supplementary Figure 1 and Supplementary Tables 2 and 4). A total of 14 recurrent focal gene targets and 10 recurrent genomic imbalances were identified (Supplementary Table 5). Among these, the following were significantly more common in the R/IF group compared with the 170 successfully analyzed cases without such events: deletions/UPDs of *ADD3* (chr10:111,775,607-111,830,275), *ATP10A* (chr15:26,033,764-26,093,401), *IKZF1* (chr7:50,418,242-50,422,230), *NR3C1* (chr5:142,781,168-143,058,402), *PAN3* (chr13:28,691,097-28,806,503), *SPRED1* (chr15:38,403,504-38,558,017), del(6)(p22.2p22.2) [chr6:26,153,335-26,167,951], del(16)(p13.3p13.3) [chr16:15,257,80-16,706,91], del(16)(q22.1q22.1) [chr16:67,473,040-67,879,400], and del(17)(p11.2p13.2) [chr17:47,523,93-16,232,477]. Eleven of the 58 patients who subsequently had R/IF harbored two or more of these deletions.

The recurrent gene targets/imbalances differed between the T-ALL and BCP ALL cases. In T-ALL, the only recurrent changes were deletions/pUPDs of *CDKN2A* (chr9:21,970,901-21,970,989), *PAX5* (chr9:36,927,364-37,010,622), and del(13)(q14.2q14.2) [chr13:49,015,957-49,070,345]. The frequencies of these changes did not vary significantly between T-ALL patients with or without R/IF (Supplementary Table 6).

Among the BCP ALL cases with R/IF, the following changes were recurrent as well as significantly more frequent than in those without such events: deletions/UPDs of *ADD3*, *ATP10A*, *EBF1* (chr5:158,366,263-158,502,378), *IKZF1*, *NR3C1*, *PAN3*, *SPRED1*, and *TBL1XR1* (chr3:176,911,471-177,336,402), and deletion of the pseudoautosomal region 1 (PAR1) [chrX:14,011,68-15,666,46], del(6)(p22.2p22.2), del(16)(p13.3p13.3), and del(17)(p11.2p13.2). When focusing on only the 38 patients who relapsed, eight target genes

and one genomic imbalance were significantly more common than in those who did not relapse (Table 2).

The recurrent gene targets and genomic imbalances in cases that subsequently had R/IF also varied among the different BCP ALL cytogenetic subgroups (Supplementary Tables 7 and 8). None of the recurrent aberrations found in the HeH, near-haploid, t(9;22), der(11)(q23)/*MLL*, and t(12;21) groups was more common in cases that subsequently relapsed. However, among the remaining BCP ALL cases, comprising those with NK, cytogenetic failure, or other cytogenetic abnormalities, with R/IF a total of six different gene targets and two imbalances were recurrent: deletions/pUPDs of *ATP10A*, *CDKN2A*, *ETV6*, *IKZF1*, *PAX5*, and *SPRED1*, and deletion of PAR1 and del(6)(p22.2p22.2). Of these, deletions/pUPDs of *ATP10A*, *IKZF1*, *SPRED1*, and PAR1 were significantly more common than in cases without R/IF (data not shown). When considering only samples from patients who relapsed, three gene targets and PAR1 deletions were recurrent, but only *IKZF1* aberrations were significantly associated with relapse (Table 3).

When comparing specific gene aberrations between diagnostic and R/IF samples, *MSH6* deletions (chr2:47,857,914-48,035,137) were only recurrent among the R/IF samples, *IKZF1* deletions at diagnosis were always preserved at R/IF, and deletions of *BTG1* (chr12:92,278,448-92,537,956) and *NR3C1* were enriched at R/IF (as exemplified in Supplementary Figure 3).

Survival in relation to clinical and genetic features

Neither clinical variables (age, WBC count, and gender) nor recurrent genetic abnormalities were significantly associated with pEFS or pOS among the 23 T-ALL patients treated according to the 1992 and 2000 NOPHO protocols.

Among the 209 BCP ALL patients, age <10 years and WBC counts <100 x10^9/l were significantly associated with superior 10-yr pEFS (Figure 1A and B), whereas only age <10

years was associated with favorable 10-yr pOS ($P = 0.004$). Gender had no impact on pEFS or pOS (data not shown). Modal chromosome numbers showed no significant associations with pEFS or pOS and there were no pEFS and pOS differences between the cases with (n = 169) or without (n = 40) known modal numbers (data not shown). Among the cytogenetic subgroups, cases with t(9;22), *MLL* rearrangements, and near-haploidy had an inferior 10-yr pEFS compared with those with HeH, t(12;21), t(1;19), NK, or other cytogenetic abnormalities (Figure 1C). However, this did not translate into differences as regards pOS (data not shown). Eighty-two (39%) BCP ALL cases were grouped as standard risk, 83 (40%) as intermediate risk, and 44 (21%) as high risk; these groups differed significantly as regards 10-yr pEFS (Figure 1D) but not pOS ($P = 0.059$).

SNP array analyses were successfully performed on 145 (69%) of the 209 BCP cases treated according to the 1992 and 2000 NOPHO protocols; there were no differences in 10-yr pEFS (73% vs. 77%, $P = 0.724$) or 10-yr pOS (85% vs. 87%, $P = 0.797$) between those analyzed or not. Among the gene targets/imbalances recurrent in patients who relapsed (Table 2), deletions of *ATP10A*, *IKZF1*, *SPRED1*, and PAR1 were significantly associated with decreased pEFS rates (Figure 2). Deletions of *IKZF1* and *SPRED1* were also significantly associated with poor pOS (Figure 3).

IKZF1 deletions are an independent risk factor for decreased EFS irrespective of risk group assignment

Multivariate Cox regression analyses revealed that deletions of *IKZF1* were the strongest independent risk factor for inferior pEFS in BCP ALL when taken into consideration age, WBC counts, the cytogenetic subgroups NK, HeH, t(1;19), der(11)(q23)/*MLL*, t(12;21), and cytogenetic failures/other cytogenetic abnormalities, risk group assignment, and PAR1 deletions (Table 4). *IKZF1* was still an independent risk factor when including t(9;22), near-

haploidy, and deletions of *ATP10A* and *SPRED1* (significantly associated with EFS in univariate analyses; Figure 2).

IKZF1 deletions were more common in the high risk group (Supplementary Table 9; P = 0.001), but *IKZF1* status was also the strongest risk factor for pEFS among the standard and intermediate risk groups. In contrast, the *IKZF1* status was not associated with pOS; the only parameter associated with pOS in the multivariate analysis was age >10 years (data not shown).

Discussion

The present large scale SNP array analysis of a uniformly treated pediatric ALL patient cohort was undertaken for four main reasons: i) to identify gene targets and genomic imbalances of importance for the leukemogenic process; ii) to analyze the clonal relationship between diagnostic and relapse samples; iii) to ascertain genetic changes that are more prevalent at diagnosis in patients with subsequent R/IF and hence possibly important for treatment failure; and iv) to pinpoint genetic aberrations that confer a significant prognostic impact in unselected pediatric ALL patients. Although such issues have been addressed previously, the current study provides additional and novel data pertaining to the four above-mentioned goals. First, we investigated a population-based series, not focusing solely on high risk ALL,[4] T-ALL,[15] specific cytogenetic subgroups in BCP ALL,[16,17] or excluding some subgroups.[13] Also, none of our patients was lost to follow-up in contrast to several prior studies and for some of our cases the observation time was close to 20 years with a median follow-up of 10 years, whereas the maximum follow-up time has been 10 years or less in earlier studies,[14,17,18,20,21] (Figures 1 and 2). Furthermore, the SNP arrays used provide higher resolution (>1 M SNPs) compared with prior SNP array-based ALL studies (250K-500K),[4,13-18] making it possible to delineate imbalances in greater detail and to identify previously unknown gene targets, as exemplified below.

Among the recurrent gene targets (Table 2), focal deletions of *SPRED1* have never been reported before. The reason for this may partly be due to the smaller number of samples analyzed in most previous studies, because when reviewing the supplementary data from published SNP array analyses of ALL,[4,13,14,16] we identified only one relapse sample, reported by Mullighan et al.[4], with a deletion including *SPRED1* among other genes; this is the only prior study comprising a similar number of patients as our study. Furthermore, it is possible that the higher resolution of our SNP arrays could be an additional reason, since two of our *SPRED1* deletions were small focal deletions that could have escaped detection in previous studies. SPRED1 is highly expressed in hematopoietic cells and acts as a negative regulator of RAS/RAF/MAPK. Germline loss-of-function mutations of the *SPRED1* result in increased RAS-MAPK signal transduction and cause Legius syndrome, a disorder that displays a "mild" neurofibromatosis type 1 phenotype and that may be associated with acute myeloid leukemia.[22,23] *SPRED1* has previously not been implicated in ALL but mutations of other RTK-RAS genes, such as *FLT3*, *KRAS*, *NRAS*, and *PTPN11*, have been reported to be enriched at ALL relapses.[16,24]

The only genomic imbalance significantly associated with relapse (Table 2) was del(6)(p22.2p22.2), involving the histone genes *HIST1H2BD* and *HIST1H1E* in the smallest overlapping region. HIST1H2BD and HIST1H1E are part of the nucleosome structure of the chromosomal fiber and essential for cytokinesis.[25] Although these genes have not been reported to be deleted in ALL or otherwise associated with this disease, the observed 6p imbalances overlap to some extent with 6p deletions reported in Down syndrome-associated ALL and other histone clusters on 6p have been shown be deleted in pediatric ALL, with methylation arrays suggesting that histone deletions are associated with methylation alterations.[26,27] Thus, *HIST1H2BD* and *HIST1H1E* may be added to the growing list of acute leukemia-associated genes, for example *DNMT3*, *EZH2*, *HOX* family, and *MLL*, that

contribute to the leukemogenic process through deregulated CpG methylation or histone modification.[28-31]

Among the other recurrent gene targets, most – *CDKN2A*, *EBF1*, *ETV6*, *IKZF1*, *PAX5*, *RAG1*, and *TBL1XR1* – have been thoroughly discussed previously.[17,19,27,32,33] However, three of the presently identified gene targets, *ADD3*, *ATP10A* and *PAN3*, have been less emphasized in previous studies. ADD3 plays an important role in the skeletal organization of the cell membrane in erythrocytes,[34] ATP10A is an aminophospholipid translocase responsible for transporting amphipathic molecules,[35] and PAN3 is involved in degradation of poly(A) tails in cytoplasmic mRNA.[36] Both *ADD3* and *PAN3* have been reported to play a role in ALL – *ADD3* is a *NUP98* partner in T-ALL[37] and significantly associated with a gene expression cluster group with poor outcome in high risk BCP ALL[38] and *PAN3* is recurrently deleted in high hyperdiploidy ALL.[39] Prior to this report, deletions of *ATP10A* have not been clearly associated with ALL. However, when reviewing supplementary data published by Mullighan et al.[4], we identified two high risk ALL cases with deletion of this gene.

It is worthy of note that *PAN3* was the only gene target specifically associated with a particular cytogenetic subgroup – all *PAN3* deletions were identified in the HeH subgroup. The other gene targets were either involved in at least two cytogenetic subgroup, such as *ADD3*, *SPRED1*, and *RAG1* in HeH- and t(12;21)-positive BCP ALLs, or, as *CDKN2A* and *PAX5*, in all BCP ALL subtypes, strongly suggesting that different cytogenetic subgroups evolve through similar co-operative submicroscopic changes.

The analyses of the paired samples revealed that the R/IF clones, in relation to those present at diagnosis, were identical, displayed clonal evolution, or reflected evolution from an ancestral clone, i.e., a preleukemic clone from which both the diagnostic and the relapse clones evolve; the latter clones may hence harbor both additional, identical as well as fewer changes when compared (Supplementary Table 3).[4] This agrees well with previous

immunogenotypic, FISH, and cytogenetic studies of ALL.[7-12] However, in contrast to prior SNP array-based analyses,[4,13,14] we identified fewer clones arising from ancestral clones and more identical clones at the time of the event. This may partly be due to the fact that we also analyzed IF samples, of which 3 of 4 showed identical clones, indicating that the time to this event is too short for evolution to occur. In fact, when considering only the cases with relapse, 4 of 13 showed identical clones at diagnosis and relapse, well in agreement with Kawamata et al.[14] who reported identical clones in 4 of 14 cases. Furthermore, the higher frequencies of evolution from ancestral clones reported by Mullighan et al.[4] and Yang et al.[13] may partly be due to the fact that they either only studied high risk cases or included a larger number of such cases, since both high risk cases analyzed in our diagnosis/relapse cohort displayed clonal evolution from ancestral clones. Nor did we observe any significant frequency differences as regards genomic imbalances/UPDs between diagnostic and R/IF samples, as previously reported,[4,13,16] apart from a slightly increased frequency of deletions at relapse. This may be due to the fact that we investigated a consecutive series of patients since similar findings were also reported in a previous population-based study.[18] It should be stressed, however, that the present results do not refute that specific subgroups, such as HeH and t(12;21), may harbor more changes at relapse.[16,17]

Gene targets overrepresented in, or even unique for, relapse samples are most likely associated with treatment resistance and hence important to identify already at the time of diagnosis – perhaps being present only in a minor diagnostic subclone[40] – in order to adjust treatment accordingly. We identified deletions of *MSH6*, *BTG1*, and *NR3C1* to be enriched at relapse. MSH6 is a critical component of the DNA mismatch repair system and it has been shown that decreased *MSH6* expression is associated with relapse and drug insensitivity in childhood BCP ALL.[13] BTG1 is antiproliferative and acts as a cofactor involved in transcriptional regulation, mRNA turnover, and histone modification.[41] *BTG1* deletions have

retrospectively been found in subclones present at diagnosis that subsequently became the major clones at relapse[42] and loss of *BTG1* expression causes glucocorticoid resistance in ALL cell lines.[43] Although requirements of glucocorticoid receptors for glucocorticoid-induced response is well known, acquired aberrations of the glucocorticoid receptor-encoding gene *NR3C1* have previously been considered a rare contributor to ALL relapse.[44] However, our findings add to a prior study showing *NR3C1* deletions to be enriched in relapse samples from BCP ALL patients.[4] Furthermore, *NR3C1* abnormalities initially observed at relapse have retrospectively been detected in subclones at diagnosis, something that most likely contributes to the glucocorticoid resistance in such cases.[40] Thus, taken together, aberrations of *MSH6*, *BTG1*, and *NR3C1* may influence treatment response.

In recent years, a few genetic changes in T-ALL have been shown to correlate with outcome, such as aberrant expression of *TAL1*, *LYL1*, and *TLX3*.[45] However, for the majority of aberrations identified in T-ALL either no such impact is seen or remains to be elucidated. In fact, to the best of our knowledge, no T-ALL-associated genetic changes are at present used in clinical routine to stratify patients into different risk groups. So, perhaps not surprisingly, we were unable to pinpoint any gene targets or genomic imbalances that could be used for prognostication and thus treatment stratification of T-ALL in general.

In contrast to T-ALL, several clinical and genetic features were associated with outcome of BCP ALL, with the following significantly associated with a poor 10-yr EFS in univariate analyses: age ≥10 years, WBC counts ≥100 x 10^9/l, and the presence of *BCR/ABL1*, *MLL* rearrangement, and near-haploidy (Figure 1). Furthermore, three gene targets and one genomic imbalance were also significantly associated with a poor 10-yr EFS, namely *ATP10A*, *IKZF1*, *SPRED1*, and PAR1 deletions (Figure 2). Deletions of *EBF1* showed a trend towards conferring decreased 10-yr EFS ($P = 0.055$). EBF1 is a transcription factor that plays

a central role in development of normal B-cells and aberrations of this gene are clearly involved in the leukemogenic process.[13,27,46]

High age and deletions of *IKZF1* and *SPRED1* were also significantly associated with a poor 10-yr OS (Figure 3). The present finding that deletions of *SPRED1* are recurrent and that they provide a negative prognostic impact in BCP ALL is clinically important, not least considering that SPRED1 is part of MAPK signaling and that inhibitors of this pathway currently are undergoing clinical trials and hence may be novel therapeutic options.[24] The multivariate analyses strongly indicated that *IKZF1* deletions were the strongest independent risk factor for poor outcome (Table 4). The transcription factor IKZF1 is essential for B-cell development, with loss of *IKZF1* leading to arrest of lymphoid differentiation.[46,47] *IKZF1* abnormalities were initially associated with an inferior outcome of high risk BCP ALL only,[21,48] but the present data and two previous studies[18,20] clearly show that *IKZF1* aberrations also predict poor outcome in the standard and intermediate risk groups. In our series, deletions/pUPDs of *IKZF1* were the only genetic change significantly associated with relapse in cases without any known risk-stratifying aberrations (Table 3), as also reported in a previous study.[21] Furthermore, we and others[13,18] show that all *IKZF1* lesions at diagnosis are preserved at relapse, again supporting the poor prognostic impact of *IKZF1* aberrations.

Deletions involving the PAR1 region, associated with deregulation of *CRLF2*,[49,50] were also a significant independent risk factor (Table 4). However, all samples with PAR1 deletions from patients with subsequent R/IF also harbored *IKZF1* deletions, whereas all PAR1 deletion-positive cases without *IKZF1* abnormalities remain in CR1 (Supplementary Table 10), again indicating that *IKZF1* is the most significant factor for inferior EFS. Although *SPRED1* deletions co-occurred with *IKZF1* changes (Supplementary Table 10) and the number of cases is small, it does not negate an important prognostic impact of *SPRED1* in BCP ALL, not least since all cases with *SPRED1* deletions relapsed or had induction failure.

Thus, we suggest that analyses of *IKZF1* and *SPRED1* at diagnosis provide clinically important information and that the *IKZF1* status should be risk stratifying in future study protocols, in agreement with a recent study,[51] whereas further investigations of *SPRED1* aberrations are needed to elucidate their independent prognostic impact.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary information is available at *Leukemia*s website.

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Figure legends

Figure 1. **Kaplan-Meyer estimates of EFS of the 209 BCP ALL patients in relation to clinical and cytogenetic features.** The 10-yr pEFS in the total patient cohort enrolled in the NOPHO ALL 1992 and 2000 treatment protocols was 0.75 (0.03) (not shown in the plots). (A) Age <10 years: 10-yr pEFS 0.78 (SE 0.04) vs. age 10 years or more: 0.56 (0.10). (B) WBC count <10 x 10^9/l: 10-yr pEFS 0.76 (0.05) vs. 10-50 x 10^9/l: 0.81 (0.07) vs. 51-100 x 10^9/l: 0.67 (0.11) vs. >100 x 10^9/l: 0.25 (0.15). (C) Cytogenetic subgroups high hyperdiploidy (HeH): 10-yr pEFS 0.77 (0.06) vs. t(12;21): 0.72 (0.10) vs. t(9;22): 0.00 (0.00) vs. t(1;19): 1.00 vs. *MLL* rearrangement: 0.50 (0.35) vs. near-haploidy (NH): 0.00 (0.00) vs. normal karyotype (NK): 0.93 (0.07) vs. other (comprising other cytogenetic abnormalities and cytogenetic failures): 0.65 (0.08). (D) Risk groups standard: 10-yr pEFS 0.79 (0.06) vs. intermediate: 0.80 (0.06) vs. high: 0.54 (0.09).

Figure 2. Kaplan-Meyer estimates of EFS of the 145 BCP ALL cases analyzed by SNP arrays. The 10-yr pEFS of the analyzed patient cohort enrolled in the NOPHO ALL 1992 and 2000 treatment protocols was 0.73 (0.04) (not shown in the plots). In each plot, the curves representing gene targets and imbalances are denoted in blue and those representing unaffected gene targets/imbalances in green. (A) *ATP10A*: 10-yr pEFS 0.00 (0.00) vs. 0.75 (0.04). (B) *IKZF1*: 10-yr pEFS 0.45 (0.10) vs. 0.80 (0.04). (C) *SPRED1*: 10-yr pEFS 0.00 (0.00) vs. 0.75 (0.04). (D) Pseudoautosomal region 1 (PAR1) on Xp/Yp: 10-yr pEFS 0.25 (0.20) vs. 0.75 (0.04).

Figure 3. Kaplan-Meyer estimates of OS of the 145 BCP ALL cases analyzed by SNP arrays. The 10-yr pOS in the analyzed patient cohort enrolled in the NOPHO ALL 1992 and 2000 treatment protocols was 0.85 (0.03) (not shown in the plots). In each plot, the curves representing gene targets and imbalances are denoted in blue and those representing unaffected gene targets/imbalances in green. (A) *IKZF1*: 10-yr pOS 0.73 (0.09) vs. 0.88

(0.03). (B) *SPRED1*: 10-yr pOS 0.33 (0.27) vs. 0.86 (0.03).

