What is the relevance of *Ikaros* gene deletions as a prognostic marker in pediatric Philadelphia-negative B-cell precursor acute lymphoblastic leukemia?

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ABSTRACT

New prognostic markers are needed for upfront identification of patients with acute lymphocytic leukemia with a high risk of relapse or who are not likely to respond to the most aggressive chemotherapy. We focused our analysis on *Ikaros* (*IKZF1*) gene deletions in a homogeneous cohort of 410 pediatric patients with Philadelphia chromosome-negative, B-cell precursor acute lymphoblastic leukemia enrolled in Italy into the AIEOP-BFM ALL2000 study. We confirm their reported poor prognostic value, although the associated event-free survival was relatively high (approximately 70%). The difference in the cumulative incidence of relapse between patients positive or not for *IKZF1* deletions was not marked: 24.2% (5.9) *versus* 13.1% (1.8) overall and 23.9% (6.6) *versus* 16.5% (2.5) in the intermediate-risk subgroup. In line with this, *IKZF1* deletions were not an independent prognostic factor for the hazard of relapse. Most *IKZF1*-deleted cases stratified in the high-risk group relapsed, suggesting that once identified, patients with these deletions require an alternative treatment. In conclusion, the need of and benefit from introducing *IKZF1* deletions as an additional stratification marker for patients with Philadelphia-negative B-cell precursor acute lymphoblastic leukemia remain questionable.

Introduction

In the AIEOP-BFM ALL2000 study of patients with acute lymphocytic leukemia (ALL), risk-adapted treatment, with the risk group stratification largely based on minimal residual disease monitoring as a measure of early response to therapy, led to a cure rate of over 80%. However, relapse is still the most frequent adverse event, occurring mainly in the largest and heterogeneous subgroup of non-high-risk patients.[1] This emphasizes the need for new prognostic markers for upfront identification of patients with a high risk of relapse or of patients who are likely not to respond to the most aggressive chemotherapy.

Recently, genomic abnormalities of *Cytokine receptor like factor 2* (*CRLF2*) and *Ikaros* (*IKZF1*) genes have been reported, not only in patients with Down syndrome or Philadelphia chromosome-positive disease, but also in patients without known chromosomal aberrations, although with different incidences.[2-6] Indeed, *IKZF1* deletions are rare in T-ALL (about 5%),[7] very frequent in Philadelphia chromosome-positive ALL (about 80%)[8] and frequent in patients with Down syndrome and ALL (reported incidence, 35%).[9] The most frequent *IKZF1* alterations identified in ALL patients were deletions encompassing the whole gene or involving only some exons.[5,7-15] All these deletions cause the loss of *IKZF1* activity.[16]

IKZF1 deletions were shown to be related to poor outcome in pediatric ALL patients,[5,7-15] but their prognostic impact could be different in specific subgroups.

The potential benefit of the early identification of a new prognostic marker should be assessed within the subgroup of patients who are not at high risk due to other features and evaluated in a homogeneous cohort of cases. A recent study by Dorge *et al.*[7] showed that patients with an *IKZF1* deletion had an inferior outcome compared to those who did not have a deletion and it was, therefore, concluded that *IKZF1* deletions may be a strong candidate for changing the stratification strategy. However, although the outcome of the patients with deletions was inferior to that of patients without deletions, it was still relatively favorable, since patients with deletions had a 5-year event-free survival of about 70%. Thus, *IKZF1* deletions, although potentially useful for stratification, are not associated with a really poor prognosis. The aim of our study was to assess the prognostic value of *IKZF1* deletions in a cohort of patients whose stratification and treatment[17] were very similar to those in the study by Dorge *et al.*[7]

Our investigation was focused on a subgroup of ALL patients for whom a change in risk stratification could be most relevant in clinical practice. We, therefore, screened a cohort of 410 non-Down syndrome patients with non-T, Philadelphia chromosome-negative, B-cell precursor ALL enrolled in the AIEOP-BFM ALL2000 study in Italy and recently analyzed for *CRLF2* alterations for evaluation of the prognostic role of *IKZF1*.[18]

 doi:10.3324/haematol.2012.075432
The online version of this article has a Supplementary Appendix.
Manuscript received on October 10, 2012. Manuscript accepted on March 25, 2013.
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Design and Methods

