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Published in:
Genes, Chromosomes and Cancer

DOI:
10.1002/gcc.22349

2016

Document Version:
Peer reviewed version (aka post-print)

Patterns and Frequencies of Acquired and Constitutional Uniparental Isodisomies in Pediatric and Adult B-Cell Precursor Acute Lymphoblastic Leukemia

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Running title: Uniparental isodisomies in ALL

Supported by: the Swedish Childhood Cancer Foundation; the Swedish Cancer Society; the Swedish Research Council; and Governmental Funding of Clinical Research within the National Health Service.

Additional Supporting Information may be found in the online version of this article.

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Single nucleotide polymorphism (SNP) arrays are increasingly being used in clinical routine for genetic analysis of pediatric B-cell precursor acute lymphoblastic leukemias (BCP ALL). Because constitutional DNA is not readily available as a control at the time of diagnosis, it is important to be able to distinguish between acquired and constitutional aberrations in a diagnostic setting. In the present study we focused on uniparental isodisomies (UPIDs). SNP array analyses of 143 pediatric and 38 adult B-cell precursor acute lymphoblastic leukemias and matched remission samples revealed acquired whole chromosome or segmental UPIDs (wUPIDs, sUPIDs) in 32 cases (18%), without any age- or gender-related frequency differences. Acquired sUPIDs were larger than the constitutional ones (mean 35.3 Mb vs. 10.7 Mb; $P<0.0001$) and were more often terminally located in the chromosomes (69% vs. 4.5%; $P<0.0001$). Chromosomes 3, 5, and 9 were most often involved in acquired wUPIDs, whilst recurrent acquired sUPIDs targeted 6p, 9p, 9q, and 14q. The majority (56%) of sUPID9p was associated with homozygous *CDKN2A* deletions. In pediatric ALL, all wUPIDs were found in high hyperdiploid (51-67 chromosomes) cases and an extended analysis, also including unmatched diagnostic samples, revealed a higher frequency of wUPID-positivity in higher modal number (56-67 chromosomes) than in lower modal number (51-55 chromosomes) high hyperdiploid cases (34% versus 11%; $P=0.04$), suggesting different underlying mechanisms of formation of these subtypes of high hyperdiploidy.

INTRODUCTION

Constitutional uniparental heterodisomies and isodisomies (UPHDs, UPIDs) arise as a consequence of duplication of a maternal or paternal chromosome or chromosomal region with a concurrent loss of the other parental chromosome/alleles (Engel, 1980). Uniparental hetero- and isodisomies can lead to developmental disorders, such as the Angelman, Beckwith-Wiedemann, Prader-Willi, and Silver-Russell syndromes, which are caused by imprinting defects involving chromosomal regions that harbor genes expressed in a parent-of-origin-specific manner. The imprinting abnormalities hence result either in two abnormally active alleles or in two silent alleles, leading to gene over-expression or loss of function, respectively. Furthermore, UPIDs may also result in duplication of recessive mutations (Yamazawa et al., 2010).

Although uniparental disomy was initially proposed to explain certain genetic peculiarities of a few constitutional disorders, it is now well recognized that UPIDs may also be somatic tumor-associated changes of pathogenetic importance. Acquired whole chromosome and segmental UPIDs (wUPIDs, sUPIDs), also frequently referred to as copy neutral loss of heterozygosity, have been identified by single nucleotide polymorphism (SNP) array analyses of numerous tumor entities, including several types of myeloid malignancy. The pathogenetic impact of somatic wUPIDs is, in most instances, unknown, whereas sUPIDs often result in homozygous mutations of, for example, *CEBPA* and *FLT3* in acute myeloid leukemia, *JAK2* in polycythemia vera and other myeloproliferative neoplasms, *NF1* in juvenile myelomonocytic leukemia, and *TET2* in myelodysplastic syndromes and myeloproliferative neoplasms (Baxter et al., 2005; Fitzgibbon et al., 2005; Raghavan et al., 2005; Stephens et al., 2006; Paulsson et al., 2010b). In contrast, there is a paucity of information on the patterns and frequencies of wUPIDs and sUPIDs in B-cell precursor acute lymphoblastic leukemia (BCP ALL). In fact, most studies of such leukemias have focused primarily on sUPIDs of 9p, revealing that they are often associated with homozygous deletions of the *CDKN2A* gene at 9p21.3 (Kuiper et al., 2007; Mullighan et al., 2007; Kawamata et al., 2008; Paulsson et al., 2010a).

The aims of this study were twofold: i) to ascertain the patterns and frequencies of wUPIDs and sUPIDs in pediatric and adult BCP ALL and to delineate chromosomes and chromosomal regions that may harbor genes of importance in the leukemogenic process, and ii) to compare the frequencies, locations, and sizes of acquired and constitutional sUPIDs found at diagnosis and

remission, respectively, in order to distinguish acquired and constitutional sUPIDs in a diagnostic setting.

MATERIALS AND METHODS

Patients

DNA of sufficient quality and quantity for SNP array analysis was available from 181 diagnostic BCP ALL samples, comprising 143 pediatric and 38 adult patients diagnosed between 1992 and 2014 and 1985 and 2014, respectively, which had been genetically investigated at the Department of Clinical Genetics, Lund, Sweden. In the pediatric cases, fluorescent in situ hybridization (FISH) or reverse-transcription polymerase chain reaction (PCR) analyses were used to screen for the translocations/gene fusions t(1;19)(q23;p13) [*TCF3-PBX1*], t(9;22)(q34;q11) [*BCR-ABL1*], and t(12;21)(p13;q22) [*ETV6-RUNX1*]. FISH or Southern blot analyses were used to identify 11q23/*MLL* rearrangements and SNP array analysis was applied to ascertain cases with intrachromosomal amplification of chromosome 21 (iAMP21) or aneuploidy, such as high hyperdiploidy (51-67 chromosomes). As regards the adult cases, no targeted molecular genetic analyses were compulsory during most of the study period; however, RT-PCR or FISH analyses of *BCR-ABL1* were performed on the majority of cases during the last two decades.