Table 1. Clinical and genetic features of the 77 ALL cases with relapse/induction failure

Clinical features	N (%)	Genetic features	N (%)
Sex		**Subgroup**	
Female	29 (38)	HeH/(51-67 chromosomes)	17 (22)
Male	48 (62)	NH/(23-29 chromosomes)	4 (5.2)
Age (years)		t(1;19)(q23;p13)/*TCF3-PBX1*	0 (0)
<1	8 (10)	t(9;22)(q34;q11)/*BCR-ABL1*†	4 (5.2)
1-9	52 (68)	11q23/*MLL* rearrangement±	9 (12)
10-17	17 (22)	t(12;21)(p13;q22)/*ETV6-RUNX1*	13 (17)
Immunophenotype		Normal karyotype	6 (7.8)
B-lineage	67 (87)	Other	24 (31)
T-lineage	10 (13)	**SNP array analysis of diagnostic samples**	
WBC count (x10^9/l)		Yes	58 (75)
0-9	31 (40)	No	12 (16)
10-49	15 (19)	Failure	7 (9.1)
50+	31 (40)	**SNP array analysis of remission samples**	
Events		Yes	33 (43)
R	60 (78)	No	41 (53)
BM	44 (73)	Failure	3 (3.9)
CNS	8 (13)	**SNP array analysis of R/IF samples**	
Testis	5 (8.3)	Yes	21 (34)
CNS+testis	2 (3.3)	No	46 (60)
Ovary	1 (1.7)	Failure	10 (6.5)
IF	17 (22)		
Alive			
Yes	40 (52)		
No	37 (48)		

ALL, indicates acute lymphoblastic leukemia; BM, bone marrow; CNS, central nervous system; HeH, high hyperdiploidy; IF, induction failure; N, number; NH, near-haploidy; R, relapse, SNP, single nucleotide polymorphism; WBC, white blood cell.

†Of the 4 cases with *BCR-ABL1* fusion, two had the P190 transcript and one had the P210 transcript; the type of transcript was unknown in one case.

±Of the 9 cases with *MLL* rearrangement, four had *MLL-AFF1* [t(4;11)(q21;q23)], three had *MLL-MLLT1* [t(11;19)(q23;p13.3)], one had *MLL-GAS7* [t(11;17)(q23;p13)], and one had an unknown partner gene

Table 2. Frequencies of recurrent gene targets/imbalances in the diagnostic BCP ALL samples from patients with relapse compared with patients without such an event

Genes targets/ Imbalances	38 with R N (%)	146 without R N (%)	*P*-value±
Gene targets†			
ADD3 (10q25.1)¤	5 (13)	2 (1.4)	**0.005**
ATP10A (15q12)¤	5 (13)	1 (0.7)	**0.002**
CDKN2A (9p21.3)¤	11 (29)	36 (25)	0.677
EBF1 (5q33.3)¤	6 (16)	4 (2.7)	**0.006**
ETV6 (12p13.2)¤	8 (21)	33 (23)	1.000
IKZF1 (7p12.2)¤	15 (39)	15 (10)	**<0.001**
PAN3 (13q12.2)¤	4 (11)	3 (2.1)	**0.034**
PAX5 (9p13.2)¤	13 (34)	36 (25)	0.232
RAG1 (11p12)¤	5 (13)	5 (3.4)	**0.033**
SPRED1 (15q14)¤	5 (13)	1 (0.7)	**0.002**
TBL1XR1 (3q26.31)¤	5 (13)	5 (3.4)	**0.027**
Imbalances			
del(3)(q13.2q13.2)*	6 (16)	10 (6.8)	0.104
del(6)(p22.2p22.2)*	6 (16)	6 (4.1)	**0.015**
del(6)(q14.1q25.3)*	7 (18)	12 (8.2)	0.077
dup(8)(q24.21q24.21)*	3 (7.9)	3 (2.1)	0.104
del(13)(q14.2q14.2)*	5 (13)	10 (6.8)	0.199
PAR1 deletion*	5 (13)	6 (4.1)	0.051

BCP ALL indicates B-cell precursor acute lymphoblastic leukemia; N, number; PAR1, pseudoautosomal region 1 on Xp/Yp; R, relapse.

†Focal and large deletions, whole chromosome losses (rare), and partial and whole chromosome UPDs combined.

±*P*-values as ascertained by Fisher´s exact test. Significant *P*-values are indicated in bold type.

¤Smallest overlap: *ADD3* (chr10:111,775,607-111,830,275); *ATP10A* (chr15:26,033,764-26,093,401); *CDKN2A* (chr9:21,970,901-21,970,989); *EBF1* (chr5:158,366,263-158,502,378); *ETV6* (chr12:11,943,969-12,015,706); *IKZF1* (chr7:50,418,242-50,422,230); *PAN3* (chr13:28,691,097-28,806,503); *PAX5* (chr9:36,927,364-37,010,622); *RAG1* (chr11:36,481,900-36,608,273); *SPRED1* (chr15:38,403,504-38,558,017); and *TBL1XR1* (chr3:176,911,471-177,336,402).

*Smallest overlap: chr3:112,069,766-112,208,750; chr6:26,153,335-26,167,951; chr6: 107,146,121-109,614,226; chr8:130,572,304-130,626,097; chr13:49,015,957-49,070,345; and chrX:14,011,68-15,666,46.

Table 3. Frequencies of recurrent gene targets/imbalances in the diagnostic BCP ALL samples with normal karyotypes, cytogenetic failures, or other cytogenetic abnormalities from patients with relapse compared with patients without such an event

Genes targets/ Imbalances	10 with R N (%)	48 without R N (%)	*P*-value±
Gene targets†			
CDKN2A (9p21.3)¤	6 (60)	15 (31)	0.089
IKZF1 (7p12.2)¤	7 (70)	7 (15)	**0.001**
PAX5 (9p13.2)¤	6 (60)	16 (33)	0.112
Imbalances			
PAR1 deletion*	3 (30)	5 (10)	0.131

BCP ALL indicates B-cell precursor acute lymphoblastic leukemia; N, number; PAR1, pseudoautosomal region 1 on Xp/Yp; R, relapse.

†Focal and large deletions, whole chromosome losses (rare), and partial UPDs combined.

±*P*-values as ascertained by Fisher´s exact test. Significant *P*-values are indicated in bold type.

¤Smallest overlap: *CDKN2A* (chr9:21,970,901-21,970,989); *IKZF1* (chr7:50,418,242-50,422,230); and *PAX5* (chr9:36,927,364-37,010,622).

*Smallest overlap: chrX:14,011,68-15,666,46.

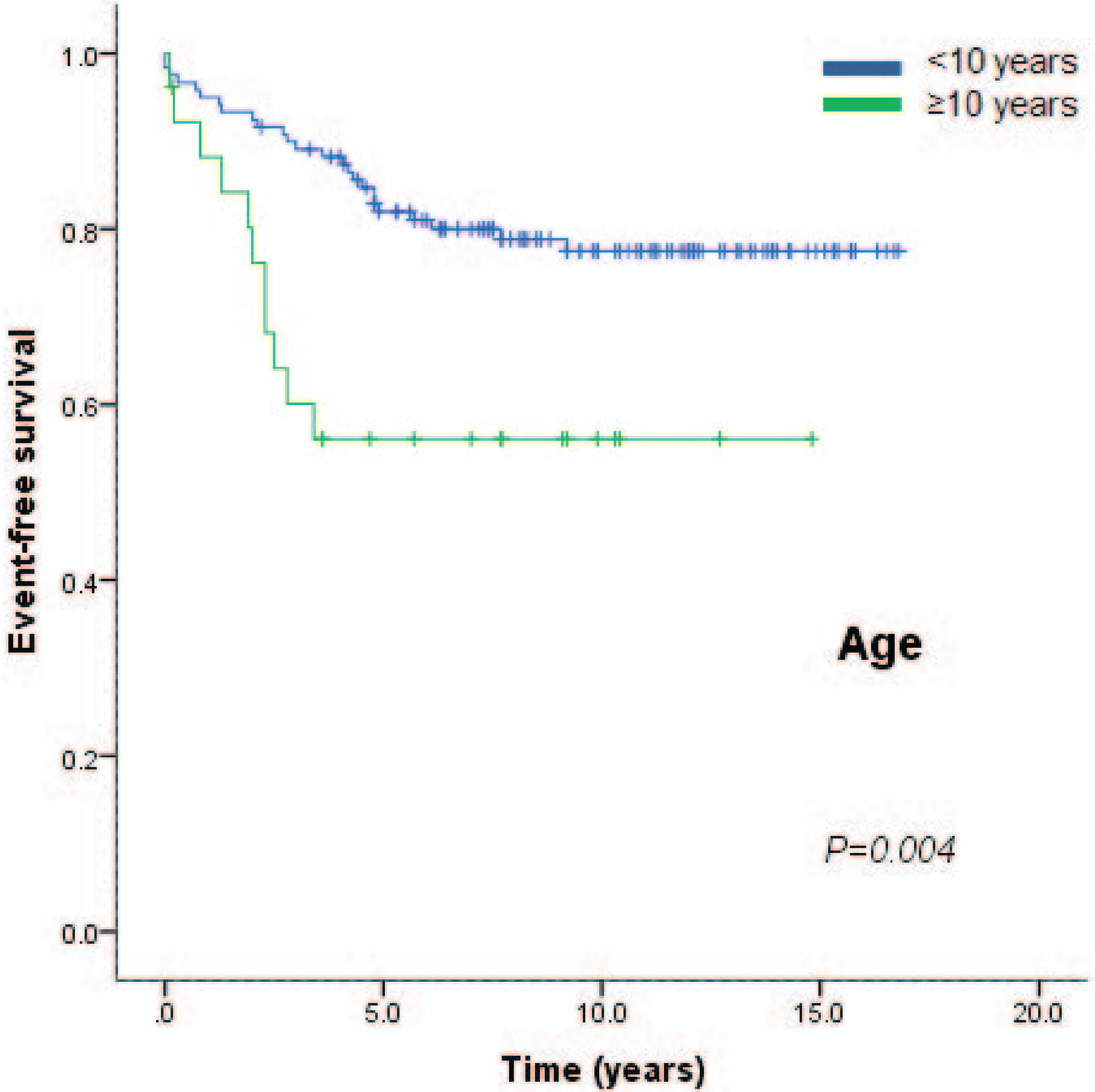
Table 4. Multivariate Cox regression analyses of EFS[a]

Risk factor	N	*P*-value±	HR	10-yr pEFS
WBC count (x10^9/l)		0.218	1.58	
<10	78			0.76
10-50	39			0.81
50-100	17			0.67
>100	7			0.25
Cytogenetic subgroup		0.618	1.88	
HeH	52			0.77
t(12;21)	32			0.72
t(1;19)	5			1.00
MLL	2			0.50
NK	14			0.93
Other	36			0.65
IKZF1		**0.010**	3.11	
Yes	25			0.45
No	116			0.80
PAR1 deletion		**0.036**	4.26	
Yes	6			0.25
No	135			0.75
Risk group		**0.049**	0.18	
Standard	53			0.79
Intermediate	58			0.80
High	30			0.54
Age (0-16)		**0.017**	0.23	
≤10	116			0.78
>10	25			0.56

CI indicates confidence interval; EFS, event-free survival; HeH, high hyperdiploidy (51-67 chromosomes); HR, hazard ratio; N, number; NK, normal karyotype; PAR1, pseudoautosomal region 1 on Xp/Yp; WBC, white blood cell.

[a]Based on 141 cases (cases with t(9;22) or near-haploidy are excluded).