Patients

The study cohort was constituted by 410 non-Down syndrome, non-T, Philadelphia chromosome-negative, B-cell precursor ALL patients consecutively enrolled in the AIEOP-BFM ALL2000 study in AIEOP Centers from February 2003 to July 2005, who were included in the previous study on *CRLF2* alterations and for whom DNA was still available.[18] Data on recurrent genomic aberrations were available for most patients.[19] *P2RY8-CRLF2* rearrangement was tested by reverse transcriptase polymerase chain reaction analysis in 372 (90.7%) patients.[18]

As shown in *Online Supplementary Table S1*, there was an unbalance toward more unfavorable features with respect to treatment response (prednisone-poor response and high minimal residual disease levels) in the non-investigated group. Despite this difference, the event-free survival curve of the analyzed patients was not different from that of the not analyzed patients diagnosed in AIEOP centers in the study period (2003-2005) (*Online Supplementary Figure S1*).

The project was approved by the AIEOP ALL Scientific Committee.

Risk group definitions and treatment outlines have already been reported[17] and are summarized in the *Online Supplementary Material*.

DNA copy number variations

IKZF1 deletions, together with deletions in other genes (*CDKN2A/B*, *PAX5*, *ETV6*, *BTG1*, *RB1* and *EBF1*) were investigated by multiplex ligation-dependent probe amplification (MLPA) using the Salsa MLPA P335-A3 ALL-IKZF1 kit (MRC-Holland, Amsterdam, the Netherlands) according to the manufacturer's instructions.[7,18,20] Patients positive for *IKZF1* deletions were further analyzed by the more specific Salsa MLPA P202-A1 IKZF1 kit (MRC-Holland, Amsterdam, the Netherlands) to confirm and better define the extension of the alteration.

Samples from pediatric ALL patients in complete remission were used as wild-type controls.

Statistical analysis

Event-free survival time was calculated from the date of diagnosis to the date of an event, which was resistance, relapse, death or second neoplasm, whichever occurred first. Patients were censored at last follow-up if no events occurred. Event-free survival was estimated according to Kaplan-Meier, and compared using the log-rank test. The cumulative incidence of relapse at 5 years was estimated by adjusting for competing risks of other events and compared using Gray's test.[18] Multivariate Cox models for event-free survival and cause-specific hazard of relapse were applied to assess, with the Wald test, the impact of *IKZF1* deletions, after accounting for the risk group, age and white blood cell count at diagnosis, and the presence of *P2RY8-CRLF2* aberration. The Cox model was also applied for each variable separately (univariate analysis).

Results

IKZF1 deletions at diagnosis

IKZF1 deletions were detected in 54/410 cases (13.2%), in keeping with incidence data reported in the literature.[3,13] In 25 cases (6.1%) the deletion was intra-genic, involving only some exons of the *IKZF1* gene, while in 29 cases (7.1%) the deletion encompassed the whole *IKZF1* gene. In detail, we identified nine cases with lack of exons 4-7 (Δ4-7), three cases with Δ2-8, two cases for each of the following deletions: Δ2-7, Δ4-8, Δ1-3, Δ2-3 and single cases for: Δ1-4, Δ4-5, Δ4-6, Δ6-8 and Δ2 (exon numbering according to Iacobucci *et al.*[6]) (*Online Supplementary Table S2*).

The clinical characteristics of the patients are presented in Table 1. The major difference regards treatment response, with lower proportions of patients with a prednisone-poor response among the *IKFZ1*-deleted group and of patients with high minimal residual disease levels among the non-*IKFZ1*-deleted group. The percentages of

Table 1. Clinical features of the study cohort patients positive or negative for an *IKZF1* deletion.