DNA from paired remission samples was available in all 181 cases; additional remission samples without corresponding diagnostic samples could also be analyzed in 12 pediatric and five adult patients. Thus, in total, constitutional UPIDs could be ascertained in 198 patients. Details on all aberrations identified, focusing on microdeletions rather than on wUPIDs/sUPIDs, in 129 of the pediatric and 37 of the adult cases have been reported previously (Olsson et al., 2014; Safavi et al., 2015). Basic clinical and cytogenetic data on the cases with wUPIDs and/or sUPIDs are presented in Supporting Information Tables 1 and 2.

SNP Array Analyses

Details on the SNP array analyses have been described (Olsson et al., 2014; Safavi et al., 2015). In short, the SNP array systems HumanOmni1-Quad (~1.1 million markers), Human1M-Duo (~1.1 million markers), or HumanOmni5-Quad BeadChip (~5 million markers) (Illumina, San Diego, CA) were used. The analyses were done according to the manufacturer's instructions

and the B-allele and the $\log_2$ ratios were analyzed with the Genome studio v2011.1 software (Illumina), extracting probe positions from the GRCh37 genome build. The $\log_2$ ratio is used for determining copy number, where ratios above and below zero indicate gains and losses, respectively. The B-allele frequency indicates genotype. Thus, homozygous SNP reporters have a value of 0 or 1, whereas heterozygous reporters have a value of 0.5. In this study, regions with $\log_2$ ratios of 0, indicating diploidy, in combination with a B-allele frequency value of 0 or 1, indicating loss of heterozygosity, was defined as an UPID. This was done by visual inspection. The threshold for a constitutional sUPID was set to ≥5 Mb, in line with previous studies (Kuiper et al., 2007; Dougherty et al., 2011; Ninomiya et al., 2012; Sund et al., 2013). A lower cut-off would have "diluted" the findings because sUPIDs <5 Mb are frequent in the general population, being ancestral markers of an outbred population (Kuiper et al., 2007; Sund et al., 2013). Although a germline region of homozygosity in the vast majority of cases reflects homozygosity by descent (McQuillan et al., 2008; Sund et al., 2013) and not, in a formal sense, sUPID, the latter term is nevertheless used herein, partly because the SNP array patterns of regions of homozygosity and sUPIDs are the same and partly to avoid using different terms when comparing constitutional and acquired sUPIDs.

In the leukemic samples, all sUPIDs that were not present in the remission samples were classified as sUPIDs. The X and Y chromosomes in males were not included in the analyses. The investigation was reviewed and approved by the Research Ethics Committee at Lund University.

Statistical Analyses

The Chi-square with Yates' correction (two-tailed), Fisher exact probability (two-tailed), and Mann-Whitney tests were applied to compare the frequencies of acquired and constitutional UPIDs between children and adults, females and males, and among cytogenetic subgroups. The unpaired *t* test was used for comparison of the mean sizes of acquired and constitutional sUPIDs. All analyses were performed at the VassarStats website for statistical computation (http://vassarstats.net/).

RESULTS

Frequencies, Locations, and Sizes of Acquired wUPIDs and sUPIDs in BCP ALL

Among the 143 pediatric BCP ALL samples analyzed, 24 (17%) harbored wUPIDs and/or sUPIDs (Fig. 1 and Supporting Information Tables 1, 3, and 4). A total of 16 wUPIDs were identified in nine cases. Twenty sUPIDs were found in 18 cases, 14 (70%) of which were terminal and six (30%) interstitial. The following sUPIDs were recurrent: sUPID9p (25%), sUPID9q (15%), and sUPID14q (10%). The sUPIDs varied in size between 2.1 and 81.8 Mb, with a mean length of 36.9 Mb.

Of the 38 adult cases, 8 (21%) had wUPIDs and/or sUPIDs (Fig. 1 and Supporting Information Tables 1, 3, and 4). A total of 13 wUPIDs were identified in three cases. Six sUPIDs were observed in five cases; of these sUPIDs, 4 (67%) were terminal and two (33%) interstitial. Recurrent sUPIDs comprised sUPID9p (50%) and sUPID6p (33%). The sUPIDs spanned 13.0–43 Mb (mean 29.9 Mb).

There were no significant frequency differences of acquired wUPIDs and sUPIDs between children and adults or between females and males (Supporting Information Table 3).

Overall Distribution of Acquired UPIDs in BCP ALL

When combining all 29 wUPIDs identified in the entire cohort of 181 BCP ALLs, chromosomes 3, 5, and 9 were most often affected (>2 wUPIDs; Fig. 1). Of the 26 sUPIDs detected, chromosome arm 9p was by far the most commonly affected, followed by 9q, 6p, and 14q. The minimally involved regions were 6p22.2–pter [chr6:1–26172219], 9p21.1–21.3 [chr9:20464928–29470565; encompassing the *CDKN2A* gene], 9q12–21.2 [chr9:71033538 – 80355515], 9q31.1–33.3 [chr9:104010913–127661645], and 14q12–qter [chr14:31188832–107306640]. Of the nine cases with sUPID9p, five (56%) had homozygous *CDKN2A* deletions.

Acquired UPIDs in Relation to Cytogenetic Subgroups

Among the 143 pediatric BCP ALLs, all cases with wUPID belonged to the cytogenetic subgroup high hyperdiploidy ($P<0.0001$) whilst the occurrence of sUPIDs did not vary significantly in relation to cytogenetic subgroup (Table 1). When investigating the distribution of high hyperdiploid cases with and without wUPIDs in relation to lower (51-55 chromosomes) and higher (56-67 chromosomes) modal numbers, the analysis was extended to include also 36 cases

without matched remission samples that had been previously analyzed by SNP arrays (Olsson et al., 2014). The rationale for including also non-paired samples is the rarity of constitutional wUPIDs (Eggermann et al., 2015; present study). Among a total of 70 high hyperdiploid cases, 35 had 51-55 chromosomes and of these four (11%) harbored wUPIDs. The corresponding frequency of the 35 cases with 56-67 chromosomes was 12 (34%) (P=0.04).