±*P*-values as ascertained by Fisher´s exact test. Significant *P*-values are indicated in bold type.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≤10 years
≥10 years
Age
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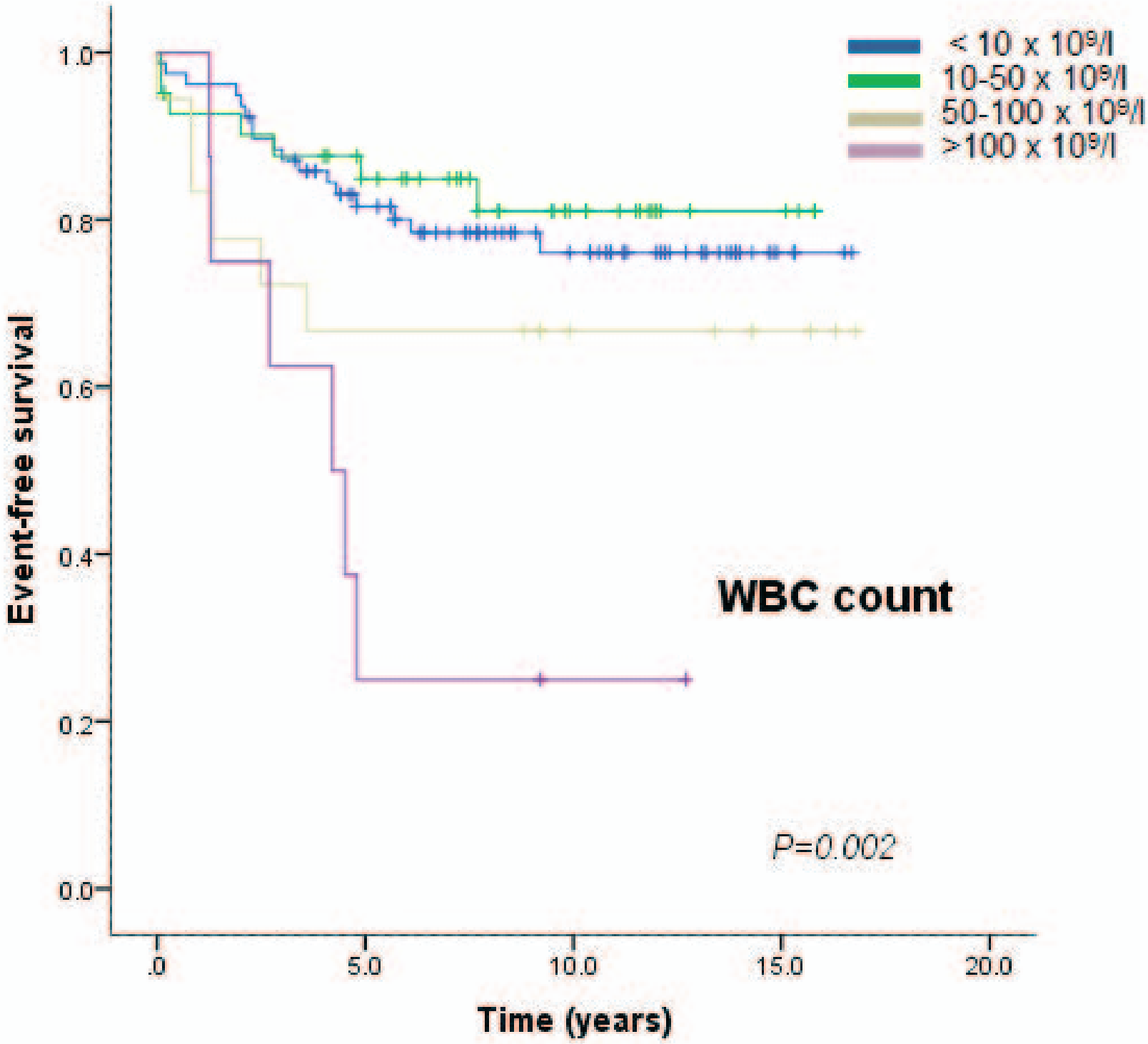
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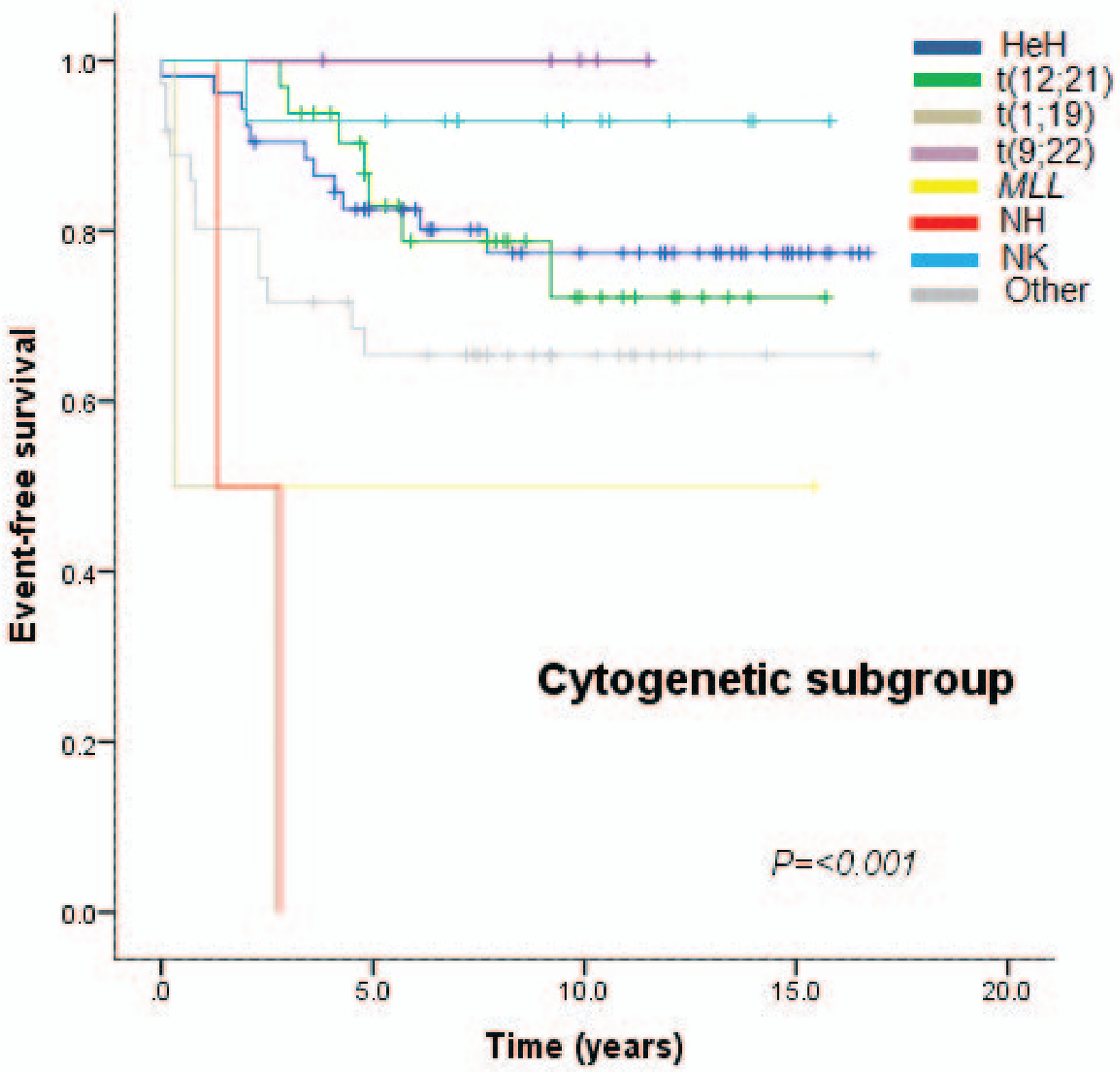
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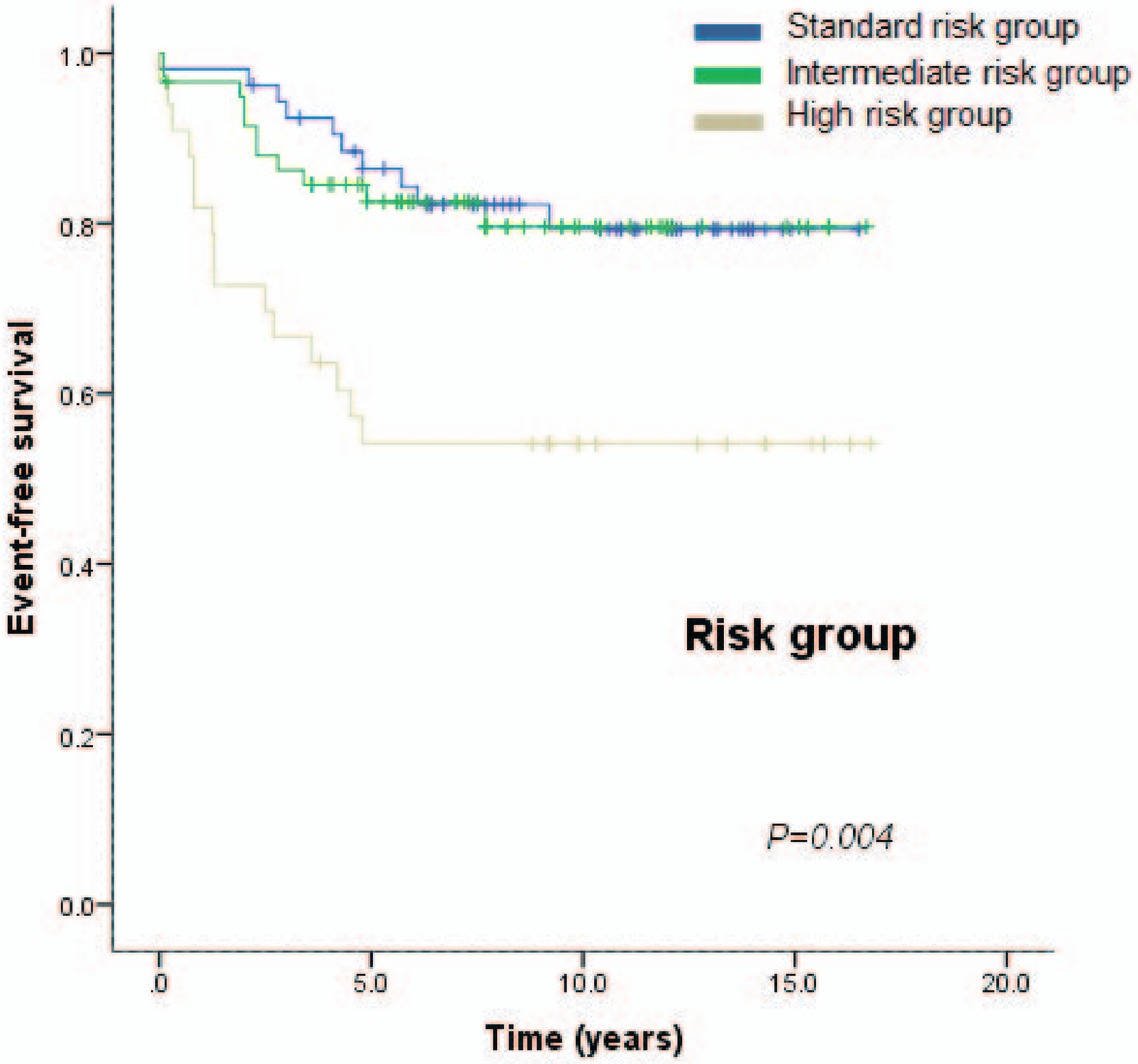
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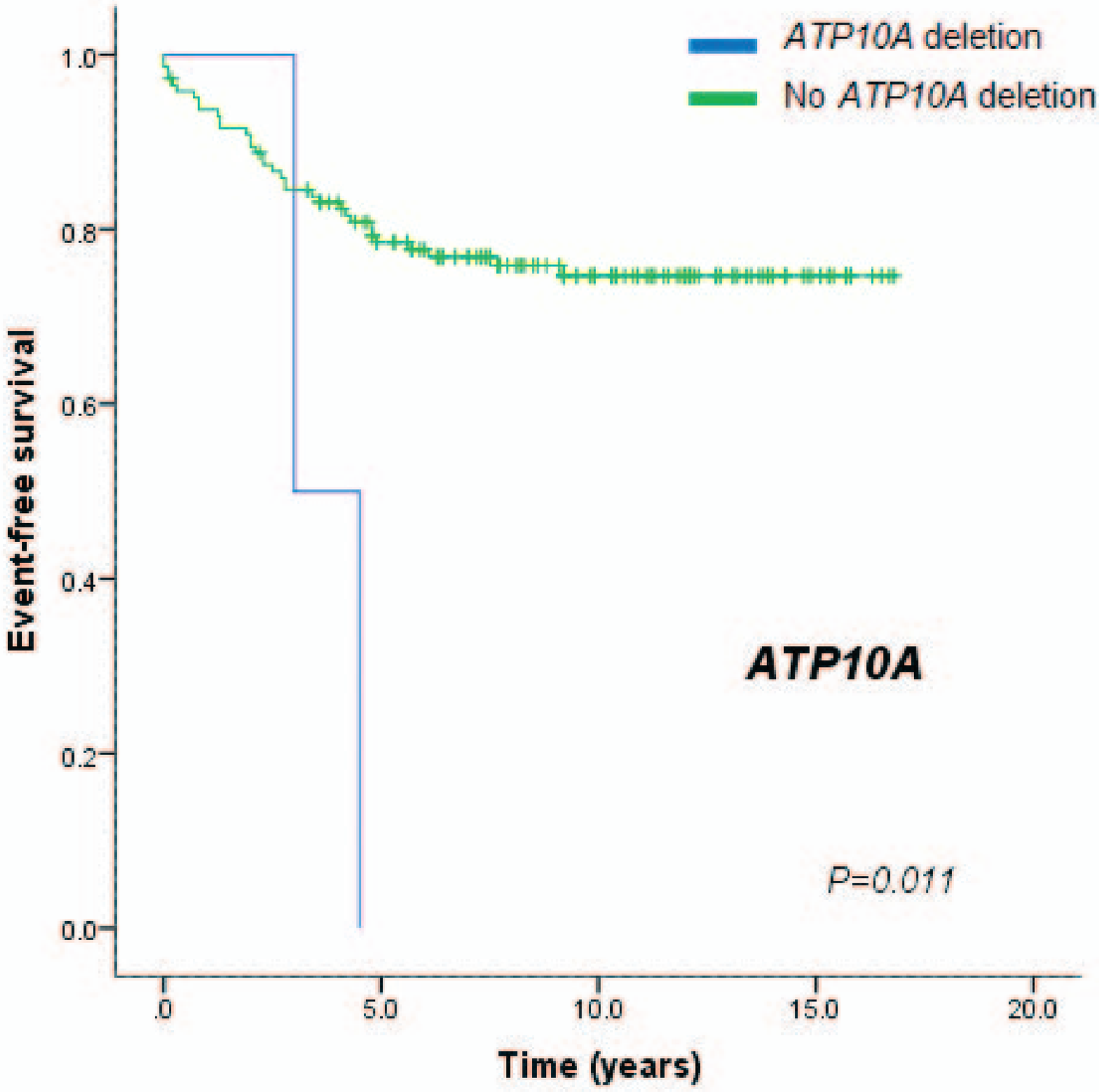
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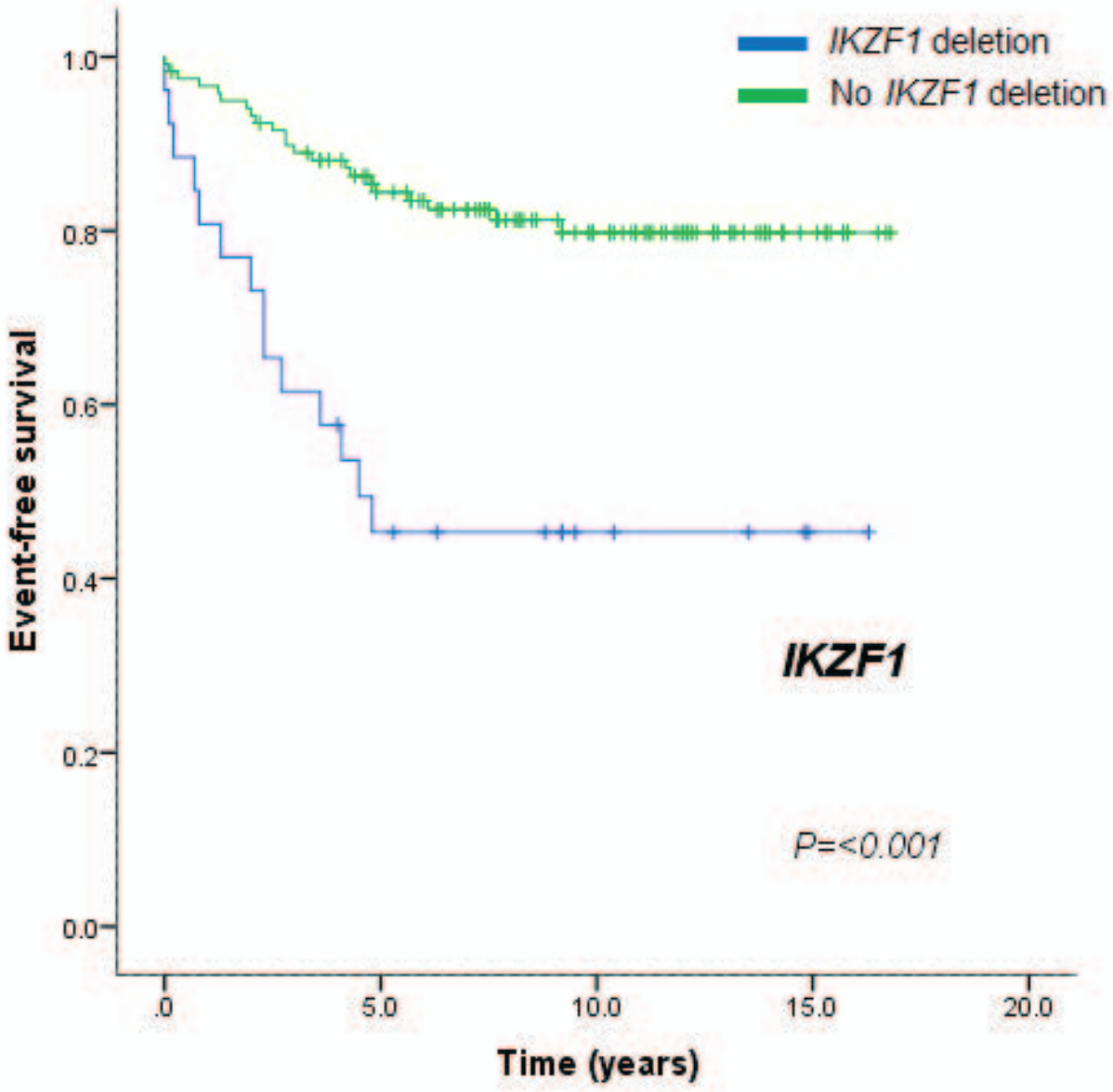
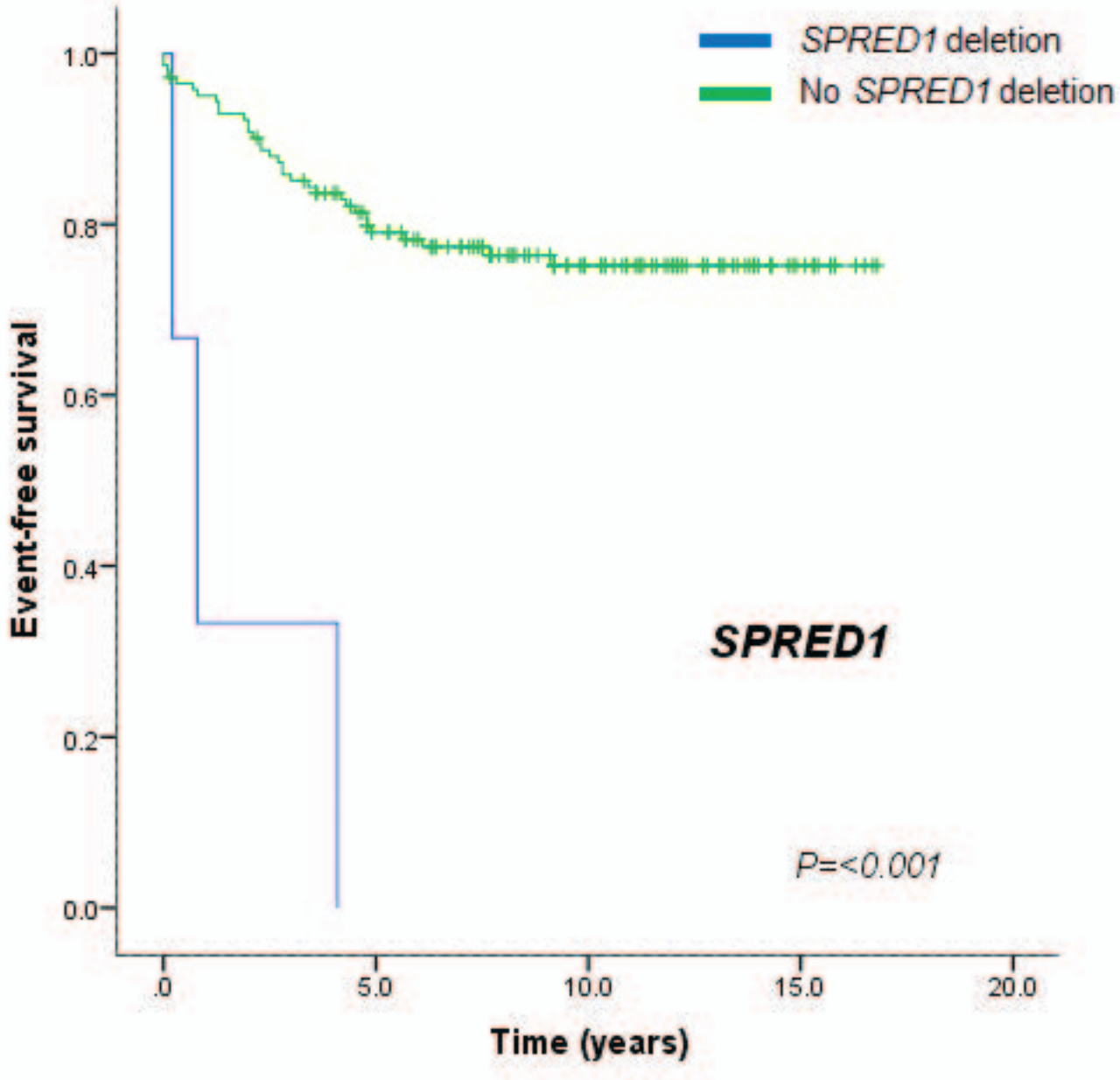
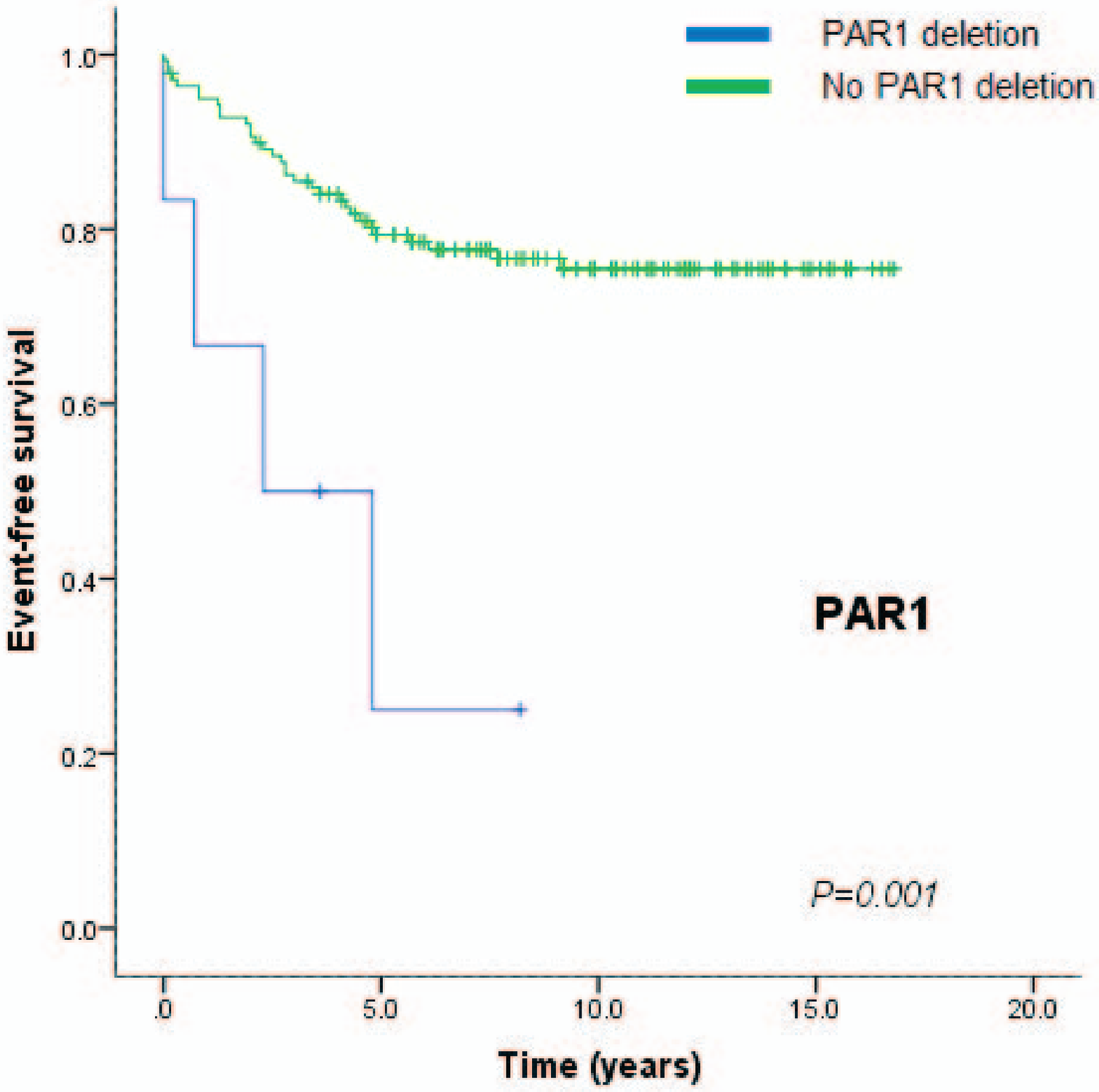
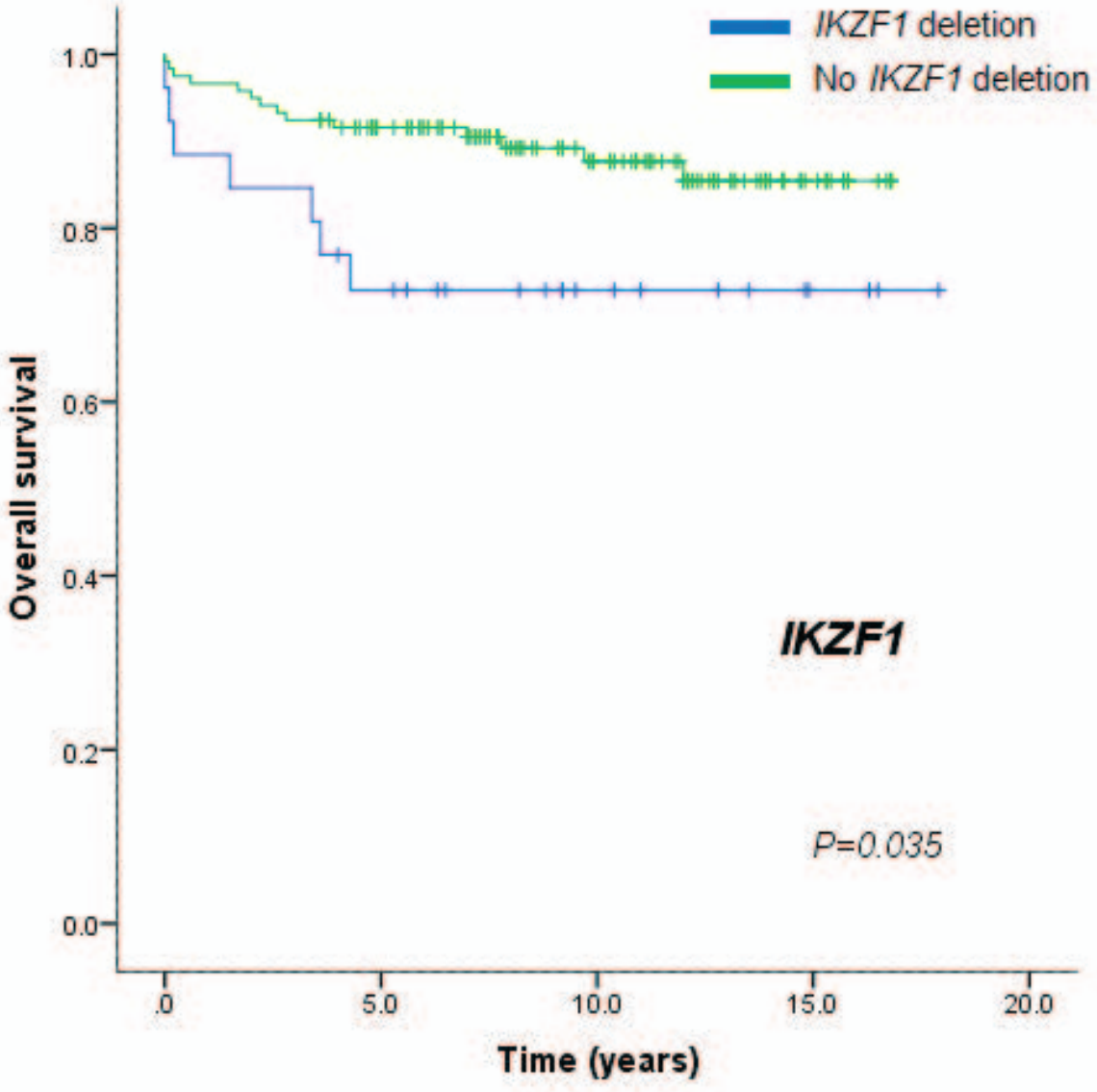
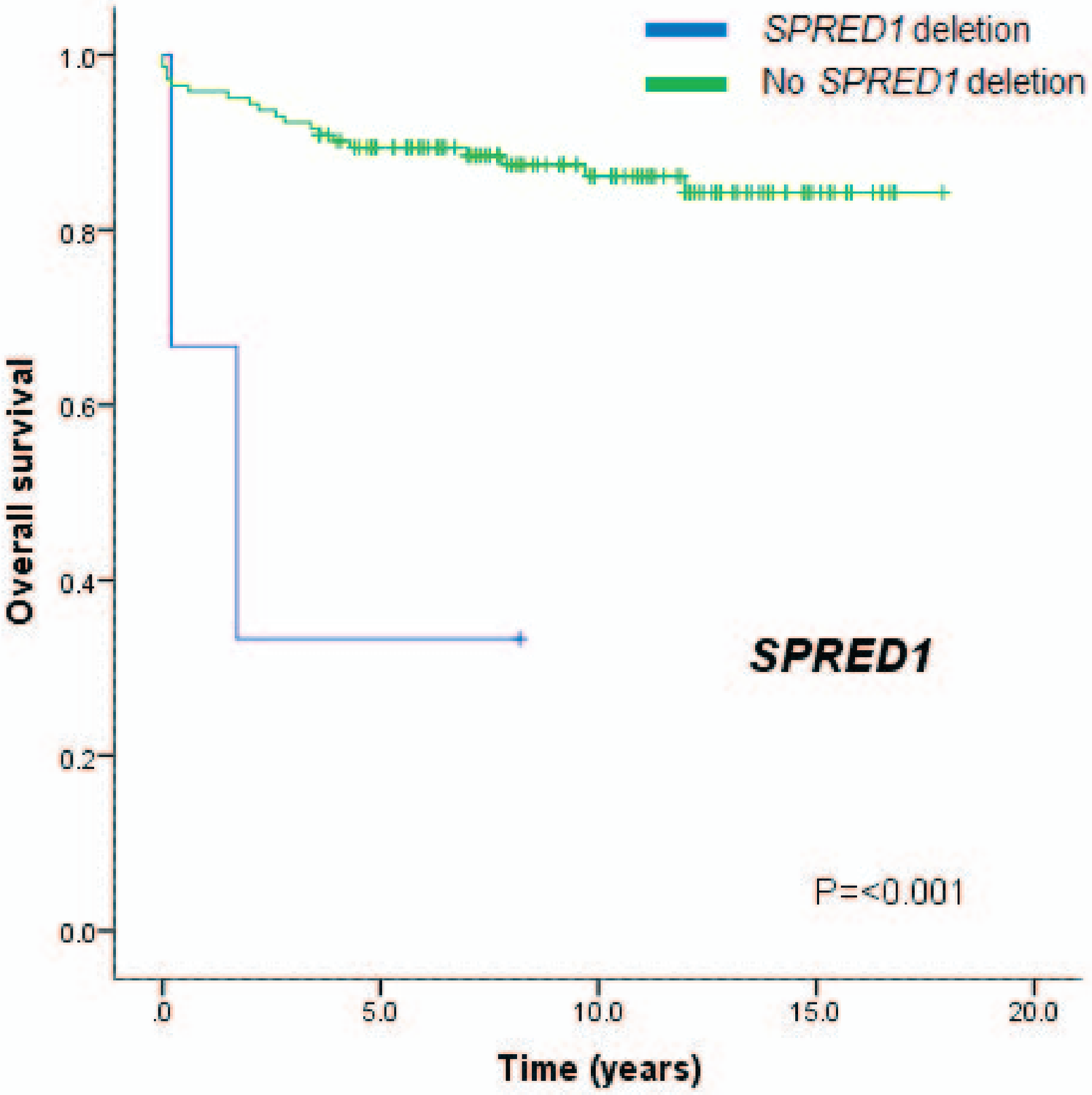
20.0
Time (years)