	IKZF1 deletions				*P* value
	No		Yes		
	N	%	N	%	
All patients	356		54		
Gender					
Male	187	52.5	27	50.0	0.73
Female	169	47.5	27	50.0	
Age					
1-5 years	239	67.1	27	50.0	0.02
6-9 years	68	19.1	12	22.2	
10-17 years	49	13.8	15	27.8	
WBC(x10⁹/L)					
<20	254	71.4	39	72.2	0.97
20-100	79	22.2	12	22.2	
≥100	23	6.5	3	5.6	
Translocations					
t(4;11)					
Positive	3	0.8	0		0.50
Negative	351	99.2	54	100.0	
Not known	2		0		
t(12;21)					
Positive	82	24.3	1	2.0	<0.001
Negative	256	75.7	50	98.0	
Not known	18		3		
Prednisone response					
Good	333	94.1	53	98.2	0.22
Poor	21	5.9	1	1.8	
Not known	2		0		
Minimal residual disease					
Standard risk	116	41.4	8	21.1	<0.001
Intermediate risk	162	57.9	27	71.0	
High risk	2	0.7	3	7.9	
Not known	76		16		
Final protocol strata					
Standard risk	109	30.6	8	14.8	0.05
Intermediate risk	222	62.4	42	77.8	
High risk	25	7.0	4	7.4	
P2RY8-CRLF2					
No	307	95.0	46	93.9	0.73
Yes	16	5.0	3	6.1	
Not known	33		5		
NCI criteria					
Standard	267	75.0	34	63.0	0.06
High	89	25.0	20	37.0	
DNA index					
≥1.16 and <1.6	76	23.0	5	10.2	0.04
<1.16 or ≥1.6	255	77.0	44	89.8	
Not known	25		5		

WBC: white blood cell count.

patients allocated to the high-risk group were, however, the same (7%) for patients with or without the *IKFZ1* deletion. The relative incidence of major deletion subgroups did not vary according to final risk group assignment (*Online Supplementary Table S2*). Among the patients with an *IKZF1* deletion, one was positive for the chromosomal translocation t(12;21) and none was positive for t(4;11). Only three *IKZF1*-deleted cases also carried a *P2RY8-CRLF2* fusion (Table 1). The differences in the incidence of double-deleted cases reported in this and other studies[2,3,5,7,11] is probably due to the relatively low number of patients in all studies.

Using the MLPA technique we further analyzed the presence of copy number variations of other genes frequently deleted in B-cell precursor ALL and known to be involved in lymphoid development (*PAX5, ETV6, EBF1*) or in cell cycle regulation (*CDKN2A/B, BTG1, RB1*).[10,20-22] We did not find statistically significant differences in the incidence of these genetic alterations in children positive or negative for *IKZF1* deletions (*Online Supplementary Table S3*). Most of these genetic alterations occurred simultaneously in the same patients and are described in detail in *Online Supplementary Table S2*. Twenty-five of the 54 patients with an *IKZF1* deletion, and in particular seven of the nine carrying a Δ4-7 deletion, were negative for any additional tested alterations (*Online Supplementary Table S2*), although copy number variations of exons not detected by MLPA assays cannot be excluded. Moreover, aberrations present in less than 20-50% of cells would not have been detected because of the limited sensitivity of the MLPA assay.

Prognostic impact of IKZF1 *deletions*

Compared to patients without a deletion of *IKZF1*, those with a deletion of part or all of this gene had an inferior event-free survival [70.2% (6.2) *versus* 85.2% (1.9) at 5 years, *P*=0.007] and a significantly higher cumulative incidence of relapse [24.2% (5.9) *versus* 13.1% (1.8) at 5 years, *P*= 0.049] (Figure 1A-B). The corresponding survival figures at 5 years were 87.0%(4.6) *versus* 93.0%(1.4) (*P*-value=0.10).

These data are in accordance with those from other studies reported in the literature, in particular with those recently published by Dorge *et al.* who analyzed ALL patients enrolled in the AIEOP-BFM ALL2000 study in Germany [event-free survival 69% (5) *versus* 85% (1), *P*=<0.001 and cumulative incidence of relapse 21% (4) *versus* 10% (1), *P*=0.001].[7]

The negative prognostic impact of *IKZF1* deletions was retained, although without statistical significance, when