In the 38 adult BCP ALLs, the frequencies of wUPIDs and sUPIDs did not differ among the cytogenetic subgroups (Table 2).

Frequency, Location, and Size of Constitutional wUPIDs and sUPIDs

Of the 155 pediatric remission samples analyzed, 10 (6.5%) harbored a total of 22 sUPIDs spanning at least 5 Mb; all except one (95%) were interstitial (Supporting Information Fig. 1 and Supporting Information Tables 5 and 6). The sUPIDs varied in size between 5.0 and 19.7 Mb (mean length 11.2 Mb). No constitutional wUPIDs were detected.

SNP array analyses of the 43 adult remission samples identified 10 patients (23%) who had a total of 22 sUPIDs; all but one (95%) were interstitial (Supporting Information Fig. 1 and Supporting Information Tables 5 and 6). The sizes of the sUPID spanned 5.3–30.5 Mb (mean 10.3 Mb). There were no constitutional wUPIDs.

Constitutional sUPIDs were significantly more common in adults, whereas there was no gender-related frequency difference (Supporting Information Table 6).

Acquired and Constitutional sUPIDs in Relation to Size and Location

The 26 acquired sUPIDs, found in all pediatric and adult BCP ALL cases combined, varied in size between 2.1 and 81.8 Mb (mean 35.3 Mb), whereas the 44 constitutional sUPIDs identified spanned 5.0–30.5 Mb (mean 10.7 Mb) (P<0.0001). Of the acquired sUPIDs, 18 (69%) were terminal and eight (31%) interstitial; the corresponding frequencies among the constitutional sUPIDs were 2 (4.5%) and 42 (96%) (P<0.0001).

DISCUSSION

Already in the early 1980s, acquired sUPIDs were identified in dominantly inherited tumors, such as retinoblastoma and Wilms' tumor; they constitute the "second hit" according to Knudson's two-hit hypothesis, leading to homozygosity of the germline mutation (Cavenee et al.,

1983; Fearon et al., 1984). With the advent of the SNP array technology, it became apparent that acquired sUPIDs also result in duplication of somatic mutations, which hence are heterozygous prior to the recombination event, as initially shown in myeloid malignancies (Baxter et al., 2005; Fitzgibbon et al., 2005; Raghavan et al., 2005). In fact, the association between sUPIDs and homozygous mutations is so pronounced that mapping of sUPIDs by SNP arrays has been used successfully to identify novel leukemia-associated genes (Score and Cross, 2012). This notwithstanding, surprisingly few SNP array-based studies of BCP ALL have focused on the patterns and frequencies of wUPIDs and sUPIDs. Instead, they have mainly reported, often *en passant*, the overall frequency of UPIDs in BCP ALL (20-30%) (Kawamata et al., 2008), investigated specific cytogenetic subtypes, e.g., high hyperdiploidy, near-haploidy, and low hypodiploidy (Paulsson et al., 2010a; Safavi et al., 2013), or emphasized the association between sUPID9p and *CDKN2A/B* deletions (Kuiper et al., 2007; Kawamata et al., 2008; Sulong et al., 2009; Okamoto et al., 2010).

We performed a detailed analysis of the patterns and frequencies of acquired as well as constitutional wUPIDs/sUPIDs in childhood and adult BCP ALL patients, aiming to identify distinguishing features between acquired and constitutional UPIDs, to delineate chromosomal regions where homozygous gene mutations or imprinting abnormalities may reside, and to ascertain possible associations with age, gender, and cytogenetic subtype. The most salient findings are that constitutional and acquired sUPIDs differ significantly in size and location and that wUPIDs vary among the cytogenetic subgroups in pediatric BCP ALL.

Constitutional sUPIDs were identified in ~10% of the patients, irrespective of gender. An unexpected finding was that constitutional sUPIDs were significantly more common in adults (Supporting Information Table 6). This may possibly be due to a higher degree of consanguinity among the parents to the adults, perhaps reflecting lower population mobility in former generations. However, this is quite speculative; the observed difference between children and adults is based on few individuals and may well be fortuitous.

Considering that SNP arrays are increasingly being used in clinical routine for genetic analysis of pediatric BCP ALL and that constitutional DNA is not readily available as a control at the time of diagnosis, it is important to be able to distinguish between acquired and constitutional sUPIDs in a diagnostic setting. A few studies have addressed this issue, focusing on the locations and the sizes of the sUPIDs. Constitutional sUPIDs, using the same cut-off (>5 Mb) as in the

present study, were identified in approximately 10% of lymphoblastoid cell lines derived from healthy individuals (Score and Cross, 2012). Because the sUPIDs were rarely >20 Mb in length, the authors suggested that this cut-off could be used to differentiate between germline and acquired sUPIDs in the absence of constitutional DNA. Our findings agree very well with that suggestion – the length of a germline sUPID exceeded 20 Mb in only one patient, in whom it most likely was the result of the parents belonging to the same kinship (case 40; Supporting Information Table 5). In fact, the presence of multiple, often large constitutional sUPIDs on different chromosomes, as found in a few of our patients (cases 38, 40, and 41; Supporting Information Tables 2 and 5), is strongly indicative of parental consanguinity (Sund et al., 2013). Thus, the occurrence of several sUPIDs in a case of BCP ALL would definitely suggest that they are constitutional, not least considering that the number of acquired sUPIDs in our series only ranged between 0 and 2, with a mean of less than one per case (Supporting Information Tables 1 and 3). Also the location of an sUPID may help separate germline and acquired sUPIDs. Two previous studies, comparing the distribution of acquired and constitutional sUPIDs in hematologic malignancies, reported that the former ones were almost always terminally located at the chromosomes whereas the latter were predominantly interstitial (O'Keefe et al., 2010; Dougherty et al., 2011). This was clearly confirmed in the present study – the acquired sUPIDs were significantly more often terminal and larger than the germline sUPIDs (Fig. 1 and Supporting Information Fig. 1). Thus, based on our results and previous findings we conclude that if 1-3 large telomeric sUPIDs are present in a case of BCP ALL they are most likely acquired.