IKZF1 deletion
No IKZF1 deletion
Event-free survival
1.0
0.8
0.6
0.4
0.2
0.0
.0
5.0
10.0
15.0
20.0
Time (years)
IKZF1
P=<0.001


SPRED1 deletion
No SPRED1 deletion
Event-free survival
1.0
0.8
0.6
0.4
0.2
0.0
SPRED1
P=<0.001
.0
5.0
10.0
15.0
20.0
Time (years)


PAR1 deletion
No PAR1 deletion
1.0
0.8
0.6
0.4
0.2
0.0
Event-free survival
PAR1
P=0.001
.0
5.0
10.0
15.0
20.0
Time (years)


IKZF1 deletion
No IKZF1 deletion
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
IKZF1
P=0.035
.0
5.0
10.0
15.0
20.0
Time (years)


SPRED1 deletion
No SPRED1 deletion
1.0
0.8
0.6
0.4
0.2
0.0
Overall survival
SPRED1
P=<0.001
.0
5.0
10.0
15.0
20.0
Time (years)

Supplementary Table 1. Clinical and genetic features of the 307 ALL cases

Clinical features	N (%)	Genetic features	N (%)
Sex		**Karyotype**	
Female	129 (42)	Abnormal	246 (80)
Male	178 (58)	Normal	38 (12)
Age (years)		Failure	23 (7.5)
<1	16 (5.2)	**Modal chromosome number**	
1-9	234 (76)	<45	3 (1.0)
10-17	57 (19)	45	9 (2.9)
Mb Down†		46	121 (39)
No	292 (96)	47	32 (10)
Yes	11 (3.6)	48	7 (2.3)
Immunophenotype		49	5 (1.6)
B-lineage	273 (89)	50	2 (0.7)
T-lineage	33 (11)	51-67	70 (23)
Biphenotypic	1 (0.3)	>67	2 (0.7)
WBC count (x10^9/l)		NK	56 (18)
0-9	152 (50)	**t(1;19)(q23;p13)/*TCF3-PBX1***	
10-49	77 (25)	Yes	11 (3.6)
50+	78 (25)	No	235 (77)
Treatment protocols		NK	61 (20)
NOPHO ALL 1992	138 (45)	**t(9;22)(q34;q11)/*BCR-ABL1***	
NOPHO ALL 2000	94 (31)	Yes±	6 (2.0)
NOPHO ALL 2008	56 (18)	No	248 (81)
Other	19 (6.2)	NK	53 (17)
Events		**11q23/*MLL* rearrangement**	
CR1	216 (70)	Yes#	15 (4.9)
R	60 (20)	No	265 (86)
DCR1	10 (3.3)	NK	27 (8.8)
IF	17 (5.5)	**t(12;21)(p13;q22)/*ETV6-RUNX1***	
SMN	4 (1.3)	Yes	55 (18)
Alive		No	209 (68)
Yes	256 (83)	NK	43 (14)
No	51 (17)		

ALL, indicates acute lymphoblastic leukemia; CR1, complete remission 1; DCR1, death in CR1; IF, induction failure; N, number; NK, not known; NOPHO, Nordic Society of Paediatric Haematology and Oncology; R, relapse; SMN, secondary malignant neoplasm; WBC, white blood cell.

†Data on Mb Down missing in four cases.
±Of the six cases with *BCR-ABL1* fusion, three had the P190 transcript and two had the P210 transcript; the type of transcript was not ascertained in one case.
#Of the 15 cases with *MLL* rearrangement, four had *MLL-AFF1* [t(4;11)(q21;q23)], four had *MLL-MLLT1* [t(11;19)(q23;p13.3)], two had *MLL-MLLT3* [t(9;11)(p21;q23)], one had *MLL-MLLT10* [t(10;11)(p12;q23)], one had *MLL-GAS7* [t(11;17)(q23;p13)], and three had unknown partner genes.

Supplementary Table 2. Clinical and cytogenetic data on the 77 ALL cases with R/IF

Case No.	Sex/ Age	WBC† ($x10^9$/l)	Time to event (mo)	Type of event	Pheno-type	Sub-group	Karyotype at diagnosis/ karyotype at R/IF	SNP± Array/Build GRCh36.1/37
1#	F/10	2.3	28	R	BCP	Other	46,XX,del(1)(p22),+3,del(11)(q23),-12,-21,+der(?)t(?;1)(?;p22)	Y/37
				(BM)			46,XX,der(1;?)t(1;?)(q42;?)?t(1;12)(p22;q24),+?i(3)(p10),del(11),der(12) t(1;12)(p22;q24),-21	Y/37
2#	M/3	3.4	73	R	BCP	HeH	55,XY,+X,+4,+6,+10,+14,+17,+18,+21,+21	Y/37
				(BM)			53-55,XY,+X,+4,+6,+10,+14,+17,+21,inc	Y/37
3#	M/7	290	30	R	T	NK	46,XY	Y/37
				(BM)			47,XY,-8,-13,?der(17)t(13;17)(q1?;p1?),+19,+2mar	Y/37
4#	F/5	6.3	52	R	BCP	HeH	53,XX,+4,+6,+10,+14,+18,+21,+21	Y/37
				(BM)			53,XX,+4,+6,+10,+14,+18,+21,+21	Y/37
5#	M/3	51	43	R	BCP	HeH	55,XY,+X,dup(1)(q12q44),+4,+5,+6,idic(7)(p11),+8,+10,+14,+17,+21	Y/37
				(BM)			52-54,XY,+X,+4,+6,idic(7),+10,+14,+17,+1-2mar	Y/37
6	F/10	55	30	R	BCP	Other	Failure	Y/37
				(BM)			47,XX,+X,t(1;7)(q23;q32),del(9)(p21p21),der(9)t(9;12)(p11;q21),der(12) t(9;12)del(9) [partly identified by FISH]	Y/37
7#	F/12	23	33	R	BCP	NH	26,X,+X,+14,+21/52,idemx2	Y/37
				(BM)			26,X,+X,+14,+21/52,idemx2	Y/37
8#	M/15	59	10	R	BCP	Other	50,XY,+X,+14,+21,+21	Y/37
				(BM)			50,XY,+X,+14,+21,+21 [relapses 1 and 2]	Y/37
9#	M/6	3.2	49	R	BCP	HeH	55,XY,+X,+4,i(7)(q10),+8,+9,+10,+14,+18,+21,+21	Y/37
				(BM)			??,X?,+8,+21,+21 [identified by FISH]	Y/37
10#	M/7	187	6	R	T	Other	??,X?,del(9)(p21p21)x2 [identified by FISH]	Y/36.1

				(BM)			??,X?,del(9)x2 [identified by FISH]	Y/37
11#	M/5	2.2	25	R	BCP	HeH	55,XY,+X,+6,+9,+14,+14,+17,+18,+21,+21/55,idem,dup(4)(p15p16),	Y/37
				(BM)			dup(10)(q11q26)	
							54,XY,+21,+21,inc	Y/37
12#	F/2	10	17	R	BCP	NH	27,X,+X,+14,+18,+21/54,idemx2	Y/37
				(BM)			27,X,+X,+14,+18,+21/54,idemx2	Y/37
13	F/0	137	6	R	BCP	MLL	46,XX,t(11;19)(q23;p13.3)	Y/37
				(BM)			??,X?,der(11)(q23) [identified by FISH]	Y/37
14	M/2	194	0	IF	BCP	t(9;22)	46,XY,t(9;22)(q34;q11)/45,idem,dic(12;20)(p11;q11)	Y/37
				(d 15)			??,X?,t(9;22) [identified by FISH]	Y/37
15	M/10	3.2	0	IF	BCP	Other	??,X?,+21 [identified by FISH]	Y/37
				(d 15)			??,X?,+21 [identified by FISH]	Y/37
16	M/6	8.2	0	IF	BCP	HeH	??,X?,+X,+6,+8,+8,+10,+14,+14,+18,+18,+21,+21 [identified by FISH]	Y/37
				(d 15)			??,?X,+8,+8,+21,+21 [identified by FISH]	Y/37
17	M/1	71	0	IF	BCP	Other	46,XY,t(12;17)(p13;q11-12)/47,idem,+21	Y/37
				(d 15)			??,X?,+21 [identified by FISH]	Y/37
18	F/3	77	0	IF	BCP	Other	46,XX,add(12)(p12),-21,+mar	Y/37
				(d 29)			Not analyzed	N
19#	M/11	3.9	23	R	BCP	HeH	54,XY,+X,+4,+6,+14,+del(17)(p11),+18,+21,+21/55,idem,+9	Y/37
				(BM)			52-53,XY,+X,+6,+14,+17,+18,+21,+21,inc	N
20#	M/2	496	54	R	BCP	Other	Failure	Y/37
				(BM)			45,XY,dic(9;20)(p11;q11)/45,idem,del(6)(q21q25)	N
21	F/1	61	16	R	BCP	NH	25,X,+X,+21/50,idemx2	Y/36.1
				(BM)			50,XX,-7,-10,+6mar/50,idem,-2,+mar	N
22	M/14	29	24	R	BCP	NK	46,XY	Y/37

				(CNS)			46,XY	N
23	F/1	93	9	R	BCP	Other	46,XX,+2mar,inc	Y/36.1
				(BM)			Not analyzed	N
24#	F/1	44	1	IF	BCP	Other	46,X,-X,-9,-10,-11,-12,+3mar	Y/36.1
				(d 29)			Not analyzed	N
25#	F/3	109	58	R	BCP	t(12;21)	46,XX,del(12)(p13p13),der(21)t(12;21)(p13;q22),inc [identified by FISH]	Y/37
				(BM)			44,X,-X,?der(1)add(1)(p36)t(1;21)(q?;q?),-4,-5,del(6)(q?21),add(11)(p11), -12,del(12),der(21)t(12;21),+der(?) [partly identified by FISH]	N
26#	F/2	129	15	R	BCP	HeH	53,XX,+X,+8,+14,+15,+17,+21,+21	Y/37
				(BM)			52-54,XX,+X,+8,+14,+17,+21,inc/52-54,idem,+21	N
27#	M/3	14	92	R	BCP	HeH	56,XY,+X,+4,+6,+8,+10,+14,+17,+18,+21,+21	Y/37
				(testis)			46,XY	N
28#	M/2	768	0	IF	T	NK	46,XY	Y/36.1
				(d 29)			Not analyzed	N
29#	M/8	4.4	0	IF	BCP	HeH	59,XXY,+Y,-1,-2,-3,-7,-8,-11,-12,del(12)(p12p13),-13,-15,-16,+18,-19,-20, +21,-22	Y/37
				(d 29)			Not analyzed	N
30#	F/15	3.5	41	R	BCP	HeH	57,XX,+X,+X,+4,+6,der(8)t(8;14)(p11;q12),+10,+14,+14,+17,+18,+21,+21	Y/37
				(BM)			57,XX,+X,+X,+4,+5,+6,+10,+11,+14,+17,+18,+21,+21	N
31	M/8	7.6	8	R	BCP	Other	46,XY,i(8)(q10)	Y/36.1
				(BM)			46,XY	N
32	F/5	15	3	R	BCP	t(9;22)	46,XX,t(9;22)(q34;q11)	Y/37
				(BM)			47,XX,t(4;9)(q25;p12),t(9;22),+der(22)t(9;22)	N
33	M/0	189	16	R	BCP	NK	46,XY	Y/36.1
				(CNS)			46,XY	N

34	M/9	132	32	R	BCP	t(9;22)	46,XY,t(9;22)(q34;q11)	Y/37
				(testis)			Not analyzed	N
35#	M/13	12	1	IF	T	Other	46,Y,t(X;14)(p11;q11)	Y/37
				(d 29)			Not analyzed	N
36#	M/9	0.9	110	R	BCP	t(12;21)	47,XY,t(12;21)(p13;q22),+der(21)t(12;21) [identified by FISH]	Y/37
				(CNS)			??,X?,t(12;21),+der(21)t(12;21) [identified by FISH]	N
37#	M/9	54	10	R	T	Other	47,XY,+9,del(9)(p21p21)x2 [partly identified by FISH]	Y/37
				(BM)			Not analyzed	N
38#	M/8	65	32	R	BCP	t(9;22)	47,dup(X)(q21q28),t(Y;14)(p11;q32),del(9)(p13p21),t(9;22)(q34;q11),	Y/37
				(BM)			del(11)(q22),+21c	
							??,X?,+21c [identified by FISH]	N
39#	M/6	4.5	68	R	BCP	t(12;21)	??,X?,t(12;21)(p13;q22),+der(21)t(12;21) [identified by FISH]	Y/36.1
				(CNS+testis)			46,XY	N
40	M/10	5.2	28	R	BCP	Other	Failure	Y/36.1
				(CNS)			44-45,XY,inv(9)(p11q12)c,-10,-18	N
41#	F/14	424	0	IF	T	Other	47,XX,t(12;14)(p13;q11),+mar	Y/37
				(d 29)			47,XX,t(1;8;19)(p34;q22;q13),t(12;14),+mar	N
42#	F/2	9.7	24	R	BCP	HeH	54,XX,+X,+6,+10,+14,+17,+18,+21,+21	Y/37
				(CNS)			46,XX	N
43	F/3	4.0	34	R	BCP	t(12;21)	46-47,XX,der(2)t(2;5)(p13;q13),del(4)(q11),del(5)(q13),der(6)t(2;6)	Y/36.1
				(BM)			(p13;p22),-9,del(12)(p11),der(12)t(4;12)(q11;p12),?add(13)(q?),-15,+21,	
							der(21)t(12;21)(p13;q22)x2,+der(?)t(?;6)(?;p?),+mar/46-47,idem,del(3)(q27),	
							-?add(13),+der(13)?t(3;13)(q27;q?) [partly identified by FISH]	
							Not analyzed	N
44#	M/17	67	0	IF	T	Other	46,XY,?t(11;12)(q13;q23),?del(21)(q22)	Y/36.1

				(d 29)			Not analyzed	N
45	M/2	1.6	58	R	BCP	Other	46,XY,der(2)ins(2;7)(q3?;?),der(7)del(7)(?p?)?inv(7) [partly identified by	Y/36.1
				(testis)			FISH]	N
							46,XY	
46#	M/13	17	1	IF	BCP	Other	47,XY,idic(7)(p11),+21c	Y/36.1
				(d 29)			Not analyzed	N
47	M/4	164	50	R	BCP	t(12;21)	??,X?,t(12;21)(p13;q22) [identified by FISH]	Y/36.1
				(BM)			Not analyzed	N
48	F/5	5.9	36	R	BCP	t(12;21)	45,XX,add(6)(q15),del(12)(p11),t(12;21)(p13;q22),-13,add(15)(q22) [partly	Y/36.1
				(CNS)			identified by FISH]	N
							??,X?,del(12)(p13p13),t(12;21) [identified by FISH]	
49	M/13	492	15	R	BCP	MLL	46,XY,t(4;11)(q21;q23)	Y/36.1
				(testis)			??,X?,der(11)(q23) [identified by FISH]	N
50#	M/2	7.8	0	IF	T	Other	46,XY,del(9)(p21p21) [identified by FISH]	Y/36.1
				(d 29)			46,XY,del(9) [identified by FISH]	N
51#	F/14	1.6	0	IF	BCP	Other	47,XX,dup(8)(q21q24),del(13)(q13q34),dup(14)(q32q32),del(15)(q13q21),	Y/36.1
				(d 29)			del(15)(q26q26),+21c	
							Not analyzed	N
52	F/6	14	59	R	BCP	t(12;21)	??,XX,t(12;21)(p13;q22),inc [identified by FISH]	Y/36.1
				(ovary)			??,X?,t(12;21) [identified by FISH]	N
53	F/0	184	13	R	BCP	MLL	46,XX,t(4;11)(q21;q23)	Y/36.1
				(BM)			46,XX,t(4;11),add(7)(p14)	N
54	F/1	134	8	R	T	Other	46,XX,del(9)(p21p21)x2 [identified by FISH]	Y/36.1
				(BM)			Not analyzed	N
55	M/2	14	4	R	BCP	HeH	54-56,XY,+X,+4,+6,+10,+14,+17,+18,+18,?+der(19)t(1;19)(q11;p13),	Y/37

				(CNS)			+21,+21	
							Not analyzed	N
56	F/1	228	13	R	T	NK	46,XX	Y/37
				(BM)			Not analyzed	N
57	F/0	160	4	R	BCP	MLL	46,XX,t(11;19)(q23;p13)	Y/37
				(BM)			Not analyzed	N
58	M/3	5.1	2	IF	BCP	Other	45,XY,?der(1)t(1;12)(q44;p13),dic(7;12)(p11;p11),del(12)(p13),-14,ins(14;?)	Y/37
				(d 15)			(q24;?),+der(?)t(?;12)(?;p13) [partly identified by FISH]	
							??,X?,der(12)(p13)x2 [identified by FISH]	N
59	F/15	0.8	58	R	BCP	NK	46,XX	N
				(BM)			46,XX	Y/36.1
60#	M/4	3.0	41	R	BCP	NH	46,XY	N
				(BM)			28,X,+X,+Y,+Y,+14,+18,+21/56,idemx2	Y/37
61#	M/2	6.0	31	R	BCP	HeH	53,XY,+X,+6,+14,+17,+18,+21,+21	N
				(BM)			54-56,XY,+X,del(1)(q32),der(1)t(1;?9)(q21;q13),+del(6)(?q13q21),-9,	Y/37
							+add(11)(q23),+14,add(15)(q2?5),+17,+19,+21,+21,+der(?)t(?;13)(?;q12)	
							[partly identified by FISH]	
62	M/4	9.6	34	R	BCP	t(12;21)	46,XY,t(12;21)(p13;q22) [identified by FISH]	N
				(BM)			46,XY,t(12;21) [identified by FISH]	Y/37
63	M/0	30	18	R	BCP	MLL	46,XY,t(4;11)(q21;q23)	N
				(BM)			Not analyzed	N
64#	M/4	2.9	41	R	BCP	t(12;21)	46,XY,t(4;19)(q21;q13),der(7)t(7;9)(q31;q32),add(9)(q22),t(12;21)(p13;q22),	N
				(BM)			add(14)(q21) [partly identified by FISH]	
							46,XY,t(4;19),der(7)t(7;9),add(9),t(12;21),add(14) [partly identified by	N
							FISH]	