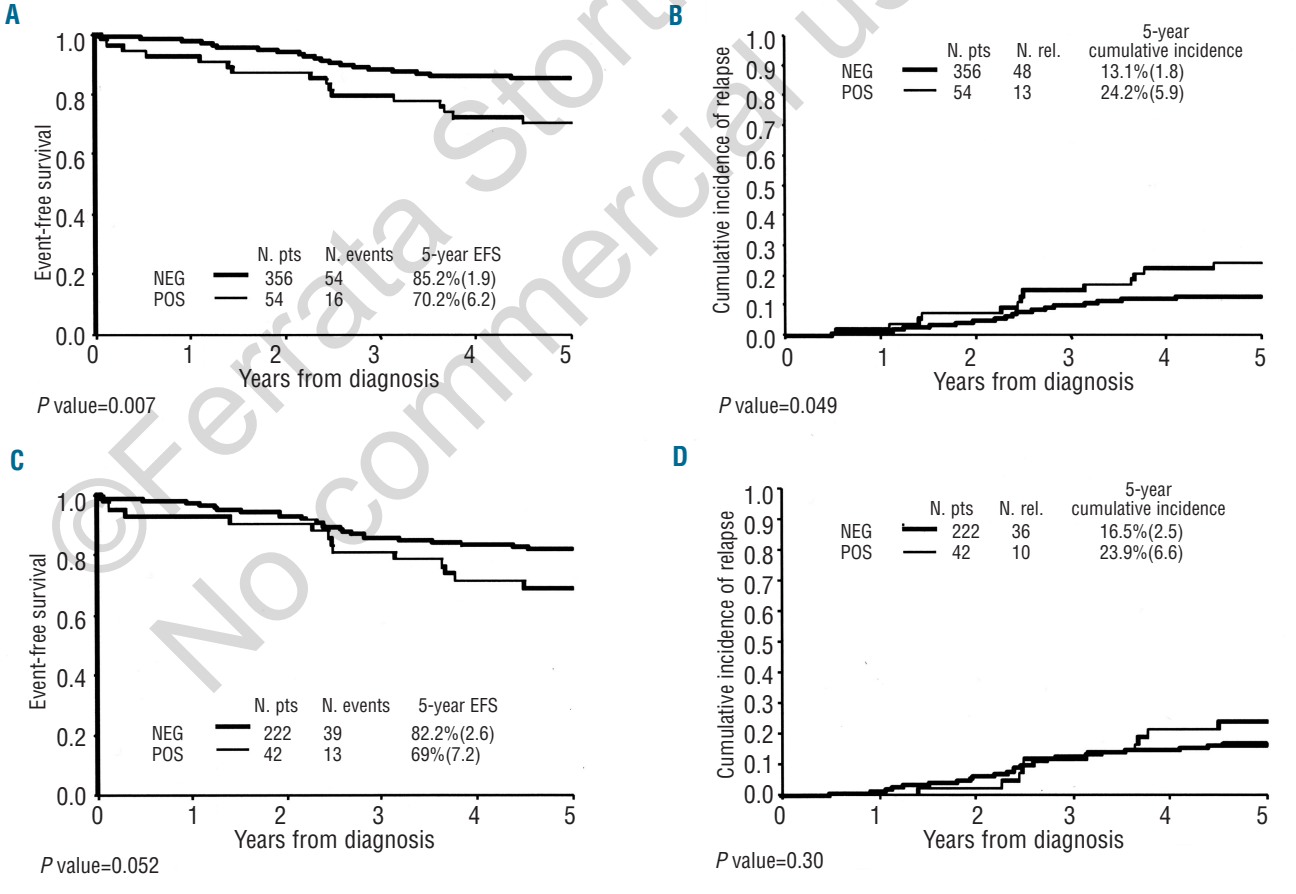

Figure 1. Association of *IKZF1* deletions and treatment outcome. (A) Event-free survival and (B) cumulative incidence of relapse of study cohort patients according to the presence or absence of *IKZF1* deletions. (C) Event-free survival and (D) cumulative incidence of relapse of intermediate risk patients according to the presence or absence of *IKZF1* deletions.

the favorable factor t(12;21) was excluded from the analysis (*Online Supplementary Figure S2A,B*) and also when patients with hyperdiploidy were excluded (*Online Supplementary Figure S2C,D*). Patients positive for the Δ4-7 deletion, predicted to encode a dominant-negative *IKZF1* isoform, did not show a worse outcome (3/9 relapsed) (*Online Supplementary Table S2*). We also analyzed the impact of *IKZF1* deletions alone or in combination with additional copy number abnormalities. Interestingly, only three out of 25 patients positive for the *IKZF1* deletion only relapsed compared with 10/28 who had additional alterations, pointing to a poor outcome when a major genetic instability was observed. Specifically, all three cases positive for both *IKZF1* deletions and the *P2RY8-CRLF2* fusion relapsed (*Online Supplementary Table S2*), but the limited numbers do not allow any conclusions to be drawn on a possible synergic effect of *IKZF1* alterations with other coexistent abnormalities.