Acquired sUPIDs most frequently involved 9p and 9q, but were also recurrent at 6p and 14q (Fig. 1). All sUPID9p identified herein included the genomic position of *CDKN2A*, a gene frequently deleted in BCP ALL (Moorman et al., 2014), and 67% of the sUPID9p-postive cases harbored homozygous *CDKN2A* deletions, in line with previous findings (Kuiper et al., 2007; Kawamata et al., 2008; Okamoto et al., 2010; Paulsson et al., 2010a). The functional outcome of the other sUPIDs identified is unknown. They may well harbor homozygous mutations but as of yet no genes known to be mutated in ALL reside in the chromosome segments recurrently involved.

The most likely mechanisms causing acquired sUPIDs are mitotic homologous recombinations and double strand break repair (Raghavan et al., 2010). Both acquired and

inherited defects and polymorphisms in the DNA repair system may lead to mitotic recombination events, perhaps at fragile sites, thus increasing the risk of sUPID formation. The possible involvement of fragile sites, which are particularly sensitive to interference during DNA synthesis and thus increase the likelihood of chromosomal lesions due to replication failure (Arlt et al., 2006; Lukusa and Fryns, 2008), is noteworthy considering that some of the acquired sUPIDs in the present study were in close vicinity to, or directly overlapped with, well-known common fragile sites, such as FRA6C (at 6p22.2), FRA9C (9p21), FRA9F (9q12), FRA9E (9q32), and FRA11G (11q23.3) (Lukusa and Fryns, 2008).

Chromosomes 2, 6, 10, 12, 14, 18, 21, and 22 were not involved in any acquired wUPIDs in the present study (Fig. 1), but wUPIDs of most of these chromosomes have been observed in BCP ALL previously (Irving et al., 2005; Kawamata et al., 2008; Paulsson et al., 2010a; Ninomiya et al., 2012; Safavi et al., 2013). However, chromosome 21 is clearly an "outlier" in this context. Although Rogan et al. (1995) described a case of Down syndrome-associated BCP ALL with an acquired wUPID21, no further BCP ALL cases with acquired wUPID21 have been reported, to the best of our knowledge (Irving et al., 2005; Kawamata et al., 2008; Paulsson et al., 2010a; Ninomiya et al., 2012; Safavi et al., 2013). One possible explanation for the absence of wUPID21 could be that there are imprinted genes on chromosome 21 and that a wUPID21 therefore could result in detrimental epigenetic changes that would kill the leukemic cells, in effect constituting an evolutionary dead end for the malignant clone. However, imprinted loci on chromosome 21 remain to be identified (Petersen et al., 1992; Ledbetter and Engel, 1995; http://igc.otago.ac.nz/).

All pediatric BCP ALL cases with wUPIDs were high hyperdiploid (Table 1). Based on the findings of equal dosage for maternal and paternal alleles on tetrasomic chromosomes in high hyperdiploid cases, it has been suggested that the high hyperdiploid karyotype usually arises by simultaneous gain of chromosomes during a single abnormal cell division (Onodera et al., 1992; Paulsson et al., 2003, 2005, 2010a). However, such an allele pattern would also be seen if high hyperdiploidy arose by an initial tetraploidization of a normal diploid cell with subsequent chromosome losses (Paulsson and Johansson, 2009). If that was the underlying mechanism of formation, then one would expect, on average, one-third of all disomies to be wUPIDs – when the four homologues are reduced to three, the allele ratio will by default be 2:1, and when these trisomies are reduced to disomies, the allele ratio will be 2:0 (wUPID) in one-third of instances.

If this "tetraploid pathway" were to be followed, then the ensuing high hyperdiploid cases would perhaps be characterized by higher chromosome modal numbers than the median of 55 chromosomes. The present observation of a significantly higher proportion of wUPID-positive high hyperdiploid cases among those with 56-67 chromosomes (34%) than in those with 51-55 chromosomes (11%) (P=0.04) is hence noteworthy, suggesting that some high hyperdiploid cases may well originate through an initial polyploidization followed by chromosome losses. If so, such cases may possibly display some distinct clinical features. Indeed, it has been reported that high hyperdiploid cases with high (>53/55) modal chromosome numbers have a superior outcome compared with those with lower modes (Raimondi et al., 1996; Moorman et al., 2003; Paulsson et al., 2013).

In conclusion, the present study shows significant differences in size and chromosomal location between germline and acquired UPIDs, something that should be considered when using SNP array analyses in a diagnostic setting where constitutional DNA is not readily available for comparison. Furthermore, the chromosome segments found to be involved in acquired sUPIDs (Supporting Information Tables 1 and 4) may guide future studies in search of ALL-associated mutated genes.