65	M/16	1.9	9	R (BM)	BCP	HeH	52-70,XXY,+1,-2,-3,-4,-5,+6,+10,-12,-13,-14,-15,-16,-18,-19,-20,+21,+21, +21,-22	N
							Not analyzed	N
66	M/1	1.8	31	R (BM)	BCP	Other	Failure	N
							46,XY	N
67#	M/3	99	130	R (BM)	BCP	t(12;21)	46,XY,add(9)(p12),add(12)(p12),t(12;21)(p13;q22) [partly identified by FISH]	N
							??,X?,t(12;21) [identified by FISH]	N
68#	M/6	3.7	34	R (CNS+testis)	BCP	t(12;21)	46,XY,del(12)(p12),der(12)t(12;21)(p13;q22),ider(21)(q10)t(12;21) [identified by FISH]	N
							Not analyzed	N
69#	M/3	40	75	R (BM)	BCP	t(12;21)	46,XY,t(12;21)(p13;q22) [identified by FISH]	N
							47,Y,dup(X)(q25q28),t(12;21),+der(21)t(12;21) [partly identified by FISH]	N
70	M/0	130	7	R (BM)	BCP	MLL	46,XY,del(11)(q23),der(19)t(11;19)(q23;?)/46,XY,der(1)ins(1;11) (p36;q13q23),del(3)(q13),der(11)t(3;11)(q13;q13),der(19)t(11;1) [partly identified by FISH]	N
							Failure	N
71#	M/3	1.3	20	R (BM)	BCP	HeH	54-56,XY,+X,?add(1)(p?),+?3,+6,+?7,+11,+14,+17,+21,+21,+21,inc	N
							56,XY,+X,+4,+6,+8,+10,+14,+17,+21,+21,+21/57,idem,+15	N
72	M/1	22	76	R (CNS)	BCP	Other	46,XY,del(1)(q21),-7,-12,+mar,inc	N
							45,XY,-22	N
73#	F/1	3.1	15	R (BM)	BCP	MLL	46,XX,t(11;17)(q23;p13)	N
							46,XX,del(6)(q23),i(7)(q10),t(11;17)	N
74#	F/7	1.8	58	R (BM)	BCP	HeH	57-58,XXX,-1,-2,-3,-7,-9,-11,-12,-13,+14,-15,-16,+18,-19,-20,+21,-22	N
							??,XX,+X,+4,+6,+8,+8,+10,+14,+14,+17,+18,+18,+21,+21 [identified by	N

							FISH]	
75	F/0	215	1	IF	BCP	MLL	46,XX,t(4;11)(q21;q23),inc	N
				(d 29)			46,XX	N
76	M/2	3.1	52	R	BCP	t(12;21)	??,?X,t(12;21)(p13;q22),+der(21)t(12;21) [identified by FISH]	N
				(testis)			??,X?,del(12)(p13p13),t(12;21),+der(21) [identified by FISH]	N
77	F/0	802	0	IF	BCP	MLL	45,XX,-11,?der(19)del(19)(p13p13)t(11;19)(q23;q?13) [partly identified by	N
				(d 29)			FISH]	N
							??,X? [identified by FISH]	

ALL, indicates acute lymphoblastic leukemia; BCP, B-cell precursor; BM, bone marrow; CNS, central nervous system; d, day; F, female; FISH, fluorescence in situ hybridization; HeH, high hyperdiploidy (51-67 chromosomes); IF, induction failure; M, male; mo, months; N, no; NH, near-haploidy (23-29 chromosomes); NK, normal karyotype; R, relapse; SNP, single nucleotide polymorphism; T, T-cell; WBC, white blood cell count, Y, yes.

†At the time of diagnosis.

± SNP array analysis performed and informative at the time of diagnosis and/or at the time of R/IF.

The original karytypes of these cases have previously been reported.[1-11]

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Supplementary Table 3. Genomic aberrations that differed between the 17 paired diagnostic and R/IF samples

Case No.	Sub-Group[#]	Genomic imbalances/gene targets	Genetic relationship
1Dx	Other	del(7)(p11.2p13)/*IKZF1*[subclonal only]	Clonal evolution
1R		del(1)(p21.3p21.3),dup(1)(q21.1q41),del(1)(q41q44),del(2)(p16.3p16.3)/*MSH6*,*FBXO11*,del(3)(q26.32q26.32)/*TBL1XR1*†,dup(5)(q14.1q14.3),del(7)(p11.2p13)/*IKZF1*,del(17)(p13.1p13.1)/*GAS7*†	
2 Dx	HeH	None	Clonal evolution
2R		dup(1)(q12q32.2),del(16)(q13q22.1)	
3Dx	NK	None	Clonal evolution
3R		del(8)(p23.3q12.3),dup(13)(p13q12.13),UPD(13)(q12.13q14.13),del(13)(q14.13q34),+19,del(20)(q13.32q13.33)	
4Dx	HeH	None	Identical clones
4R		None	
5Dx	HeH	dup(1)(q21.1q44),+8,+10	Ancestral clone
5R		UPD(10)	
6Dx	Other	+X[subclonal only],dup(X)(q21.31q28)[subclonal only],del(9)(p13.2p13.3)/*PAX5*[subclonal only], del(12)(q21.33q21.33)/*BTG1*†	Clonal evolution
6R		+X,del(9)(p21.3p22.3),del(9)(p21.3p21.3)x2/*CDKN2A*/*B*,del(9)(p21.2p21.3),del(9)(p21.1p21.1),del(9)(p13.1p13.2)/*PAX5*,del(12)(q21.32q21.33),del(12)(q21.33q21.33)x2/*BTG1*†,del(12)(q22q22)	
7Dx	NH	None	Identical clones
7R		None	
8Dx	Other	UPD(12)(q14.1q24.33)/*BTG1*	Ancestral clone
8R		UPD(12)(q15q24.33)/*BTG1*,dup(16)(p13.2p13.3)	
9Dx	HeH	None	Clonal evolution
9R		del(5)(q31.3q31.3)/*NR3C*†	

10Dx	Other	None	Identical clones
10R		None	
11Dx	HeH	dup(4)(p15.2p16.3),dup(10)(q11.22q26.3),del(19)(p13.3p13.3)/*TCF3*[subclonal only]	Clonal evolution
11R		UPD(16)(p11.1p13.3)	
12Dx	NH	None	Clonal evolution
12R		+18,UPD(X)	
13Dx	MLL	None	Identical clones
13R		None	
14Dx	t(9;22)	None	Identical clones
14IF		None	
15Dx	Other	None	Identical clones
15IF		None	
16Dx	HeH	None	Clonal evolution
16IF		del(8)(q21.11q21.11),dup(21)(q22.11q22.12)	
17Dx	Other	None	Identical clones
17IF		None	

Dx, indicates diagnostic sample; HeH, high hyperdiploidy (51-67 chromosomes); IF, induction failure; NH, near-haploidy (23-29 chromosomes); NK, normal karyotype; R, relapse; UPD, uniparental isodisomy.

†Focal deletion in only the specified gene.

#Complete karyotypic data are given in Supplementary Table 2.

Supplementary Table 4. All genetic aberrations detected by SNP array analysis of 77 childhood ALL cases with R/IF

Case	Chr	Abnor-mality	LNS	Pos of LNS	FAS	Pos of FAS	LAS	Pos of LAS	FNS	Pos of FNS
1Dx	1	1+0	rs3828085	108143671	rs12049132	108163649	rs17019802	108267732	rs7519428	108281720
1Dx	5	1+0	rs26653	96139250	rs34761	96153624	rs2255564	96249115	rs10069631	96284803
1Dx	6	1+0	rs806973	26148326	rs9379827	26153335	rs16891484	26242930	kgb1575446	26248840
1Dx†	**7**	**1+0sc**	**rs3934887**	**44333582**	**rs10216205**	**44338223**	**rs10237524**	**56036024**	**rs7778601**	**56057893**
1Dx	11	1+0	rs11226868	105735093	rs1939153	105751726	qtel			
1Dx	12	1+0	rs7959807	11768558	rs7298077	11787103	rs2855711	12030306	rs2238133	12031465
1Dx	12	1+0	rs4485143	92238373	rs11106308	92255225	rs7977284	92332231	rs4542452	92338833
1Dx	12	1+0	rs2302689	110456175	rs2287174	110474070	kgp22851589	111856187		
1Dx	12	0+0			rs12301866	111863589	rs6490162	111941120		
1Dx	12	1+0			rs11065934	111946837	rs12314862	112322482	kgp19140377	112368013
1Dx	21	iAMP	rs4818659	15244894	rs2207836	15212271	qtel			
1R	**1**	**1+0**	**rs1514497**	**97617831**	**rs6683351**	**97645313**	**rs2811179**	**97974243**	**rs7533902**	**98079228**
1R	1	1+0	rs3828085	108143671	rs12049132	108163649	rs17019802	108267732	rs7519428	108281720
1R	**1**	**2+1**	**rs6424340**	**145161772**	**rs10797652**	**145564518**	**rs7546586**	**222168464**		
1R	**1**	**1+0**			**rs2800856**	**222174101**	**qtel**			
1R	**2**	**1+0**	**rs6736039**	**47778096**	**rs4952894**	**47857914**	**rs12105860**	**48185303**	**rs10203759**	**48234050**
1R	**3**	**1+0**	**rs7638794**	**176839656**	**rs6774257**	**176867736**	**rs7611527**	**176929742**	**rs3923106**	**176940408**
1R	**5**	**2+1**	**rs10074882**	**78602863**	**rs9293769**	**78629346**	**rs157566**	**89378726**	**rs16868203**	**89396257**
1R	5	1+0	rs26653	96139250	rs34761	96153624	rs2255564	96249115	rs10069631	96284803
1R	6	1+0	rs806973	26148326	rs9379827	26153335	rs16891484	26242930	kgb1575446	26248840

1R	**7**	**1+0**	**rs3934887**	**44333582**	**rs10216205**	**44338223**	**rs10237524**	**56036024**	**rs7778601**	**56057893**
1R	11	1+0	rs11226868	105735093	rs1939153	105751726	qtel			
1R	12	1+0	rs7959807	11768558	rs7298077	11787103	rs2855711	12030306	rs2238133	12031465
1R	12	1+0	rs4485143	92238373	rs11106308	92255225	rs7977284	92332231	rs4542452	92338833
1R	12	1+0	rs2302689	110456175	rs2287174	110474070	kgp22851589	111856187		
1R	12	0+0			rs12301866	111863589	rs6490162	111941120		
1R	12	1+0			rs11065934	111946837	rs12314862	112322482	kgp19140377	112368013
1R	**17**	**1+0**	**rs8069470**	**9901667**	**rs17810527**	**9917061**	**rs9907602**	**10016708**	**rs3764429**	**10025298**
1R	21	iAMP	rs4818659	15244894	rs2207836	15212271	qtel			
2Dx	4	2+1			ptel		qtel			
2Dx	6	2+1			ptel		qtel			
2Dx	10	2+1			ptel		qtel			
2Dx	14	2+1			ptel		qtel			
2Dx	17	2+1			ptel		qtel			
2Dx	18	2+1			ptel		qtel			
2Dx	21	2+2			ptel		qtel			
2Dx	X	2+0			ptel		qtel			
2R	**1**	**2+1**			**cen**		**rs7530104**	**210555619**	**rs910032**	**210611882**
2R	4	2+1			ptel		qtel			
2R	6	2+1			ptel		qtel			
2R	10	2+1			ptel		qtel			
2R	14	2+1			ptel		qtel			
2R	**16**	**1+0**	**rs7189433**	**57336624**	**rs1117361**	**57361346**	**rs2862780**	**68639338**	**rs7186053**	**68839293**

2R	17	2+1			ptel		qtel			
2R	18	2+1			ptel		qtel			
2R	21	2+2			ptel		qtel			
2R	X	2+0			ptel		qtel			
3Dx	9	1+0	rs1869203	21674949	rs7874607	21704498	kgp5244470	21852191		
3Dx	9	0+0			kgp10384822	21854159	kgp18533982	22038354		
3Dx	9	1+0			kgp1853747	22040290	rs7870973	23041233	rs7019344	23051397
3R	**8**	**1+0**			**ptel**		**rs2956319**	**65989848**	**rs7815138**	**66180525**
3R	9	1+0	rs1869203	21674949	rs7874607	21704498	kgp5244470	21852191		
3R	9	0			kgp10384822	21854159	kgp18533982	22038354		
3R	9	1+0			kgp1853747	22040290	rs7870973	23041233	rs7019344	23051397
3R	**13**	**2+1**			**ptel**		**rs9634341**	**26676511**		
3R	**13**	**3+0**			**rs1886455**	**26749216**	**rs9526073**	**46006512**		
3R	**13**	**1+0**			**rs9534150**	**46026549**	**qtel**			
3R	**19**	**2+1**			**ptel**		**qtel**			
3R	**20**	**1+0**	**rs723506**	**57044774**	**rs6070510**	**57134366**	**rs6061834**	**60379718**	**rs6089291**	**60467860**
4Dx	4	2+1			ptel		qtel			
4Dx	6	2+1			ptel		qtel			
4Dx	9	1+0	rs7852051	36 851 358	rs4074255	36878744	rs3824344	37000684	rs4880051	37007475
4Dx	10	2+1			ptel		qtel			
4Dx	13	1+0	rs4771218	28655311	rs7992211	28691097	rs1286887	28806503	rs1830792	28873907
4Dx	14	2+1			ptel		qtel			
4Dx	14	1+1	rs1534815	22302152	rs2320063	223270490	rs11157596	22907068	rs3811215	22954777

4Dx	14	1+1	rs17753885	78543376	rs11159324	78548438	rs1124299	78882921	rs17107538	78889839
4Dx	18	2+1			ptel		qtel			
4Dx	18	1+1	rs4797686	12431506	rs481103	12445407	rs11873650	13163903	rs4797728	13175481
4Dx	21	2+2			ptel		qtel			
4Dx	X	2+0			ptel		qtel			
4R	4	2+1			ptel		qtel			
4R	6	2+1			ptel		qtel			
4R	9	1+0	rs7850607	36872314	rs4074255	36878744	rs3824344	37000684	rs4880051	37007475
4R	10	2+1			ptel		qtel			
4R	13	1+0	rs4771218	28655311	rs7992211	28691097	rs1286887	28806503	rs1830792	28873907
4R	14	2+1			ptel		qtel			
4R	14	1+1	rs1534815	22302152	rs2320063	223270490	rs11157596	22907068	rs3811215	22954777
4R	14	1+1	rs17753885	78 543 376	rs11159324	78 548 438	rs1124299	78 882 921	rs17107538	78 889 839
4R	18	2+1			ptel		qtel			
4R	18	1+1	rs4797686	12431506	rs481103	12445407	rs11873650	13163903	rs4797728	13175481
4R	21	2+2			ptel		qtel			
4R	X	2+0			ptel		qtel			
5Dx	**1**	**2+1**	**rs2495288**	**120392355**	**rs2479584**	**145475728**	**qtel**			
5Dx	4	2+1			ptel		qtel			
5Dx	5	2+1			ptel		qtel			
5Dx	6	2+1			ptel		qtel			
5Dx	7	1+0			ptel		rs4948093	56024287		
5Dx	7	2+1			rs6970237	61779325	qtel			

5Dx	**8**	**2+1**			**ptel**		**qtel**			
5Dx	**10**	**2+1**			**ptel**		**qtel**			
5Dx	13	1+0	rs4771218	28655311	rs7992211	28691097	rs1286887	28806503	rs1830792	28873907
5Dx	14	2+1			ptel		qtel			
5Dx	17	2+1			ptel		qtel			
5Dx	21	2+1			ptel		qtel			
5Dx	X	2+0			ptel		qtel			
5R	4	2+1			ptel		qtel			
5R	5	2+1			ptel		qtel			
5R	6	2+1			ptel		qtel			
5R	7	1+0			ptel		rs4948093	56024287		
5R	7	2+1			rs6970237	61779325	qtel			
5R	**10**	**2+0**			**ptel**		**qtel**			
5R	13	1+0	rs4771218	28655311	rs7992211	28691097	rs1286887	28806503	rs1830792	28873907
5R	14	2+1			ptel		qtel			
5R	17	2+1			ptel		qtel			
5R	21	2+1			ptel		qtel			
5R	X	2+0			ptel		qtel			
6Dx	**9**	**1+0sc**	**rs10738931**	**34565781**	**rs2279790**	**34917851**	**rs7867764**	**37436105**	**rs7865834**	**37518761**
6Dx	**12**	**1+0**	**rs10507004**	**92274855**	**rs11834329**	**92278448**	**rs28399541**	**92537956**	**rs7977912**	**92563472**
6Dx	**X**	**2+1sc**			**ptel**		**qtel**			
6Dx	**X**	**2+1**	**rs959060**	**86667108**	**rs4631605**	**86811737**	**qtel**			
6R	**9**	**1+0**	**rs2105317**	**15799343**	**rs6474977**	**15836848**	**rs10811474**	**21114237**		

6R	**9**	**0+0**			**rs1424853**	**21122462**	**rs18667821**	**22600088**		
6R	**9**	**1+0**			**kpg18454305**	**22601619**	**rs7046442**	**26087907**	**rs10967199**	**26102954**
6R	**9**	**1+0**	**rs10967253**	**26233664**	**rs1434857**	**26241359**	**rs7849166**	**26583020**	**rs17692544**	**26597540**
6R	**9**	**1+0**	**rs16933266**	**36386218**	**rs2480462**	**36401167**	**rs7853023**	**38772575**	**cnvi0065351**	**38865868**
6R	**12**	**1+0**	**rs17013677**	**86569348**	**rs839156**	**86595690**	**rs10507004**	**92274855**		
6R	**12**	**0+0**			**rs11834329**	**92278448**	**rs28399541**	**92537956**		
6R	**12**	**1+0**			**rs7977912**	**92563472**	**rs8699**	**96051883**	**rs7959749**	**96051177**
6R	**X**	**2+1**			**ptel**		**qtel**			
7Dx	1	2+0			ptel		qtel			
7Dx	2	2+0			ptel		qtel			
7Dx	3	2+0			ptel		qtel			
7Dx	4	2+0			ptel		qtel			
7Dx	5	2+0			ptel		qtel			
7Dx	6	2+0			ptel		qtel			
7Dx	7	2+0			ptel		qtel			
7Dx	8	2+0			ptel		qtel			
7Dx	9	2+0			ptel		qtel			
7Dx	10	2+0			ptel		qtel			
7Dx	11	2+0			ptel		qtel			
7Dx	12	2+0			ptel		qtel			
7Dx	13	2+0			ptel		qtel			
7Dx	14	2+2			ptel		qtel			
7Dx	15	2+0			ptel		qtel			

7Dx	16	2+0	ptel	qtel
7Dx	17	2+0	ptel	qtel
7Dx	18	2+0	ptel	qtel
7Dx	19	2+0	ptel	qtel
7Dx	20	2+0	ptel	qtel
7Dx	21	2+2	ptel	qtel
7Dx	22	2+0	ptel	qtel
7Dx	X	2+2	ptel	qtel
7R	1	2+0	ptel	qtel
7R	2	2+0	ptel	qtel
7R	3	2+0	ptel	qtel
7R	4	2+0	ptel	qtel
7R	5	2+0	ptel	qtel
7R	6	2+0	ptel	qtel
7R	7	2+0	ptel	qtel
7R	8	2+0	ptel	qtel
7R	9	2+0	ptel	qtel
7R	10	2+0	ptel	qtel
7R	11	2+0	ptel	qtel
7R	12	2+0	ptel	qtel
7R	13	2+0	ptel	qtel
7R	14	2+2	ptel	qtel
7R	15	2+0	ptel	qtel