The Cox model analysis was performed on the 410 patients to assess whether, after adjusting for other relevant risk factors, *IKZF1* deletions retained a prognostic impact on event-free survival (Table 2A) or on the specific hazard of relapse (Table 2B). *IKZF1* alterations were significantly related to a higher rate of events (hazard ratio for event-free survival of 1.87; 95% CI 1.05-3.32, *P*=0.03) and, although not statistically significantly, to a higher rate of relapse (hazard ratio 1.7; 95% CI 0.9-3.18, *P*=0.1). More precisely, two deaths in induction and one death in complete clinical remission (total n=3) occurred in the 54 *IKFZ1*-deleted patients compared to three deaths in induction and two in complete clinical remission and one second malignant neoplasm (total n=6) in the 356 non-*IKFZ1*-

Table 2. Results of the univariate and multivariate analyses. Cox model on event-free survival (hazard of first event among resistance, relapse, death, second malignant neoplasm) and the hazard of relapse in 410 patients.

2A. Analysis on event-free survival.

Characteristics	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
IKZF1						
No				1		
Yes	2.1	1.21-3.68	0.009	1.87	1.05-3.32	0.03
P2RY8-CRLF2						
No				1		
Yes	3.14	1.49-6.60	0.003	3.25	1.54-6.85	0.002
Not known	1.36	0.65-2.86	0.42	1.37	0.65-2.89	0.42
Age						
1-9 years				1		
10-17 years	1.87	1.08-3.23	0.02	1.69	0.97-2.93	0.06
WBC (x10^9/L)						
<100				1		
≥100	2.31	1.10-4.82	0.03	2.19	0.97-4.92	0.06
Final risk						
Standard risk				1		
Intermediate risk	2.78	1.37-5.63	0.005	2.60	1.27-5.33	0.009
High risk	5.15	2.04-12.98	<0.001	4.30	1.64-11.23	0.003

2B. Analysis on relapse.

Characteristics	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
IKZF1						
No				1		
Yes	1.94	1.05-3.58	0.03	1.70	0.90-3.18	0.10
P2RY8-CRLF2						
No				1		
Yes	3.76	1.78-7.98	<0.001	3.73	1.75-7.93	<0.001
Not known	1.40	0.63-3.10	0.41	1.47	0.69-3.26	0.35
Age						
1-9 years				1		
10-17 years	1.59	0.86-2.94	0.14	1.45	0.78-2.70	0.24
WBC (x10^9/L)						
<100				1		
≥100	1.28	0.46-3.52	0.64	1.27	0.43-3.71	0.67
Final risk						
Standard risk				1		
Intermediate risk	2.48	1.21-5.06	0.01	2.33	1.13-4.81	0.02
High risk	3.54	1.26-9.94	0.02	3.46	1.19-10.01	0.02

deleted patients. These events contributed to the statistical significance of the difference in the event-free survival.

In both Cox model analyses, the *P2RY8-CRLF2* aberration and risk group were significantly associated with outcome. Of note, when individually analyzed, the *IKFZ1* deletion had a statistically significant effect on event-free survival and relapse, in keeping with results in Figure 1A,B.