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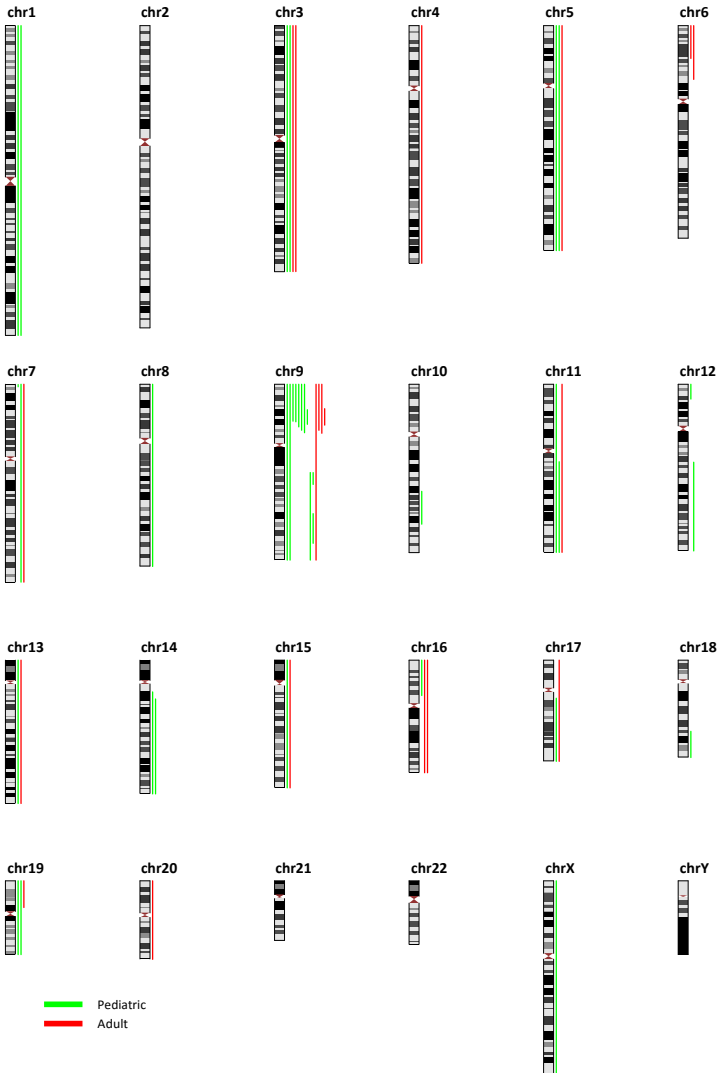


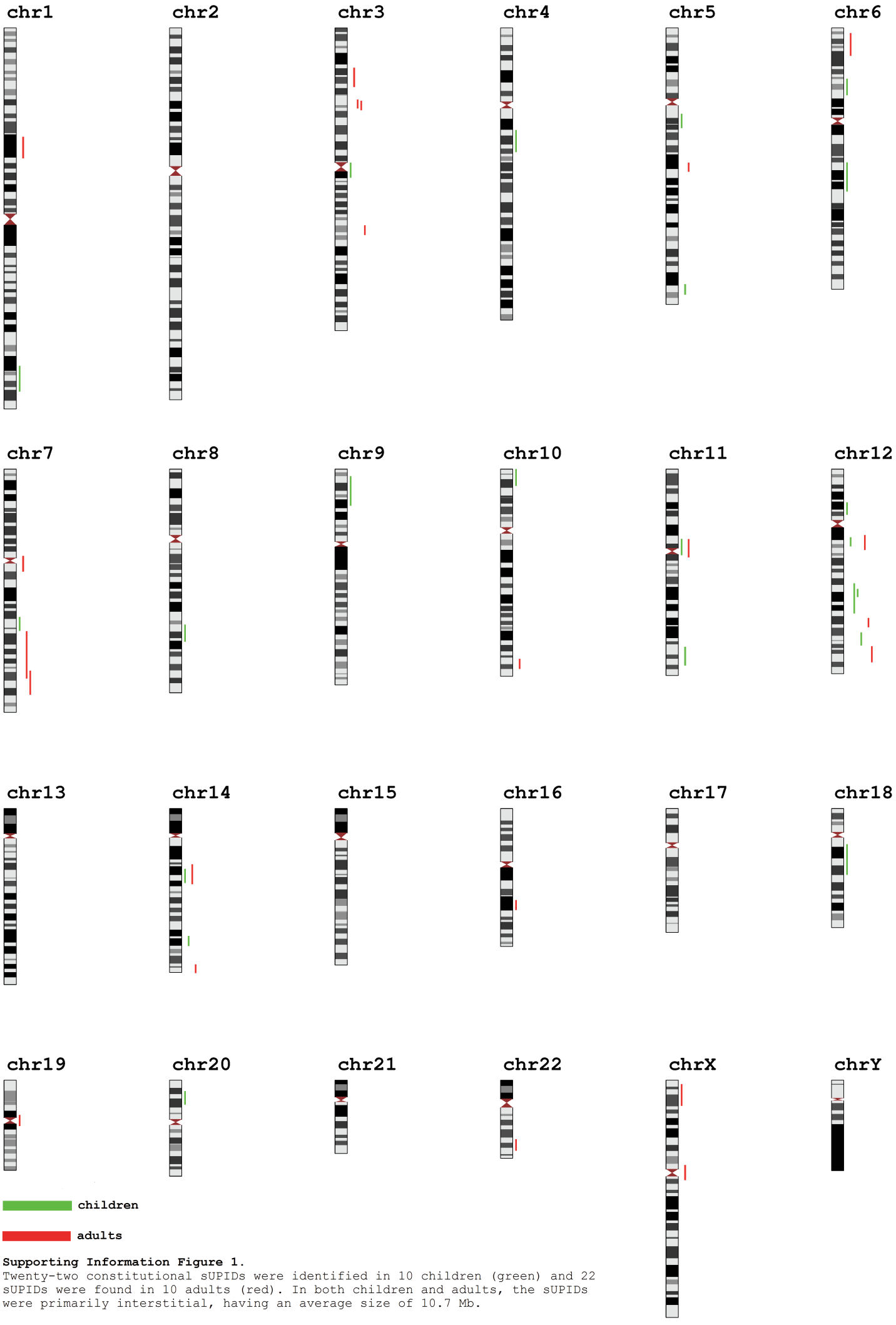
Figure 1. Nine pediatric (green) BCP ALL cases had a total of 16 wUPIDs and 18 harbored a total of 20 sUPIDs, whereas three adult (red) cases had a total of 13 wUPIDs and five harbored a total of six sUPIDs. In both childhood and adult BCP ALL, the sUPIDs were primarily terminal. The average size of the sUPIDs was 35.3 Mb.