7R	16	2+0			ptel		qtel			
7R	17	2+0			ptel		qtel			
7R	18	2+0			ptel		qtel			
7R	19	2+0			ptel		qtel			
7R	20	2+0			ptel		qtel			
7R	21	2+2			ptel		qtel			
7R	22	2+0			ptel		qtel			
7R	X	2+2			ptel		qtel			
8Dx	6	1+0	rs9793917	156574933	rs6905758	156614278	rs9397945	156875069	rs288956	156893548
8Dx	7	2+0			ptel		rs13242473	2130014	rs3800918	2167978
8Dx	**12**	**2+0**	**rs1245652**	**62600764**	**rs10877822**	**62691991**	**qtel**			
8Dx	14	2+1			ptel		qtel			
8Dx	15	1+0	rs11638085	38323263	rs17639328	38341249	rs8032812	38540364	rs8035425	38558974
8Dx	21	2+2			ptel		qtel			
8Dx	X	2+0			ptel		qtel			
8R1	6	1+0	rs9793917	156574933	rs6905758	156614278	rs9397945	156875069	rs288956	156893548
8R1	7	2+0			ptel		rs13242473	2130014	rs3800918	2167978
8R1	**12**	**2+0**	**rs1442275**	**68910449**	**rs11611360**	**69157749**	**qtel**			
8R1	14	2+1			ptel		qtel			
8R1	15	1+0	rs11638085	38323263	rs17639328	38341249	rs8032812	38540364	rs8035425	38558974
8R1	**16**	**2+1**			**ptel**		**rs10400954**	**8694634**	**rs2270286**	**8722629**
8R1	21	2+2			ptel		qtel			
8R1	X	2+0			ptel		qtel			

8R2	6	1+0	rs9793917	156574933	rs6905758	156614278	rs9397945	156875069	rs288956	156893548
8R2	7	2+0			ptel		rs3800875	2117261	rs6972752	2196551
8R2	**12**	**2+0**	**rs1442275**	**68910449**	**rs11611360**	**69157749**	**qtel**			
8R2	14	2+1			ptel		qtel			
8R2	15	1+0	rs11638085	38323263	rs17639328	38341249	rs8032812	38540364	rs8035425	38558974
8R2	**16**	**2+1**			**ptel**		**rs10400954**	**8694634**	**rs2270286**	**8722629**
8R2	21	2+2			ptel		qtel			
8R2	X	2+0			ptel		qtel			
9Dx	4	2+1			ptel		rs4862580	186793887		
9Dx	4	3+1			rs6819746	186832817	rs7677258	188486138		
9Dx	4	2+1			rs2172340	188938468	qtel			
9Dx	6	1+0	rs6908263	26129375	rs707899	26129948	rs9358913	26239404	rs11753610	26359251
9Dx	7	1+0			ptel		cen			
9Dx	7	2+1			cen		qtel			
9Dx	8	2+1			ptel		qtel			
9Dx	9	2+1			ptel		qtel			
9Dx	10	2+1			ptel		qtel			
9Dx	14	2+1			ptel		qtel			
9Dx	15	1+0	rs1393418	38379425	rs7183608	38403504	Rs8032812	38540364	Rs16966575	38558017
9Dx	18	2+1			ptel		qtel			
9Dx	21	2+2			ptel		qtel			
9Dx	21	1+0	rs283653	39753346	rs2836362	39764784	rs2836393	39805913	rs2836399	39813955
9Dx	X	2+0			ptel		qtel			

9R	4	2+1			ptel		rs4862580	186793887		
9R	4	3+1			rs6819746	186832817	rs7677258	188486138		
9R	4	2+1			rs2172340	188938468	qtel			
9R	**5**	**1+0**	**rs258747**	**142656813**	**rs17209258**	**142673397**	**rs6877893**	**142727193**	**rs11749561**	**142791677**
9R	6	1+0	rs6908263	26129375	rs707899	26129948	rs9358913	26239404	rs11753610	26359251
9R	7	1+0			ptel		cen			
9R	7	2+1			cen		qtel			
9R	8	2+1			ptel		qtel			
9R	9	2+1			ptel		qtel			
9R	10	2+1			ptel		qtel			
9R	14	2+1			ptel		qtel			
9R	15	1+0	rs1393418	38379425	rs7183608	38403504	Rs8032812	38540364	Rs16966575	38558017
9R	18	2+1			ptel		qtel			
9R	21	2+2			ptel		qtel			
9R	21	1+0	rs283653	39753346	rs2836362	39764784	rs2836393	39805913	rs2836399	39813955
9R	X	2+0			ptel		qtel			
10Dx	9	0+0	rs10123003	21610510	rs13297146	21616953	SNP9-22178039	22178039		
10Dx	9	1+0			SNP9-22180001	22180001	rs1448779	22796356	rs9298841	22801336
10R	9	0+0	rs10123003	21610510	rs13297146	21616953	SNP9-22178039	22178039		
10R	9	1+0			SNP9-22180001	22180001	rs1448779	22796356	rs9298841	22801336
11Dx	**4**	**2+1sc**			**ptel**		**9790789**	**26861656**	**10022599**	**26894656**
11Dx	6	2+1			ptel		qtel			
11Dx	9	2+1			ptel		qtel			

11Dx	**10**	**2+1sc**	**rs35578984**	**48716207**	**rs1652244**	**49458749**	**qtel**			
11Dx	14	2+2			ptel		qtel			
11Dx	17	2+1			ptel		qtel			
11Dx	18	2+1			ptel		qtel			
11Dx	**19**	**1+0sc**			**ptel**		**rs353694**	**4243792**	**rs10409783**	**4555786**
11Dx	21	2+2			ptel		qtel			
11Dx	X	2+0			ptel		qtel			
11R	6	2+1			ptel		qtel			
11R	9	2+1			ptel		qtel			
11R	14	2+2			ptel		qtel			
11R	**16**	**2+0**			**ptel**		**cen**			
11R	17	2+1			ptel		qtel			
11R	18	2+1			ptel		qtel			
11R	21	2+2			ptel		qtel			
11R	X	2+0			ptel		qtel			
12Dx	1	2+0			ptel		qtel			
12Dx	2	2+0			ptel		qtel			
12Dx	3	2+0			ptel		qtel			
12Dx	4	2+0			ptel		qtel			
12Dx	5	2+0			ptel		qtel			
12Dx	6	2+0			ptel		qtel			
12Dx	7	2+0			ptel		qtel			
12Dx	8	2+0			ptel		qtel			

12Dx	9	2+0			ptel		qtel			
12Dx	9	0+0	rs7847028	20361231	rs4675430	20430468	rs4565546	20909336	rs8406776	20928323
12Dx	10	2+0			ptel		qtel			
12Dx	11	2+0			ptel		qtel			
12Dx	12	2+0			ptel		qtel			
12Dx	13	2+0			ptel		qtel			
12Dx	14	2+2			ptel		qtel			
12Dx	15	2+0			ptel		qtel			
12Dx	16	2+0			ptel		qtel			
12Dx	17	2+0			ptel		qtel			
12Dx	18	2+2			ptel		qtel			
12Dx	19	2+0			ptel		qtel			
12Dx	20	2+0			ptel		qtel			
12Dx	21	2+2			ptel		qtel			
12Dx	22	2+0			ptel		qtel			
12Dx	X	2+2			ptel		qtel			
12R	1	2+0			ptel		qtel			
12R	2	2+0			ptel		qtel			
12R	3	2+0			ptel		qtel			
12R	4	2+0			ptel		qtel			
12R	5	2+0			ptel		qtel			
12R	6	2+0			ptel		qtel			
12R	7	2+0			ptel		qtel			

12R	8	2+0			ptel		qtel			
12R	9	2+0			ptel		qtel			
12R	9	0+0	rs7847028	20361231	rs4675430	20430468	rs4565546	20909336	rs8406776	20928323
12R	10	2+0			ptel		qtel			
12R	11	2+0			ptel		qtel			
12R	12	2+0			ptel		qtel			
12R	13	2+0			ptel		qtel			
12R	14	2+2			ptel		qtel			
12R	15	2+0			ptel		qtel			
12R	16	2+0			ptel		qtel			
12R	17	2+0			ptel		qtel			
12R	**18**	**2+1**			**ptel**		**qtel**			
12R	19	2+0			ptel		qtel			
12R	20	2+0			ptel		qtel			
12R	21	2+2			ptel		qtel			
12R	22	2+0			ptel		qtel			
12R	**X**	**2+0**			**ptel**		**qtel**			
13Dx	NA									
13R	NA									
14Dx	7	1+0	rs10251980	50366637	rs7785321	50418242	rs6964823	50460096	rs11980379	50469981
14Dx	12	1+0sc	rs12313493	9175109	rs1012588	9270835	rs4575342	38663831	rs12308157	39421767
14Dx	18	1+0	rs7230788	22927757	rs10163652	22942497	rs5003540	23111439	rs8090239	23124693
14Dx	20	1+0sc	rs6088244	32110204	rs3746460	32248163	qtel			

14IF	7	1+0	rs10251980	50366637	rs7785321	50418242	rs6964823	50460096	rs11980379	50469981
14IF	12	1+0	rs12313493	9175109	rs1012588	9270835	rs4575342	38663831	rs12308157	39421767
14IF	18	1+0	rs7230788	22927757	rs10163652	22942497	rs5003540	23111439	rs8090239	23124693
14IF	20	1+0	rs6088244	32110204	rs3746460	32248163	qtel			
15Dx	1	2+1	rs2055975	150618632	rs10788792	150638572	rs12723898	151552672	rs12122920	151588735
15Dx	9	2+0			ptel		rs1052656	34087360	rs2275003	34124860
15Dx	9	0+0			rs45476696	21970901	rs13298881	22012051		
15Dx	15	1+0	rs6576456	26009240	rs7165728	26018232	rs11637218	26093401	rs1553892	26114681
15Dx	17	1+0			ptel		rs624068	16496257	rs2349276	16650205
15IF	1	2+1	rs2055975	150618632	rs10788792	150638572	rs12723898	151552672	rs12122920	151588735
15IF	9	2+0			ptel		rs1052656	34087360	rs2275003	34124860
15IF	9	0+0			rs45476696	21970901	rs13298881	22012051		
15IF	15	1+0	rs6576456	26009240	rs7165728	26018232	rs11637218	26093401	rs1553892	26114681
15IF	17	1+0			ptel		rs624068	16496257	rs2349276	16650205
16Dx	2	2+1			ptel		qtel			
16Dx	4	2+1			ptel		qtel			
16Dx	7	2+1			ptel		qtel			
16Dx	12	2+1			ptel		qtel			
16Dx	13	2+1			ptel		qtel			
16Dx	15	2+1			ptel		qtel			
16Dx	16	2+1			ptel		qtel			
16Dx	17	2+1			ptel		qtel			
16IF	2	2+1			ptel		qtel			

16IF	4	2+1			ptel		qtel			
16IF	7	2+1			ptel		qtel			
16IF	12	2+1			ptel		qtel			
16IF	13	2+1			ptel		qtel			
16IF	15	2+1			ptel		qtel			
16IF	16	2+1			ptel		qtel			
16IF	17	2+1			ptel		qtel			
16IF	8	1+0	rs7015958	75453034	rs7845621	75457070	rs1560846	77529466	rs17348969	77539322
16IF	21	2+1	rs8128316	35721560	rs11702479	35725729	rs2834506	35907413	rs2834541	35932619
17Dx	NA									
17IF	NA									
18Dx	6	1+0	kgp17393080	26142816	kgp17155241	26143824	rs34550794	26199014	rs41266803	26199454
18Dx	7	1+0	rs7797255	50351604	rs10251980	50366637	rs12538151	50474223	rs6959427	50479414
18Dx	9	1+0	rs780607	36872314	rs1815916	36881096	rs2297105	37020622	cnvi0151506	37035456
18Dx	X	0+0			rs35437602	1303007	rs7062063	1566646		
18Dx	X	2+0			ptel		rs6653903	33630471	rs5972914	33648254
18IF	ND									
19Dx	4	2+1			ptel		qtel			
19Dx	6	2+1			ptel		qtel			
19Dx	8	2+1	rs4733711	130545445	rs6987588	130572304	rs4130415	130718712	rs4501553	130718314
19Dx	14	2+1			ptel		qtel			
19Dx	17	2+1	rs2363251	21511575	rs11869425	21717007	qtel			
19Dx	18	2+1			ptel		qtel			

19Dx	X	2+0			ptel		cnvi0162194	3734551	rs5915682	3956940
19R	ND									
20Dx	1	1+0	cnvi0157087	174724828	cnvi0111970	174800121	rs6688577	174884161	rs6701127	175090094
20Dx	5	1+0	rs7734532	118484804	rs11742202	118495671	rs3797337	118553470	rs10051559	118558400
20Dx	5	1+0	rs6190	142780337	rs10482617	142781168	rs17346995	143058402	rs7707734	143076516
20Dx	7	1+0	rs10251980	50366637	rs7785321	50418242	rs6964823	50460096	rs11980379	50469981
20Dx	9	1+0			ptel		cen			
20Dx	9	0+0			kgp9393505	21895053	rs3217992	22003223		
20Dx	12	1+0	rs7314552	110618890	rs2339404	110659314	kgp311713	112605127	rs10492014	112640554
20Dx	15	1+0	rs17637170	26017504	rs8042764	26033764	rs7166725	26106233	rs11639272	26121579
20Dx	20	1+0	rs2070090	31427635	rs6058959	31513585	qtel			
20R	NC									
21Dx	1	2+0			ptel		qtel			
21Dx	2	2+0			ptel		qtel			
21Dx	3	2+0			ptel		qtel			
21Dx	4	2+0			ptel		qtel			
21Dx	5	2+0			ptel		qtel			
21Dx	6	2+0			ptel		qtel			
21Dx	7	2+0			ptel		qtel			
21Dx	8	2+0			ptel		qtel			
21Dx	9	2+0			ptel		qtel			
21Dx	10	2+0			ptel		qtel			
21Dx	11	2+0			ptel		qtel			

21Dx	12	2+0			ptel		qtel			
21Dx	13	2+0			ptel		qtel			
21Dx	14	2+0			ptel		qtel			
21Dx	15	2+0			ptel		qtel			
21Dx	16	2+0			ptel		qtel			
21Dx	17	2+0			ptel		qtel			
21Dx	18	2+0			ptel		qtel			
21Dx	19	2+0			ptel		qtel			
21Dx	20	2+0			ptel		qtel			
21Dx	21	2+2			ptel		qtel			
21Dx	22	2+0			ptel		qtel			
21Dx	X	2+2			ptel		qtel			
21R	F									
22Dx	9	2+0			ptel		rs10971649	33703252	rs2050789	33880690
22Dx	9	0+0			kgp4863634	21827992	kgp18302985	21991752		
22Dx	9	1+0	rs12340833	36802626	rs2851695	36820262	rs13296908	37258237	rs186299	37356403
22Dx	18	1+0	rs652504	264012	rs4798013	277076	rs8083260	547239	rs595879	572336
22R	ND									
23Dx	3	1+0	rs3996189	107059601	rs4894961	107082836	rs12488982	107399150	rs12489296	107407966
23Dx	7	1+0sc	rs11506039	50315090	rs12719019	50443633	rs10225988	128005491		
23Dx	7	1+0			rs10954205	128094809	qtel			
23Dx	8	1+0	rs2616157	20728567	rs2583691	20758966	rs7845666	42420853	rs9643888	42471164
23Dx	9	1+0			ptel		rs2029647	37213751	rs10758428	37244690

23Dx	9	0+0			rs10114121	19430136	rs10811771	22760886		
23Dx	12	1+0	rs465530	63617033	rs466735	63624440	rs10467141	63852531	rs10878239	63865254
23Dx	17	1+0	rs3966782	4747877	rs7214776	4752393	rs11658826	16232477	rs35480612	16252010
23Dx	20	1+0	rs6141772	30710323	rs12480157	30726581	rs1056885	60190884	rs1760058	60194113
23R	ND									
24Dx	1	2+1	rs10888878	55015907	rs1147988	55032255	rs4111070	55968247	rs3122551	56019804
24Dx	7	1+0	rs37715	110666487	rs1978247	110680087	rs1558078	110909710	rs10251897	110919879
24Dx	8	1+0	rs4521804	16569399	rs1541933	16578568	rs1523655	16844360	rs1721109	16857563
24Dx	9	1+0	rs2039461	20135988	rs4478647	20166715	SNP9-21912184	21912184		
24Dx	9	0+0			SNP9-21907393	21907393	rs3217986	21995330		
24Dx	9	1+0			rs3217973	21999960	SNP9-22166294	22166294	SNP9-22175092	22175092
24Dx	10	1+0	rs7901991	90301297	rs12247690	90319767	rs1008013	103538856	rs10883689	103576346
24Dx	12	1+0	rs7306351	7879028	rs7965203	7891603	rs11056665	8007335	rs7964540	8022225
24Dx	12	1+0	rs1153976	46288667	rs1233059	46329712	rs1476608	46779998	rs41291959	46799294
24IF	ND									
25Dx	9	0+0	kgb18571671	21974525	rs1424853	21122462	rs18667821	22600088	rs3217973	22009960
25Dx	9	1+0	rs1573257	36896143	rs7032626	36927364	rs7031295	37020950	rs1411060	37046091
25Dx	12	1+0			ptel		rs4764141	15090372	rs2041902	15196798
25Dx	X	1+0	rs4474173	33367420	rs9887051	33393169	qtel			
25R	NC									
26Dx	8	2+1			ptel		qtel			
26Dx	14	2+1			ptel		qtel			
26Dx	15	2+1			ptel		qtel			

26Dx	17	2+1			ptel		qtel			
26R	ND									
27Dx	1	2+0			ptel		qtel			
27Dx	2	1+0	rs4076342	241846140	rs4602221	241933700	qtel			
27Dx	4	2+1			ptel		qtel			
27Dx	6	2+1			ptel		qtel			
27Dx	7	2+0			ptel		qtel			
27Dx	8	2+1			ptel		qtel			
27Dx	10	2+1			ptel		qtel			
27Dx	11	2+0			ptel		qtel			
27Dx	14	2+1			ptel		qtel			
27Dx	17	2+1			ptel		qtel			
27Dx	18	2+1			ptel		qtel			
27R	ND									
28Dx	5	1+0	rs7735001	145878088	rs7701877	145891232	rs319185	146252596	rs319167	146273237
28Dx	5	1+0	rs153750	171113842	rs4868120	171120783	rs2291045	172165671	rs9313609	172233007
28Dx	5	1+0	rs7713272	175426661	rs13163755	175651918	rs10078062	177358427	rs4073771	177417894
28Dx	9	1+0			ptel		SNP9-21900653	21900653		
28Dx	9	0+0			SNP9-21904836	21904836	rs3217986	21995330		
28Dx	9	1+0			SNP9-22000412	22000412	cen			
28Dx	9	2+1			cen		qtel			
28Dx	14	1+0	rs3850416	96934613	rs17835973	96952345	rs1026624	97295130	rs1973150	97331822
28IF	ND									

29Dx	4	2+1			ptel		qtel			
29Dx	5	2+1			ptel		qtel			
29Dx	6	2+1			ptel		qtel			
29Dx	9	2+1			ptel		qtel			
29Dx	10	2+1			ptel		qtel			
29Dx	12	1+0	rs28653187	9436446	rs2429893	9453571	rs4764291	16904214	rs10846451	17099885
29Dx	13	1+0	rs1407827	49710986	rs9591243	49759627	rs17252027	51751705	rs6561622	51807188
29Dx	14	2+1			ptel		qtel			
29Dx	17	2+1			ptel		qtel			
29IF	ND									
30Dx	3	1+0	rs2184207	175510677	rs9888045	175658506	rs9856476	178996626	rs6776229	179015775
30Dx	4	2+1			ptel		qtel			
30Dx	6	2+1			ptel		qtel			
30Dx	8	1+0			ptel		406494	37217380	rs16887011	37538022
30Dx	10	2+1			ptel		qtel			
30Dx	12	1+0	rs11048434	9153932	rs18056073	9163059	rs3825272	13155339	rs4763939	13316944
30Dx	13	1+0	rs7991143	99797929	rs7322572	99879496	rs12870762	102157767	rs1414304	102186981
30Dx	14	1+0sc	rs2145587	32981484	rs2383347	33037521	qtel			
30Dx	17	2+1			ptel		qtel			
30Dx	18	2+1			ptel		qtel			
30Dx	21	2+2			ptel		qtel			
30R	ND									
31Dx	4	1+0	rs28661998	133404111	rs2062467	133456387	rs9995035	133671104	rs13147558	133677689