We further analyzed the prognostic value of *IKZF1* deletions within the subgroups according to protocol stratification. *IKZF1* deletions were less frequent within the standard-risk group, being found in 8 out 117 standard-risk patients (6.8%), 42 out of 264 intermediate-risk patients (15.9%) and 4 out of 29 high-risk patients (13.8%) (Table 1). Interestingly, none of the eight *IKZF1* deletion-positive standard-risk patients relapsed whereas 10/42 cases (23.8%) stratified in the intermediate-risk group and three out of four cases in the high-risk group did so. In particular, in the largest risk subgroup, which was the intermediate risk subgroup, *IKZF1* deletion-positive patients had an inferior event-free survival and a higher cumulative incidence of relapse compared to the IKZF1 deletion-negative patients, but the differences did not reach statistical significance [event-free survival: 69.0%(7.2) *versus* 82.2%(2.6), *P*=0.052; cumulative incidence of relapse: 23.9%(6.6) *versus* 16.5%(2.5), *P*=0.30] (Figure 1C-D).

Discussion

Previous studies[12-14] showed that the presence of *IKZF1* deletions is a risk factor in childhood ALL and this finding was recently confirmed by Dorge *et al.*[7] in the framework of a BFM treatment strategy also for patients at so-called intermediate risk. Our findings are substantially in keeping with those reported by Dorge *et al.*[7], and yet the value of including *IKZF1* deletions as a new marker for risk stratification is challenged by our results.

Indeed, overall event-free survival for patients with *IKZF1* deletions, after excluding the confounding effects of Down syndrome, T-immunophenotype and Philadelphia chromosome-positive patients, was around 70% at 5 years also in our experience. The three patients with *IKZF1* deletions who were at high risk and relapsed had poor response to treatment (high minimal residual disease levels) and accordingly were all eligible for transplantation, thus identification of *IKZF1* deletions would not have contributed to a better stratification. In the intermediate risk group, with a 5-year event-free survival of 70%, treatment intensification could be justified to improve results. In our context, the recent AIEOP-BFM ALL 2009 study, with a more intensive use of L-asparaginase, might already provide a benefit that reduces the impact of an *IKZF1* deletion. This is especially true if we consider that in our study cohort the difference in the cumulative incidence of relapse was not so marked, being approximately 7% in the intermediate risk subgroup and 11% overall. This, as well as the lower number of events in the multivariate analysis, may explain why the presence of *IKZF1* deletions is an independent prognostic factor for event-free survival but not for the hazard of relapse alone.

In conclusion, based on our data, the suitability of *IKZF1* deletions as an additional stratification marker for Philadelphia chromosome-negative, B-cell precursor ALL patients remains questionable, at least until new target therapy becomes available.

Acknowledgments

The authors would like to thank Simona Songia, Lilia Corral, Eugenia Mella, Tiziana Villa (Monza), Elena Seganfreddo and Katia Polato (Padova) for AIEOP minimal residual disease monitoring and all medical doctors of the AIEOP centers. This work was supported by grants from: Fondazione Tettamanti (Monza), Fondazione Città della Speranza (Padova), Associazione Italiana Ricerca sul Cancro (AIRC) (to GB, AB, MGV, GteK and GC), MIUR (to GB and AB), Fondazione Cariplo (to AB, GC and GteK), and CARIPARO project of excellence (to GteK). This work was (partly) funded by the European Commission (FP7) under the contract ENCCA (NoE-2011-261474).

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Pui CH, Carroll WL, Meshinchi S, Arceci RJ. Biology, risk stratification, and therapy of pediatric acute leukemias: an update. J Clin Oncol. 2011;29(5):551-65.
2. Russell LJ, Capasso M, Vater I, Akasaka T, Bernard OA, Calasanz MJ, et al. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute lymphoblastic leukemia. Blood. 2009;114(13):2688-98.
3. Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, et al. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. Nat Genet. 2009; 41(11):1243-6.
4. Den Boer ML, van Slegtenhorst M, De Menezes RX, Cheok MH, Buijs-Gladdines JG, Peters ST, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol. 2009;10(2):125-34.
5. Mullighan CG, Su X, Zhang J, Radtke I, Phillips LA, Miller CB, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med. 2009;360(5):470-80.
6. Iacobucci I, Storlazzi CT, Cilloni D, Lonetti A, Ottaviani E, Soverini S, et al. Identification and molecular characterization of recurrent genomic deletions on 7p12 in the IKZF1 gene in a large cohort of BCR-ABL1-positive acute lymphoblastic leukemia patients: on behalf of Gruppo Italiano Malattie Ematologiche dell'Adulto Acute Leukemia Working Party (GIMEMA AL WP). Blood. 2009;114(10):2159-67.
7. Dorge P, Meissner B, Zimmermann M, Moericke A, Schrauder A, Bourquin JP, et al. IKZF1 deletion is an independent predictor of outcome in pediatric acute lymphoblastic leukemia treated according to the ALL-BFM 2000 protocol. Haematologica. 2013;98(3): 428-32.
8. Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. Nature. 2008;453(7191): 110-4.
9. Buitenkamp TD, Pieters R, Gallimore NE, van der Veer A, Meijerink JP, Beverloo HB, et al. Outcome in children with Down's syndrome and acute lymphoblastic leukemia: role of IKZF1 deletions and CRLF2 aberrations. Leukemia. 2012;26:2204-11.
10. Mullighan CG, Goorha S, Radtke I, Miller CB, Coustan-Smith E, Dalton JD, et al. Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature. 2007;446(7137):758-64.
11. Harvey RC, Mullighan CG, Chen IM, Wharton W, Mikhail FM, Carroll AJ, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood. 2010;115 (26):5312-21.
12. Waanders E, van der Velden VH, van der