Table 1. UPIDs in Relation to Cytogenetic Subgroups in 143 Pediatric BCP ALL Cases

	Cases with wUPIDs *n* = 9 (%)	**Cases without wUPIDs *n* = 134 (%)**	***P*[a]**
t(1;19)(q23;p13)	0 (0)	8 (6.0)	1.0000
t(9;22)(q34;q11)	0 (0)	4 (3.0)	1.0000
der(11q23)/*MLL*	0 (0)	8 (6.0)	1.0000
t(12;21)(p13;q22)	0 (0)	38 (28)	0.1118
iAMP21	0 (0)	1 (0.7)	1.0000
High hyperdiploidy	9 (100)	25 (19)	**<0.0001**
Low hypodiploidy	0 (0)	1 (0.7)	1.0000
Other	0 (0)	49 (37)	**0.0278**
	Cases with sUPIDs *n* = 18 (%)	**Cases without sUPIDs *n* = 125 (%)**	***P***
t(1;19)(q23;p13)	2 (11)	6 (4.8)	0.2650
t(9;22)(q34;q11)	1 (5.8)	3 (2.4)	0.4197
der(11)(q23)/*MLL*	1 (5.6)	7 (5.6)	1.0000
t(12;21)(p13;q22)	2 (11)	35 (28)	0.1577
iAMP21	0 (0)	1 (0.8)	1.0000
High hyperdiploidy	6 (33)	29 (23)	0.3829
Low hypodiploidy	0 (0)	1 (0.8)	1.0000
Other	6 (33)	43 (34)	1.0000

Table 2. UPIDs in Relation to Cytogenetic Subgroups in 38 Adult BCP ALL Cases

	Cases with wUPIDs *n* = 3 (%)	**Cases without wUPIDs *n* = 35 (%)**	***P***
t(1;19)(q23;p13)	0 (0)	3 (8.6)	1.0000
t(9;22)(q34;q11)	1 (33)	13 (37)	1.0000
der(11q23)/*MLL*	0 (0)	6 (17)	1.0000
High hyperdiploidy	0 (0)	2 (5.7)	1.0000
Near-tetraploidy	1 (33)	0 (0)	0.0789
Other	1 (33)	11 (31)	1.0000
	Cases with sUPIDs n = 5 (%)	**Cases without sUPIDs n = 33 (%)**	***P***
t(1;19)(q23;p13)	1 (20)	2 (6.1)	0.3532
t(9;22)(q34;q11)	1 (20)	13 (39)	0.6331
der(11q23)/*MLL*	0 (0)	6 (18)	0.5701
High hyperdiploidy	0 (0)	2 (6.1)	1.0000
Near-tetraploidy	0 (0)	1 (20)	1.0000
Other	3 (60)	9 (27)	0.3007



Supporting Information Figure 1.
Twenty-two constitutional sUPIDs were identified in 10 children (green) and 22 sUPIDs were found in 10 adults (red). In both children and adults, the sUPIDs were primarily interstitial, having an average size of 10.7 Mb.

Supporting Information Table 1. Clinical and Cytogenetic Data on the Pediatric and Adult Cases with Acquired UPIDs

Case No.	Gender/ age	WBC ($x10^9$/l)	wUPID	sUPID	Group	Karyotype
1[a]	M/4	25	No	9p21.1-pter	t(9;22)	50,XY,+4,+5,t(8;14)(q11;q32),t(9;22)(q34;q11),+der(14)t(8;14),der(16)t(14;16)(q11;p13)t(8;14),+21
2[a]	M/2	6.2	1, 3, 13, 19	No	HeH	62,XXY,+Y,-1,-2,-3,-4,der(5)t(1;5)(q12;q21),-7,-13,+14,-15,-16,-19,-20,+21
3	M/1	55	No	17q11.2-qter	t(1;19)	46,XY,der(19)t(1;19)(q23;p13)
4[a]	M/16	13	No	14q11-qter	Other	47,XY,t(8;14)(q11;q32),inv(12)(q13q24),der(14)t(8;14),+21c
5[a]	M/3	5.7	15	No	HeH	61,XXY,-1,-2,-3,-6,+8,-9,der(11)t(6;11)(p21;q14),-13,+14,-15,-16,-19,-20/63,idem,+18,+21
6[a]	M/2	24	No	9p21.1-21.3	MLL	47-48,XY,t(9;11)(p21;q23),+1-2mar
7[a]	M/13	66	9	17p11.2-13.2	HeH	55,XY,+X,+4,+6,add(8)(q?22),+10,+14,+der(17)t(17;19)(q?;?)del(17)(p11p13),+18,der(19)t(17;19),+21,+21
8[a]	F/4	7.4	No	9q12-q21.2, 9q31.1-33.3	HeH	58,XX,+X,+X,+4,+5,+6,der(?6)t(1;6)(q21;p25),+10,+14,idic(17)(p11),+18,+21,+21
9[a]	M/10	4.1	No	9q12-qter	HeH	54,XY,+X,del(1)(p12p36),+6,i(9)(p10),+10,+14,+17,+18,+21,+21
10[a]	F/8	5.0	3, 19	10q23.1-25.2	HeH	59,XXX,-1,-2,-3,-5,-7,-8,+10,-11,-12,-13,-16,-17,idic(17)(p11),-19,+21
11[a]	M/5	16	No	16p11.2-pter	HeH	56,XY,+X,+4,+5,+6,dup(8)(q24q24),+9,+10,dup(11)(p11p15),+14,del(16)(p11p13),+18,+21,+21/56,idem,dup(1)(q12q44)
12	M/3	3.1	No	12p13.2-pter	t(12;21)	46,XY,del(12)(p13p13),t(12;21)(p13;q22)/47,idem,+der(21)t(12;21) [based on FISH]
13	F/3	30	No	18q21.32-qter	t(12;21)	46,XX,t(12;21)(p13;q22) [based on FISH]
14	F/10	2.6	No	9p13.2-pter	t(12;21)	??,X,-X,+4,+4,+6,+6,+8,+8,+10,+10,t(12;21)(p13;q22)x1-2,+14,+14,+17,