31Dx	5	1+0	rs17771891	131772101	rs10071051	131780519	rs2244012	131929124	rs10520114	131976790
31Dx	6	1+0	rs8013	107124847	rs7756087	107146121	rs6568450	107317364	rs6920626	107332714
31Dx	6	1+0	rs1885625	157377757	rs2207227	157398783	rs1007250	157503677	rs6557534	157508658
31Dx	7	1+0	rs10251980	50337181	rs7800411	50386119	rs6962370	50422230	rs6959427	50446908
31Dx	8	1+0			ptel		rs7012896	24339182	rs17738359	24387094
31Dx	8	2+1sc	rs2926702	71330548	rs16936888	71369974	qtel			
31Dx	9	1+0	SNP9-21964525	21964525	SNP9-21969559	21969559	SNP9-22113575	22113575	SNP9-22114123	22114123
31Dx	9	1+0	rs4880034	36903925	rs12349215	36909993	rs7853360	36933396	rs4880042	36940301
31Dx	10	1+0	rs4556470	111754698	rs2060675	111763413	rs2501574	111840493	rs4495833	111859915
31Dx	11	1+0	rs2227973	36553889	rs1399599	36564848	rs12273195	36583769	rs11033726	36608716
31Dx	12	1+0	rs10744	88266035	rs1689411	88275216	rs7143172	88365848	rs4842658	88377539
31Dx	12	1+0	rs7958824	90767743	rs11106315	90783901	rs790575	91055739	rs12694	91063721
31Dx	X	1+0	rs28368841	1384265	rs28584401	1361167	rs6644734	1608783	rs5989676	1638713
31R	ND									
32Dx	NA									
32R	NC									
33Dx	8	1+0			ptel		rs4259380	30367862	rs952774	30394884
33Dx	8	2+1	rs1373803	34380636	rs4249176	34436451	rs2342618	40481325	rs11996359	40525563
33Dx	9	1+0			ptel		rs10974947	5062846		
33Dx	9	2+1			rs2230724	5071780	rs6476976	5461514	rs7862541	5594769
33Dx	9	2+1	rs1926403	7416221	rs2997573	7452598	rs13287364	8150714	rs7869449	8158457
33Dx	9	1+0	rs1959404	9178865	rs4620334	9211800	rs7467207	15736302	rs6474967	15750988
33Dx	9	1+0	rs12005048	16255063	rs7033852	16257557	SNP9-21885053	21885053		

33Dx	9	0+0			SNP9-21892510	21892510	SNP9-21996348	21996348		
33Dx	9	1+0			rs3217973	21999960	rs7035592	27224029	rs4879313	27240868
33Dx	9	2+1	rs7858982	36959671	rs4880050	36989024	rs7037234	38761831	rs7873422	38825190
33R	ND									
34Dx	7	1+0	rs10251980	50366637	rs7785321	50418242	rs11763774	50462138	rs110980379	50469981
34Dx	19	2+1sc			ptel		rs2079014	15397160	rs4809184	15471856
34IF	ND									
35Dx	4	1+0	rs4593086	165683452	rs6832922	165702921	rs17585396	166144008	rs10517833	166170390
35Dx	5	1+0	rs2914331	170726247	rs2914338	170745203	rs7732542	170967262	rs1678787	171047194
35Dx	9	1+0	rs1330320	21255150	rs1330311	21289069	rs12379721	21536423		
35Dx	9	0+0			rs7863623	21548586	rs6413463	21970989		
35Dx	9	1+0			kgp18632711	21997597	kgp364475	22087473	rs1333040	22083404
35Dx	14	1+0	rs1892233	98725340	rs2186077	98730479	rs995365	99032983	rs8017517	99055601
35Dx	16	1+0			kgp22846045	67473040	rs3809630	67879400	rs34132524	67909150
35Dx	18	1+0	rs566352	6923291	rs3810046	6941662	rs2230601	8069868	rs585416	8106925
35IF	ND									
36Dx	1	1+0	rs1591959	102899784	rs12060427	102922025	rs1607209	103024479	rs11164547	103038172
36Dx	1	0+0	rs12411121	190812882	rs17387185	190839154	rs1570704	190920137	rs1431142	190934383
36Dx	1	1+0	rs3001223	194569085	rs3009329	194583153	rs2400382	194674393	rs10801345	194703530
36Dx	2	1+0	rs4513276	65496251	rs906575	65524097	rs964505	65623189	rs17476501	65691896
36Dx	2	1+0	rs1385167	66200648	rs17606067	66219395	rs17031814	66430611	rs10196975	66450555
36Dx	3	1+0	rs13059342	111990941	rs1317244	112053565	rs11919639	112208750	rs11921669	112219428
36Dx	3	0+0	rs10936936	176911471	rs7648625	176917320	rs13083260	177336402		

36Dx	3	1+0			rs937508	177351845	rs7634430	177474472	rs1369568	177501743
36Dx	5	1+0	rs4921537	158366263	rs4921537	158366263	rs6879995	158515199	rs7732511	158530015
36Dx	5	1+0	kgp4180045	158608825	kgp22470804	158611515	rs11744690	158687153	rs4921437	158690951
36Dx	10	1+0	rs4556470	111764708	rs17126950	111775607	rs11194972	111830275	rs3731566	111886089
36Dx	12	2+1			ptel		rs2283339	12015706		
36Dx	12	1+0sc			rs2416987	12204745	rs7316007	15690733	rs11056593	15821613
36Dx	18	1+0	rs10164075	72866273	rs10164148	72934947	rs17058358	73546922	rs1870591	73591338
36Dx	21	2+1			ptel		rs2834683	36311296		
36Dx	21	1+0			rs8126567	36313618	rs2294163	36407390	rs928282	36433963
36Dx	X	0+0	rs4639691	12824758	rs10521629	12826773	rs5743782	12907240	rs850632	12909566
36R	ND									
37Dx	3	2+1	rs6763015	175479176	rs9884045	175658506	rs1499880	177243737	rs6769488	177308158
37Dx	8	1+0	rs6995235	129953936	rs10090304	130003883	rs11996876	130087172	rs11784932	130095478
37Dx	9	2+0sc			ptel		qtel			
37Dx	9	1+0			rs10511682	20811421	rs12349659	21098843		
37Dx	9	0+0	kgp18486900	21779699	kgb9789780	21782430	rs45710809	22819064		
37Dx	9	1+0			rs4369069	22834082	rs274928	23524441		
37R	ND									
38Dx	5	1+0	rs1775522	158282326	rs929626	158310631	rs6879995	158515199	rs2161357	158537119
38Dx	9	1+0sc	rs10811376	20617114	rs2780838	20629336	cen			
38Dx	10	1+0	rs10903443	1454864	rs11593949	1507145	rs4880516	1595155	rs1320077	1618713
38Dx	11	1+0	rs7945455	104130998	rs6591076	104174699	qtel			
38Dx	12	1+0	rs12368459	48090118	rs11168201	48093603	rs4760686	48547620	rs7301003	48550227

38Dx	X	2+0	rs5949769	95307942	rs12008296	95325724	qtel			
38R	ND									
39Dx	12	2+1			ptel		rs10772508	11900796	rs11054515	11969243
39Dx	18	1+0	rs2113447	51827201	rs2551457	51853684	rs2535730	51906883	rs11151567	51917790
39Dx	21	2+1			ptel		rs1475840	35200812	rs7282762	35230218
39R	ND									
40Dx	1	1+0	rs6689140	79929744	rs7539480	10874426	rs10874426	84224408	rs12121175	84241549
40Dx	1	1+0	rs1770573	84965646	rs818526	84970852	rs11161458	85044296	rs17115896	85045950
40Dx	1	1+0	rs12757818	104761380	rs2594664	104777251	rs2342893	106320233	rs12118626	106332019
40Dx	7	1+0			ptel		qtel			
40Dx	9	1+0	rs2987081	16002046	rs1887667	16023109	rs10491569	21446776		
40Dx	9	0+0			rs7861480	21460997	SNP9-22358818	22358818		
40Dx	9	1+0			SNP9-22386337	22386337	rs7020651	22962837	rs7867893	22972002
40Dx	X	1+0	rs35094631	1177936	rs34455248	1301836	rs6644734	1608783	rs6588773	1618943
40R	ND									
41Dx	9	2+0			ptel		kgp8231656	21802322		
41Dx	9	0+0			kgp22841469	21803897	rs6413463	219709989		
41Dx	9	2+0			kgp1852093	21978979	rs1411609	33137303	rs10813958	33165985
41Dx	16	2+1			ptel		cen			
41IF	ND									
42Dx	5	2+0			ptel		qtel			
42Dx	6	2+1			ptel		qtel			
42Dx	9	2+0			ptel		cen			

42Dx	10	2+1			ptel		qtel			
42Dx	14	2+1sc			ptel		rs2022738	36093840		
42Dx	14	2+1			rs378836	36491876	qtel			
42Dx	17	2+1			ptel		qtel			
42Dx	18	2+1			ptel		qtel			
42Dx	X	2+1			ptel		qtel			
42R	ND									
43Dx	6	2+1	rs2579926	102063064	rs2518261	102088471	rs9485530	102226522	rs2065938	102244947
43Dx	6	2+1	rs2852573	102365807	rs1340270	102495305	rs3995732	102709706	rs1232226	102776205
43Dx	6	1+0	rs1001145	108401163	rs9374021	108534117	rs10457242	112062128	rs706862	112110441
43Dx	12	2+0			ptel		rs2071163	11928348		
43Dx	12	1+0			rs2954930	11943969	rs746621	19288307	rs11612583	19486897
43Dx	12	2+1sc	rs11045310	20604966	rs7294946	20626915	rs936	21581003	rs10841869	21675308
43Dx	12	1+0sc	rs1500072	33176460	rs12426748	33487921	rs10844712	33852289	rs1608912	33899841
43Dx	13	2+1	rs4770908	25521887	rs301055	25598284	rs206327	31892393	rs703225	31940802
43Dx	13	1+0sc	rs421538	32448091	rs7326364	32589953	rs9576346	37205850		
43Dx	13	1+0			rs11147670	37239969	rs9548145	37465009	rs2050590	37501000
43Dx	13	1+0	rs9548396	38028199	rs11840421	38054719	qtel			
43Dx	15	1+0	rs1505272	37344088	rs16968678	37374699	rs7165595	43122220	rs269866	43181698
43Dx	21	2+1			ptel		rs2834731	35305012	rs2071029	35344348
43R	ND									
44Dx	6	1+0	rs17090905	156622440	rs9322564	156596489	cnvi0159892	157535551	cnvi0071616	157651811
44Dx	10	2+1	rs2265638	135067165	cnvi0124834	135019863	rs2987796	135229678	rs4351775	135252190

44Dx	11	1+0	rs10896958	58793269	rs10736693	58822220	cnvi0098894	60790674	rs11230654	60798616
44IF	ND									
45Dx	2	1+0	rs4389332	198185865	rs10170950	198504872	rs9807926	198804120	rs10931806	198826583
45Dx	7	1+0	rs11185584	49731908	rs7799604	49758405	rs10264309	51853658	rs10215689	51875326
45Dx	9	1+0	rs7032626	36917364	rs2297105	37010622	rs17409989	37310849	rs308504	37360553
45Dx	X	1+0	cnvi0128062	1181568	rs28497149	1332269	rs5948932	1597450	rs6588773	1618943
45R	ND									
46Dx	7	1+0			ptel		cen			
46Dx	7	2+1			cen		qtel			
46Dx	21	2+1			ptel		qtel			
46IF	ND									
47Dx	4	1+0	rs549653	149911947	rs7667838	149925222	rs10489052	150122049	rs10434101	150228685
47Dx	9	1+0	rs10973124	36899773	rs7032626	36917364	rs3013739	37021876	rs1329569	37023693
47Dx	12	1+0	rs7132680	14357287	rs7970587	14466726	rs7954515	14596622	rs10846040	14755107
47Dx	16	1+0	rs4786419	1450133	rs3946124	1465780	SNP16-1610692	1610692	rs2235487	1670312
47R	ND									
48dx	3	1+0	rs10934164	113495382	rs2399416	113541903	rs11919639	113691440	rs9855848	113734465
48Dx	4	1+0	rs7683103	148954077	rs12509618	149047197	rs756862	150123248	rs2520490	150130919
48Dx	6	1+0	rs215922	85577754	rs6454399	85613001	rs2673308	112430648	rs12196730	112452504
48Dx	7	2+1sc	rs6949790	92474705	rs42501	92623952	qtel			
48Dx	11	1+0	rs4151046	36556891	rs11033698	36562669	rs10836576	36589878	rs11033726	36608716
48Dx	12	1+0			ptel		rs12303225	31093830	rs3864918	31149819
48Dx	12	1+0	rs1025623	31298139	rs10843927	31375417	cnvi0154631	31635101	rs2049116	31665550

48Dx	13	1+0sc	rs9534995	47684077	rs9595874	47699082	rs11616485	50236993	rs7326798	50266309
48Dx	13	1+0	rs7336304	65407614	rs9529004	65429119	qtel			
48Dx	14	1+0	rs10129563	39721345	rs11157113	39709964	rs1950225	39775953	rs1950223	39787593
48Dx	14	1+0	rs10134151	95185915	rs17093106	95186036	rs8011890	95216646	rs2369305	95276038
48Dx	15	1+0	rs17637170	23568597	rs11632608	23574645	rs8039677	23647475	rs2076748	23661078
48Dx	15	1+0	rs150294	87732152	rs208829	87748046	rs11629802	88361886	rs1317722	88382020
48Dx	20	1+0	rs2423179	7760350	rs6077273	7776432	rs2076409	8731279	rs4816090	8756310
48Dx	20	1+0	rs6108571	10358320	rs6074140	10372198	rs675772	10455827	rs12106093	10472897
48Dx	20	1+0	SNP20-32851973	32851973	SNP20-32854132	32854132	SNP20-33122319	33122319	SNP20-33143285	33143285
48R	ND									
49Dx	5	1+0	rs200008	8750444	rs17289138	8756085	rs156452	8806733	rs999426	8823185
49Dx	6	2+1	rs954551	102886028	rs1538378	102900129	rs9377506	104069104	rs9404414	104089329
49Dx	7	1+0	rs10251980	50337181	rs7785321	50385736	rs10235796	50430131	rs12538151	50441717
49Dx	10	1+0	rs4370822	67742090	rs4297361	67748487	rs10997073	67783601	rs7920664	67788456
49Dx	14	1+0	rs9788429	40673884	rs7142333	40694940	rs12433301	40738955	rs1778370	40739852
49Dx	17	1+0	rs11080335	30623671	rs12952232	30667276	rs9303690	31029626	rs226090	31058172
49R	ND									
50Dx	12	1+0			ptel		rs10770486	19501196	rs3705403	19535708
50Dx	13	1+0	rs9532893	41015928	rs2166619	41542679	qtel			
50IF	F									
51Dx	1	1+0	rs6684596	178580295	rs4532796	178751248	rs6686881	179079604	rs12566450	179097218
51Dx	2	1+0	rs13021915	8035622	rs238617	8321561	rs6737440	8733187	rs13010395	8769913
51Dx	3	1+0	rs7636107	113497982	rs4682103	113538483	rs6774355	113709706	rs9855848	113734465

51Dx	5	1+0	rs2963442	157872871	rs6878978	157882703	rs17056534	158434956	rs11738949	158517192
51Dx	6	1+0	rs7755014	106930907	rs2749083	106942992	rs1341272	109614226	rs396000	109626304
51Dx	6	1+0	rs549332	116561281	rs1204846	116628714	rs1998166	117020110	rs9320571	117030289
51Dx	6	1+0	rs3822997	119591167	rs6932066	119638613	rs9489928	120648057	rs9489944	120747708
51Dx	7	1+0	rs6977025	43086455	rs4724203	43418235	rs4236210	66162183	rs4718560	66516217
51Dx	8	2+1	rs17570887	82160729	rs10958016	82426387	qtel			
51Dx	12	1+0	rs4485143	90762504	rs17019675	90814839	rs6538319	91008269	rs12694	91063721
51Dx	13	1+0	rs9576264	36886791	rs9566230	36998972	rs9538998	60469161	rs3127298	60715378
51Dx	13	1+0	rs1498265	75850132	rs283972	75976033	qtel			
51Dx	15	1+0sc	rs4485323	31370635	rs2676071	31384368	rs1980243	54562095		
51Dx	15	1+0			rs28840748	54582422	rs557832	55808030		
51Dx	15	1+0	rs8030720	87944571	rs17847337	88023576	rs2285529	89543582		
51Dx	15	1+0sc			rs8032397	89617776	qtel			
51Dx	16	1+0			ptel		rs12324971	3786950	rs8049367	3920446
51Dx	18	1+0	rs1574381	61949807	rs1490960	61961614	rs7240072	62132393	rs8095213	62157366
51Dx	21	2+1			ptel		qtel			
51IF	ND									
52Dx	2	1+0	rs1589039	45711744	rs666214	45741435	rs6707046	45863810	rs7558378	45932717
52Dx	3	1+0	rs1317244	113536255	rs2399420	113552455	rs6438081	113693968	rs11921669	113702118
52Dx	4	1+0	rs1356342	130701944	rs10518552	130755733	rs2955478	130958325	rs12233773	130975865
52Dx	5	1+0	rs11743538	8457645	rs17279186	8460305	rs10080152	8682710	rs10040826	8687454
52Dx	5	1+0	rs2900797	157335398	rs6884132	157369613	rs1173447	157533331	rs44156	157557784
52Dx	6	1+0	rs760848	18113568	rs6909725	18225347	rs9379828	26275930	rs9379830	26281746

52Dx	6	1+0	rs13362815	26311698	SNP6-26315525	26315525	SNP6-26343716	26343716	rs6935954	26363430
52Dx	6	1+0	rs3857448	80143604	rs196694	80192550	rs9483562	133565658	rs9389058	133597942
52Dx	X	1+0			ptel		rs684876	82056293		
52Dx	X	2+0			cnvi0160883	82232351	qtel			
52R	ND									
53Dx	NA									
53R	ND									
54Dx	1	1+0	rs97747	47457264	rs11211484	47480956	rs11211512	47550471	rs9436874	47567179
54Dx	6	2+1sc	rs1342005	93436228	rs9452114	93550988	rs12209602	109251998	rs2883970	109470427
54Dx	9	2+0			ptel		rs10811582	21682017		
54Dx	9	0			SNP9-21763761	21763761	SNP9-22019080	22019080		
54Dx	9	2+0			SNP9-22067085	22067085	rs7046537	24095629		
54Dx	9	2+0sc			rs674544	24182256	rs10972487	35472149	rs2295842	35549213
54Dx	13	0+0	rs2804090	47880974	rs198568	47913957	rs9332054	47968346		
54Dx	13	1+0			rs10076	47977504	rs1887154	48071539	rs9535058	48092584
54Dx	20	2+1	rs6109007	11431231	rs4814019	11456980	rs6134650	12656516	rs6041604	12690546
54R	ND									
55Dx	6	2+1			ptel		qtel			
55Dx	10	2+1			ptel		qtel			
55Dx	14	2+1			ptel		qtel			
55Dx	17	2+1			ptel		qtel			
55Dx	18	2+1			ptel		qtel			
55Dx	19	2+1sc			ptel		rs350825	4140563	rs8102860	4346348

55Dx	21	2+2			ptel		qtel			
55Dx	X	2+0			ptel		qtel			
55R	ND									
56Dx	4	1+0	rs4245926	108967846	rs4956157	108999366	rs9307319	109274125	rs12374269	109288854
56Dx	9	1+0	kgp18255016	21855308	rs7047648	21857244	kgp3764974	22043612	kgp9423146	22048683
56Dx	17	2+1	rs3809790	27955540	rs7213462	28389576	qtel			
56R	NC									
57Dx	8	2+1	rs7831581	130547994	rs6470739	130570669	rs1433585	130626097	rs4636162	130639540
57R	ND									
58Dx	1	1+0	rs9726926	236166591	rs11590845	236170665	qtel			
58Dx	7	1+0			ptel		cen			
58Dx	12	1+0	rs7972427	11724734	rs10491980	11728337	rs16932359	27974543	rs1861907	27997452
58Dx	12	1+0	rs11043316	122104893	rs35394178	122141181	rs12311114	124460703	rs10846581	124483533
58Dx	14	1+0	rs1077631	101112425	rs4905989	101124278	qtel			
58Dx	16	1+0	rs1004998	49633732	rs1004867	49635132	rs28545584	69329590	rs12925991	39372514
58IF	F									
59Dx	F									
59R	7	1+0	rs2737418	99389000	rs2023548	99417324	qtel			
59R	10	1+0	rs11471	45499799	rs11595215	45529483	rs11239391	45709496	rs2000017	45718996
59R	12	1+0			ptel		rs10846385	16780886	rs366281	16890442
59R	13	1+0	rs4151427	48880998	rs2804082	48909569	rs12866052	48987773	rs7997794	49022794
59R	21	iAMP	rs2823690	17625455	rs1389073	17631636	qtel			
60Dx	F									

60R	1	2+0	ptel	qtel
60R	2	2+0	ptel	qtel
60R	3	2+0	ptel	qtel
60R	4	2+0	ptel	qtel
60R	5	2+0	ptel	qtel
60R	6	2+0	ptel	qtel
60R	7	2+0	ptel	qtel
60R	8	2+0	ptel	qtel
60R	9	2+0	ptel	qtel
60R	10	2+0	ptel	qtel
60R	11	2+0	ptel	qtel
60R	12	2+0	ptel	qtel
60R	13	2+0	ptel	qtel
60R	14	2+2	ptel	qtel
60R	15	2+0	ptel	qtel
60R	16	2+0	ptel	qtel
60R	17	2+0	ptel	qtel
60R	18	2+2	ptel	qtel
60R	19	2+0	ptel	qtel
60R	20	2+0	ptel	qtel
60R	21	2+2	ptel	qtel
60R	22	2+0	ptel	qtel
60R	X	2+0	ptel	qtel