Schoot CE, van Leeuwen FN, van Reijmersdal SV, de Haas V, et al. Integrated use of minimal residual disease classification and IKZF1 alteration status accurately predicts 79% of relapses in pediatric acute lymphoblastic leukemia. Leukemia. 2011;25(2):254-8.
13. Kuiper RP, Waanders E, van der Velden VH, van Reijmersdal SV, Venkatachalam R, Scheijen B, et al. IKZF1 deletions predict relapse in uniformly treated pediatric precursor B-ALL. Leukemia. 2010;24(7):1258-64.
14. Yang YL, Hung CC, Chen JS, Lin KH, Jou ST, Hsiao CC, et al. IKZF1 deletions predict a poor prognosis in children with B-cell progenitor acute lymphoblastic leukemia: a multicenter analysis in Taiwan. Cancer Sci. 2011;102(10):1874-81.
15. Chen IM, Harvey RC, Mullighan CG, Gastier-Foster J, Wharton W, Kang H, et al. Outcome modeling with CRLF2, IKZF1, JAK, and minimal residual disease in pediatric acute lymphoblastic leukemia: a Children's Oncology Group study. Blood. 2012;119(15):3512-22.
16. Sun L, Liu A, Georgopoulos K. Zinc finger-mediated protein interactions modulate Ikaros activity, a molecular control of lymphocyte development. Embo J. 1996;15(19):5358-69.
17. Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grumayer R, Moricke A, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010;115(16):3206-14.
18. Palmi C, Vendramini E, Silvestri D, Longinotti G, Frison D, Cario G, et al. Poor prognosis for P2RY8-CRLF2 fusion but not for CRLF2 over-expression in children with intermediate risk B-cell precursor acute lymphoblastic leukemia. Leukemia. 2012;26(10):2245-53.
19. van Dongen JJ, Macintyre EA, Gabert JA, Delabesse E, Rossi V, Saglio G, et al. Standardized RT-PCR analysis of fusion gene transcripts from chromosome aberrations in acute leukemia for detection of minimal residual disease. Report of the BIOMED-1 Concerted Action: investigation of minimal residual disease in acute leukemia. Leukemia. 1999;13(12):1901-28.
20. Krentz S, Hof J, Mendioroz A, Vaggopoulou R, Dorge P, Lottaz C, et al. Prognostic value of genetic alterations in children with first bone marrow relapse of childhood B-cell precursor acute lymphoblastic leukemia. Leukemia. 2012 Jun 13. [Epub ahead of print].
21. Strefford JC, Worley H, Barber K, Wright S, Stewart AR, Robinson HM, et al. Genome complexity in acute lymphoblastic leukemia is revealed by array-based comparative genomic hybridization. Oncogene. 2007;26(29):4306-18.
22. Kuiper RP, Schoenmakers EF, van Reijmersdal SV, Hehir-Kwa JY, van Kessel AG, van Leeuwen FN, et al. High-resolution genomic profiling of childhood ALL reveals novel recurrent genetic lesions affecting pathways involved in lymphocyte differentiation and cell cycle progression. Leukemia. 2007;21(6):1258-66.