						+17,+18,+18,+21,+21,+21 [based on FISH]
15[a]	M/1	30	8	No	HeH	63,XXY,-1,-2,-3,-8,-9,-13,+14,-15,-19,-20,+21,+21
16	M/0	4.3	No	11q13-qter	Other	46,XY,add(7)(q3?),inc
17	M/4	17	5, 9	No	HeH	57,XY,+X,+3,+4,+6,+8,+10,+14,+16,+18,+21/55-57,idem,i(7)(q10)
18[a]	F/5	6.3	X	No	HeH	53,XX,+4,+6,+10,+14,+18,+21,+21
19[a]	M/15	59	No	7p22.3-pter, 12q14.1-qter	Other	50,XY,+X,+14,+21,+21
20[a,b]	M/10	3.2	No	9p13.3-pter	Other	??,X?,+21 [based on FISH]
21[a]	F/2	9.7	5	9p11.2-pter	HeH	54,XX,+X,+6,+10,+14,+17,+18,+21,+21
22	F/4	NK	No	14q12-qter	t(1;19)	47,XX,+idic(1)(p1?3),t(1;19)(q23;p13)
23[b]	F/2	35	No	9p21.2-24.3	Other	48,XX,+X,+21c
24[a]	M/3	14	1, 7, 11	No	HeH	56,XY,+X,+4,+6,+8,+10,+14,+17,+18,+21,+21
25[a]	M/32	15	16	No	t(9;22)	59,XY,+X,+2,+4,+6,+8,t(9;22)(q34;q11),+10,+14,+18,+19,+20,+21,+21, +der(22)t(9;22)
26[b]	M/19	NK	No	9p11.2-pter	Other	46,XY,del(12)(p13p13) [based on FISH]
27[a,b]	M/27	NK	No	9p21.1-22.1	Other	No mitoses
28[a]	M/54	122	No	6p21.1-pter, 19p12-pter	t(9;22)	46,XY,der(3)t(3;9)(p21;p22),der(9)t(3;9)t(9;22)(q34;q11),der(22)t(9;22)
29[a]	M/47	1.2	3, 11	No	HeH	No mitoses [HeH detected by SNP array analysis]
30[a,b]	F/23	5.5	No	9p13.2-pter	Other	47,XX,add(14)(q32),+12
31[a]	M/42	19	No	6p22.2-pter	t(1;19)	??,X?,der(19)t(1;9)(q23;p13) [based on FISH]
32[a]	F/32	6.6	3-5, 7, 9, 13, 15, 17, 20	No	NT	84,XXXX,-2,-3,-4,-5,+6,-7,-8,-9,+10,+14,-15,-15,-16,-17,-17,+18,-19,+21

F, female; FISH; fluorescent in situ hybridization; HeH, high hyperdiploid (51-67 chromosomes); M, male; NK, not known; NT, near-tetraploid (80-104 chromosomes); Other, cases with uninformative cytogenetics (normal karyotype, karyotypic failure, or non-characteristic aberrations); SNP, single nucleotide polymorphism; sUPID, segmental uniparental isodisomy; UPID, uniparental isodisomy; WBC, white blood cell count; wUPID, whole chromosome uniparental isodisomy.

[a]The original karyotypes of these cases have been published previously (see references below).

[b]These cases harbored homozygous *CDKN2A* deletions flanked/covered by an sUPID.

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Supporting Information Table 2. Clinical and Cytogenetic Data on the Pediatric and Adult Cases with Constitutional sUPIDs

Case No.	Gender/ age	WBC ($x10^9$/l)	sUPID	Group	Karyotype
1	M/4	25	12q23.3-24.21, 14q31.1-31.3	t(9;22)	50,XY,+4,+5,t(8;14)(q11;q32),t(9;22)(q34;q11),+der(14)t(8;14),der(16)t(14;16)(q11;p13)t(8;14),+21
2	M/2	6.2	11p11.2-q12.1	HeH	62,XXY,+Y,-1,-2,-3,-4,der(5)t(1;5)(q12;q21),-7,-13,+14,-15,-16,-19,-20,+21
3	M/1	55	4q13.2-21.21, 8q22.3-23.3, 12q21.1-22	t(1;19)	46,XY,der(19)t(1;19)(q23;p13)
33	M/5	71	12q12-13.12	Other	47,XY,del(1)(q42),del(12)(p12p13),del(12)(q21q21),dup(17)(q21q25),+21c
34	M/3	2.1	14q21.1-21.3	HeH	52,XY,+X,dup(1)(q21q42),+6,+10,+11,+21,+21
35	M/1	71	3p11.2-q11.2	Other	46,XY,t(12;17)(p13;q11-12)/47,idem,+21
36	F/2	49	5q11.2-12.3	Other	47,XX,+X,i(17)(q10)
37	M/14	27	12q21.2-21.31	t(1;19)	46,XY,der(19)t(1;19)(q23;p13)
38	M/4	164	1q41-43, 5q34-35.2, 6p21.1-21.32, 6q15-21, 9p21.3-24.1, 10p14-pter, 11q23.3-24.3, 12p11.22-12.1 18q11.2-12.3, 20p12.1-12.3	t(12;21)	??,X?,t(12;21)(p13;q22) [based on FISH]