60R	Y	2+0			ptel		qtel			
61Dx	F									
61R	1	1+0	rs4845004	210528907	rs6691759	210699389	qtel			
61R	5	1+0	rs174047	142623288	rs10482616	142781567	rs161557	143200053	rs1833523	143257604
61R	6	2+1			ptel		rs12663902	95662219		
61R	6	1+0			rs2252451	95836160	rs13196705	123760725		
61R	6	2+1			rs6569352	123885639	qtel			
61R	10	2+1			ptel		rs1188585	97837013		
61R	10	0+0			rs10748659	97842565	rs12265203	98567516		
61R	10	2+1			rs10430660	98674939	qtel			
61R	11	2+1	rs2067477	62678306	rs3017670	62744899	rs7936604	82836379	rs12269817	82858667
61R	13	2+1	rs218497	23957488	rs9510719	23969191	qtel			
61R	14	2+1			ptel		qtel			
61R	17	3+1			ptel		rs2453594	19484951	rs2453601	19505984
61R	17	2+2	rs2453594	19484951	rs2453601	19505984	rs7405782	21490090	rs11650646	21514496
61R	17	3+2	rs7405782	21490090	rs11650646	21514496	qtel			
61R	18	2+1			ptel		qtel			
61R	21	2+2			ptel		qtel			
61R	22	2+1			ptel		qtel			
61R	X	2+0			ptel		qtel			
62Dx	F									
62R	2	1+0	rs11125123	47359810	rs4953477	47438851	rs3732188	48035137	rs2651766	48044772
62R	2	1+0	rs2289951	101644299	rs2289953	101656726	rs3732131	102794603	rs10184597	102802255

62R	2	1+0	rs7596167	118367817	rs2674859	118375375	rs11904226	118847943	rs2630460	118850732
62R	2	1+0	rs3731783	231913056	rs16827799	231979073	rs3923767	239799547	rs6736036	239834334
62R	3	1+0	rs11718455	44056898	rs808727	44085852	rs11914913	47528193	rs11717374	47544794
62R	4	1+0	rs9991394	148940093	rs126050033	148987187	rs17024708	149340536	rs10026568	149347854
62R	5	1+0	rs17134154	111480534	rs17265886	111489938	rs2303071	147488367	rs2303070	147499891
62R	10	1+0	rs4747512	25417900	rs11014425	25433725	rs599641	27772869	rs10764689	27792089
62R	10	1+0	rs3862002	111165537	rs11194651	111178322	rs1341053	112624417	rs41292604	112654269
62R	10	1+0	rs12269496	114241570	rs10885355	114258451	rs11813949	114958436	rs10885488	115000814
62R	12	1+0	rs34330	12870695	rs34322	12879570	rs11048499	26556111	rs21826091	26563399
62R	12	1+0	rs4399376	91980500	rs1489895	92012201	rs28399541	92537956	rs790461	92580610
62R	15	2+1	rs1434232	100103823	rs7162940	100136381	rs729316	100623705	rs10459744	100630725
62R	19	1+0	rs12327730	34764842	rs179186	34799429	rs1007568	35980832	rs2293695	35991373
63Dx	ND									
63R	ND									
64Dx	F									
64R	F									
65Dx	ND									
65R	ND									
66Dx	ND									
66R	ND									
67Dx	ND									
67R	ND									
68Dx	ND									

68R	ND
69Dx	ND
69R	ND
70Dx	NC
70R	NC
71Dx	ND
71R	ND
72Dx	ND
72R	ND
73Dx	ND
73R	ND
74Dx	ND
74R	ND
75Dx	F
75IF	F
76Dx	ND
76R	ND
77Dx	ND
77IF	ND

ALL, indicates acute lymphoblastic leukemia; cen, centromere; Chr, chromosome; Dx, diagnosis; F, failure; FAS, first abnormal SNP; FNS, first normal SNP; iAMP, intrachromosomal amplification of chromosome 21; IF, induction failure; LAS, last abnormal SNP; LNS, last normal SNP; NA, no aberrations; NC, normal cells; ND, not done; pos, position based on *homo sapiens* high coverage assembly GRCh36.1 or GRCh37; ptel, telomere of the p-arm; qtel, telomere of the q-arm; R, relapse; sc, subclone; SNP, single nucleotide polymorphism.

†Rows in bold type indicate changes found only at diagnosis but not at the time of event (emergence of an ancestral clone) or only at the time of event (clonal evolution).

Supplementary Table 5. Frequencies of recurrent gene targets/imbalances in diagnostic ALL samples from patients with subsequent R/IF compared with patients without such events

Genes targets/ Imbalances	58 with R/IF N (%)	170 without R/IF N (%)	P-value±
Gene targets†			
ADD3 (10q25.1)¤	5 (8.6)	2 (1.2)	**0.013**
ARID1B (6q25.3)¤	5 (8.6)	6 (3.5)	0.153
ATP10A (15q12)¤	6 (10)	1 (0.6)	**0.001**
BTG1 (12q21.33)¤	5 (8.6)	9 (5.3)	0.354
CDKN2A (9p21.3)¤	23 (40)	59 (35)	0.528
EBF1 (5q33.3)¤	7 (12)	7 (4.1)	0.051
ETV6 (12p13.2)¤	13 (22)	33 (19)	0.705
IKZF1 (7p12.2)¤	20 (34)	15 (8.8)	**<0.001**
NR3C1 (5q31.3)¤	5 (8.6)	3 (1.8)	**0.027**
PAN3 (13q12.2)¤	5 (8.6)	4 (2.4)	**0.049**
PAX5 (9p13.2)¤	17 (29)	43 (25)	0.605
RAG1 (11p12)¤	5 (8.6)	5 (2.9)	0.128
SPRED1 (15q14)¤	6 (10)	1 (0.5)	**0.001**
TBL1XR1 (3q26.31)¤	5 (8.6)	5 (2.9)	0.128
Imbalances			
dup(1)(q21.3q21.3)*	2 (3.4)	14 (8.2)	0.113
del(3)(q13.2q13.2)*	7 (12)	11 (6.5)	0.171
del(6)(p22.2p22.2)*	7 (12)	6 (3.5)	**0.023**
del(6)(q21q21)*	8 (14)	12 (7.1)	0.175
dup(8)(q24.21q24.21)*	4 (6.9)	4 (2.4)	0.116
del(13)(q14.2q14.2)*	8 (14)	11 (6.5)	0.099
del(16)(p13.3p13.3)*	5 (8.6)	1 (0.6)	**0.004**
del(16)(q22.1q22.1)*	5 (8.6)	1 (0.6)	**0.004**
del(17)(p11.2p13.2)*	5 (8.6)	2 (1.2)	**0.004**
PAR1 deletion*	6 (10)	6 (3.5)	0.080

ALL indicates acute lymphoblastic leukemia; IF, induction failure; N, number; PAR1, pseudoautosomal region 1 on Xp/Yp; R, relapse.

†Focal and large deletions, whole chromosome losses (rare), and partial and whole chromosome UPDs combined.

±P-values ascertained by Fisher´s exact test. Significant P values are indicated in bold type.

¤Smallest overlap: *ADD3* (chr10:111,775,607-111,830,275); *ARID1B* (chr6:157,357,096-157,461,985); *ATP10A* (chr15:26,033,764-26,093,401); *BTG1* (chr12:92,278,448-92,537,956); *CDKN2A* (chr9:21,970,901-21,970,989); *EBF1* (chr5:158,366,263-158,502,378); *ETV6* (chr12:11,943,969-12,015,706); *IKZF1* (chr7:50,418,242-50,422,230); *NR3C1* (chr5:142,781,168-143,058,402); *PAN3* (chr13:28,691,097-28,806,503); *PAX5* (chr9:36,927,364-37,010,622); *RAG1* (chr11:36,481,900-36,608,273); *SPRED1* (chr15:38,403,504-38,558,017); and *TBL1XR1* (chr3:176,911,471-177,336,402).

*Smallest overlap: chr1:150,638,572-151,552,672; chr3:112,069,766-112,208,750; chr6:26,153,335-26,167,951; chr6:107,146,121-109,614,226; chr8:130,572,304-130,626,097; chr13:49,015,957-49,070,345; chr16:15,257,80-16,706,91; chr16:67,473,040-67,879,400; chr17:47,523,93-16,232,477; and chrX:14,011,68-15,666,46.

Supplementary Table 6. Frequencies of recurrent gene targets/imbalances in diagnostic T-ALL samples from patients with subsequent R/IF compared with patients without such events

Genes targets/ Imbalances	10 with R/IF N (%)	23 without R/IF N (%)	P-value±
Gene targets†			
CDKN2A (9p21.3)[¤1]	9 (90)	20 (87)	1.000
PAX5 (9p13.2)[¤2]	2 (20)	7 (30)	0.686
Imbalances			
del(13)(q14.2q14.2)[*]	2 (20)	1 (4.3)	0.212

ALL indicates acute lymphoblastic leukemia; IF, induction failure; N, number; R, relapse.

†Focal and large deletions and partial UPDs combined.

±P-values ascertained by Fisher´s exact test.

[¤]Smallest overlap: *CDKN2A* (chr9:21,970,901-21,970,989); and *PAX5* (chr9:36,927,364-37,010,622).

*Smallest overlap: chr13:49,015,957-49,070,345.

Supplementary Table 7. Frequencies of recurrent gene targets/imbalances in diagnostic HeH-positive BCP ALL samples from patients with subsequent R compared with patients without such an event

Genes targets/ Imbalances	11 with R N (%)	52 without R N (%)	P-value±
Gene targets†			
IKZF1 (7p12.2)¤	3 (27)	5 (9.6)	0.137
PAN3 (13q12.2)¤	2 (18)	2 (3.8)	0.137

BCP ALL indicates B-cell precursor acute lymphoblastic leukemia; HeH, high hyperdiploidy (51-67 chromosomes); N, number; R, relapse.

†Focal and large deletions and partial UPDs combined.

±P-values ascertained by Fisher´s exact test.

¤Smallest overlap: *IKZF1* (chr7:50,418,242-50,422,230); and *PAN3* (chr13:28,691,097-28,806,503).

Supplementary Table 8. Frequencies of recurrent gene targets/imbalances in diagnostic t(12;21)-positive BCP ALL samples from patients with subsequent R compared with patients without such an event

Genes targets/ Imbalances	7 with R N (%)	33 without R N (%)	P-value±
Gene targets†			
ETV6 (12p13.2)¤	4 (57)	16 (48)	1.000
Imbalances			
del(3)(q13.2q13.2)*	3 (43)	6 (18)	0.316
del(6)(q21q21)*	3 (43)	10 (30)	0.662
del(13)(q14.2q14.2)*	2 (29)	3 (9.1)	0.204

BCP ALL indicates B-cell precursor acute lymphoblastic leukemia; N, number; R, relapse.

†Focal and large deletions and partial UPDs combined.

±P-values ascertained by Fisher´s exact test.

¤Smallest overlap: *ETV6* (chr12:11,943,969-12,015,706).

*Smallest overlap: chr3:112,069,766-112,208,750; chr6:107,146,121-109,614,226; and chr13:49,015,957-49,070,345.

Supplementary Table 9. *IKZF1* status in the BCP ALL risk groups

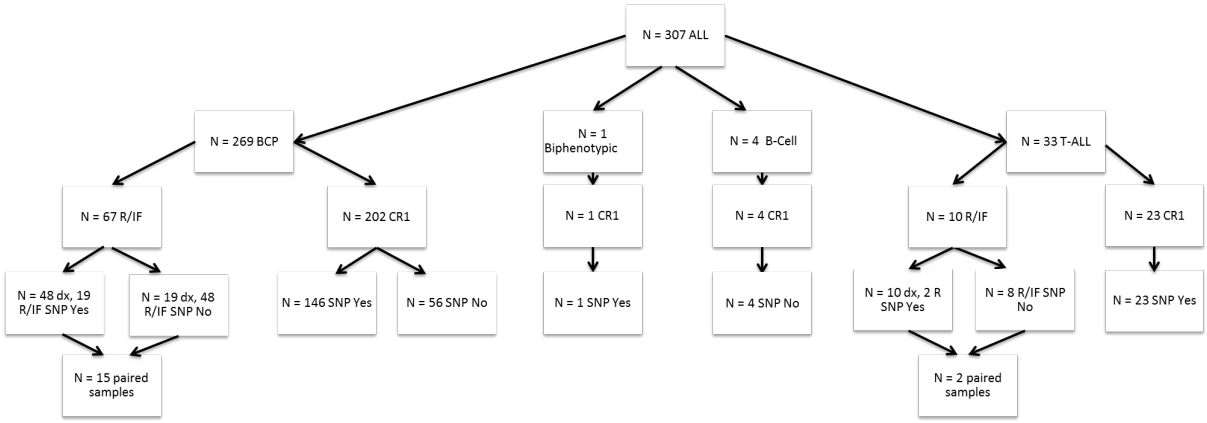
IKZF1 **Deletion**	**SR** **N (%)**	**IR** **N (%)**	**HR** **N (%)**	**Total (N = 145)**
Yes	5 (9.4)	9 (15)	12 (36)	26 (18)
CR1	3 (60)	5 (56)	4 (33)	12 (46)
R/IF	2 (40)	4 (44)	8 (67)	14 (54)
No	48 (91)	50 (85)	21 (64)	119 (82)
CR1/DCR1/SMN	40 (83)	43 (86)	15 (68)	98 (82)
R/IF	8 (17)	7 (14)	6 (32)	21 (18)

BCP ALL indicates B-cell precursor acute lymphoblastic leukemia; CR1, complete remission 1; DCR1, death in CR1; HR, high risk; IF, induction failure; IR, intermediate risk; N, number; R, relapse; SMN, secondary malignant neoplasm; SR, standard risk.

Supplementary Table 10. **Co-occurrence of *IKZF1*, *SPRED1*, and PAR1 deletions among the BCP ALL cases**

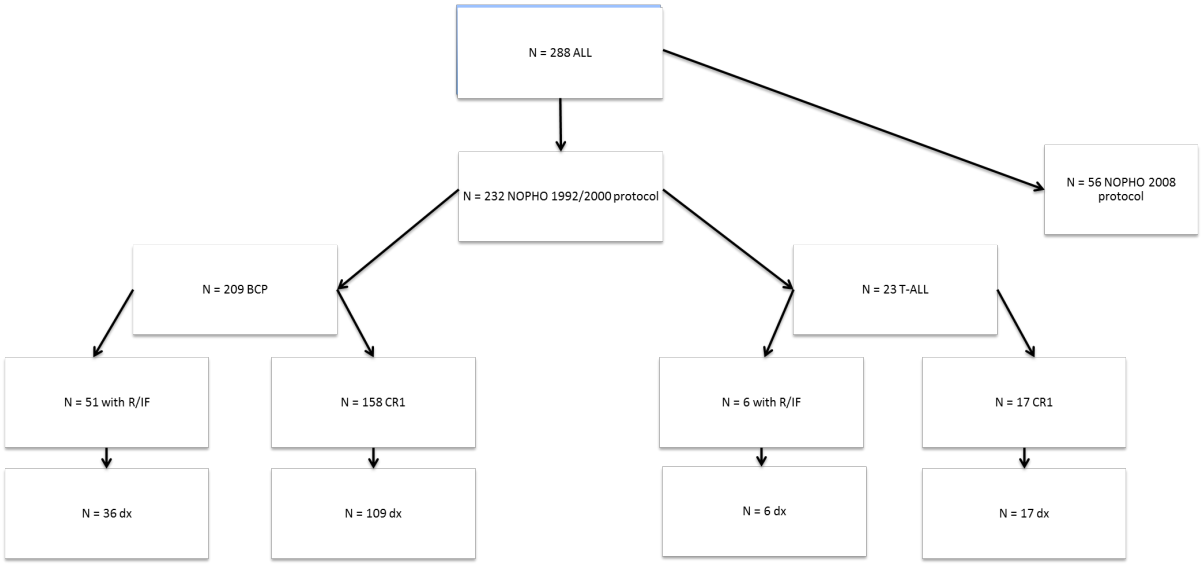
Deletion Status	**Total N**	**R/IF N**
***IKZF1* Yes**		
SPRED1 Yes	2	2
PAR1 Yes	4	4
***IKZF1* No**		
SPRED1 Yes	1	1
PAR1 Yes	5	0
***SPRED1*/PAR1 No**		
IKZF1 Yes	24	10

BCP ALL indicates B-cell precursor acute lymphoblastic leukemia; IF, induction failure; N, number; PAR1, pseudoautosomal region 1 on Xp/Yp; R, relapse.



Supplementary Figure 1. Flowchart of the 307 childhood/adolescent ALL cases diagnosed between January 1, 1992, and December 31, 2011, at the Departments of Pediatric Oncology and Hematology, Lund and Linköping University Hospitals, Sweden. The chart depicts which cohorts that could be analyzed by SNP arrays at diagnosis and/or at R/IF.

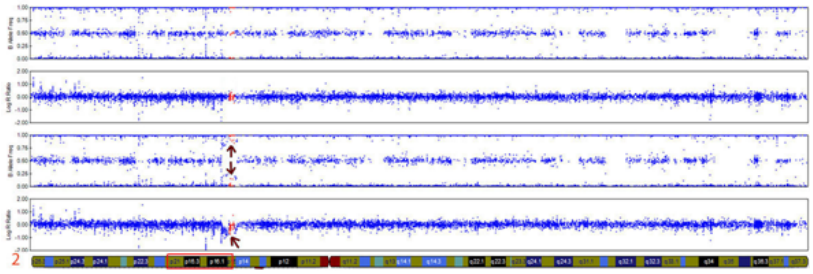
ALL indicates acute lymphoblastic leukemia; BCP, B-cell precursor; CR1, complete remission 1; dx, diagnosis; IF, induction failure; N, number; R, relapse; SNP, single nucleotide polymorphism.



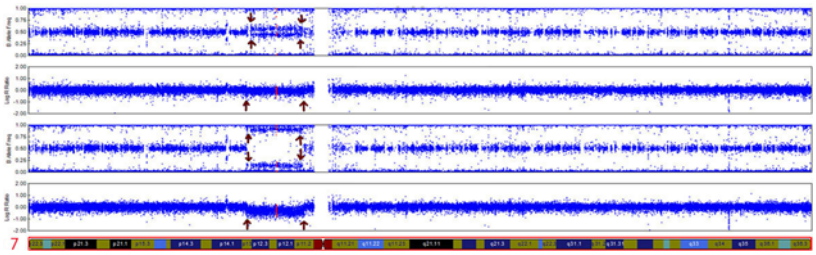
Supplementary Figure 2. Flowchart of the 288 childhood/adolescent ALL cases treated according to Nordic Society of Pediatric Hematology and Oncology protocols at the Departments of Pediatric Oncology and Hematology, Lund and Linköping University Hospitals, Sweden. The chart depicts the 1992 and 2000 cohorts with informative SNP array results that were statistically analyzed as regards the 10-year probabilities of event-free survival and overall survival in relation to clinical and genetic features.

ALL indicates acute lymphoblastic leukemia; BCP, B-cell precursor; CR1, complete remission 1; dx, diagnosis; IF, induction failure; N, number; R, relapse; SNP, single nucleotide polymorphism.

A



B



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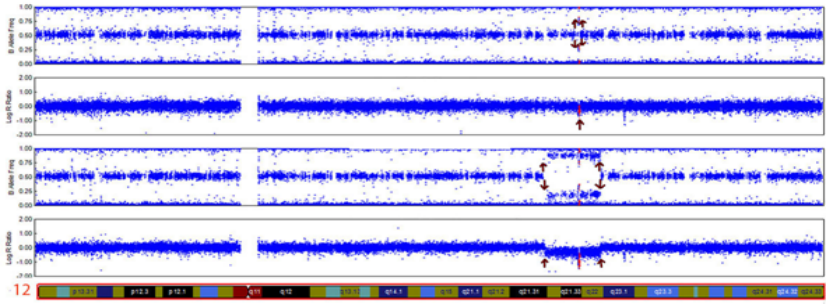

Supplementary Figure 3. SNP arrays displaying clonal diversity between diagnostic and relapse samples. The two top panels display B allele frequencies (genotypes) and log2 ratios (copy numbers), respectively, for the diagnostic sample. The two lower panels show the same for the relapse sample. The panels were extracted from the genome studio v2011.1 software (Illumina). Below the panels are the chromosomes involved. A decrease in copy number together with LOH was seen in the relapse sample of case 1 in both chromosomes 2 (A) and 7 (B), showing deletions of *MSH6* and *IKZF1* (the genes are denoted in red and the aberrations with arrows), respectively. In contrast, the diagnostic sample from case 1 harbored no chromosome 2 deletion and only a subclonal chromosome 7 deletion. (C) In case 6, the diagnostic sample had a focal decrease in copy number and LOH of chromosome 12, involving the *BTG1* gene (the gene is denoted in red and the aberrations with arrows), whereas the relapse sample carried the focal *BTG1* deletion together with a larger deletion, generating a homozygous *BTG1* deletion.