39	F/2	3.5	7q21.3-22.3	Other	45,XX,dic(7;12)(p11;p11)
25	M/32	15	3p21.1-21.31, 7p11.2-q11.21	t(9;22)	59,XY,+X,+2,+4,+6,+8,t(9;22)(q34;q11),+10,+14,+18,+19,+20,+21,+21, +der(22)t(9;22)
26	M/19	NK	11p11.2-q12.1 19p12-q12	Other	46,XY,del(12)(p13p13) [based on FISH]
40	F/67	NK	7q22.3-33, 10q26.13-26.2, 14q13.2-21.3, Xp22.2-22.33 19p12-pter	t(9;22)	46,XX,t(9;22)(q34;q11)
41	M/57	NK	1p22.3-31.1, 3q21.3-22.2, 6p22.3-25.2, 7q32.3-35, 12q12-13.13, 14q32.31-qter, 16q21	t(9;22)	45,XY,der(7;9)t(7;9)(p11-12;p13)t(9;22)(q34;q11),der(22)t(9;22)
42	M/49	NK	3p22.2-24-2	t(9;22)	45,XY,der(7;9)(q10;q10)t(9;22)(q34;q11),der(22)t(9;22)
43	F/50	NK	3p21.1-21.31, 5q14.3-15	t(9;22)	47,XX,t(7;13;7)(q32;q22;p22),t(9;22)(q34;q11),+der(22)t(9;22)/46,idem, der(17;18)(q10;q10)
44	F/54	NK	12q23.1-23.2	Other	48-49,XX,del(1)(q21),add(5)(q2?),+der(?)t(?;22)(?;q11),inc
45	F/56	NK	Xp11.21-q12	MLL	47,XX,+X,t(4;11)(q21;q23)
46	M/59	NK	12q24.21-24.32	t(9;22)	47,XY,?add(3)(q27),t(9;22)(q34;q11),?del(10)(q22),der(19)t(12;19)(q13;p11), +der(?)t(?;11)(?;q13)
47	M/47	NK	22q13.1-13.31	MLL	??,X?,t(4;11)(q21;q23) [based on FISH]

F, female; FISH; fluorescent in situ hybridization; HeH, high hyperdiploid (51-67 chromosomes); M, male; NK, not known; Other, cases with uninformative cytogenetics (normal karyotype, karyotypic failure, or non-characteristic aberrations); sUPID, segmental uniparental isodisomy; UPID, uniparental isodisomy; WBC, white blood cell count.

Supporting Information Table 3. Acquired UPIDs in 181 BCP ALL Cases in Relation to Age and Gender

	Children ***n*** **= 143**	**Adults** ***n*** **= 38**	***P***
No. of UPIDs/case	0.25	0.50	0.67[a]
No. of wUPIDs/case	0.11	0.34	0.87[a]
No. of sUPIDs/case	0.14	0.16	0.90[a]
No. of cases with UPID (%)	24 (17)	8 (21)	0.71[b]
No. of cases with wUPID (%)	9 (6.3)	3 (7.9)	0.72[b]
No. of cases with sUPID (%)	18 (13)	5 (13)	0.93[b]
No. of terminal sUPIDs/all sUPIDs (%)	14/20 (70)	4/6 (67)	1.00[c]
	Males ***n*** **= 105**	**Females** ***n*** **= 76**	***P***
No. of UPIDs/case	0.30	0.30	0.39[a]
No. of wUPIDs/case	0.14	0.18	0.79[a]
No. of sUPIDs/case	0.16	0.12	0.67[a]
No. of cases with UPID (%)	22 (21)	10 (13)	0.25[b]
No. of cases with wUPID (%)	8 (7.6)	4 (5.3)	0.74[b]
No. of cases with sUPID (%)	15 (14)	8 (11)	0.60[b]
No. of terminal sUPIDs/all sUPIDs (%)	14/17 (82)	4/9 (44)	0.08[c]

BCP ALL, B-cell precursor acute lymphoblastic leukemia; sUPID, segmental uniparental isodisomy; UPID, uniparental isodisomy; wUPID, whole chromosome uniparental isodisomy.

[a]Mann-Whitney test.

[b]Chi-square with Yates' correction.

[c]Fisher exact probability test.

Supporting Information Table 4. Genomic Positions and Sizes of Acquired UPIDs in 143 Pediatric and 38 Adult BCP ALL Cases[a]

Case No.	Chr	Type of UPID	FAS pos (bp)	LAS pos (bp)	Size (bp)[b]
Children					
1	9	S	pter	29978410	29978410
2	1	W	pter	qter	
2	3	W	pter	qter	
2	13	W	pter	qter	
2	19	W	pter	qter	
3	17	S	30625767	qter	50539270
4	14	S	31188832	qter	76120808
5	15	W	pter	qter	
6	9	S	20464928	32007381	11542453
7	9	W	pter	qter	
7	17	S	5550299	18291618	12741319
8	9	S	71033538	80355515	9321977
8	9	S	104010913	127661645	23650732
9	9	S	70984372	qter	70176573
10	3	W	pter	qter	
10	10	S	86058516	112294424	26235908
10	19	W	pter	qter	
11	16	S	pter	28218704	28218704
12	12	S	pter	11708953	11708953
13	18	S	57207198	qter	20841030
14	9	S	pter	36744730	36744730
15	8	W	pter	qter	
16	11	S	62265585	qter	72690752
17	5	W	pter	qter	
17	9	W	pter	qter	
18	X	W	pter	qter	
19	7	S	pter	2130014	2130014
19	12	S	62691991	qter	71110154
20	9	S	pter	34087360	34087360

21	5	W	pter	qter	
21	9	S	pter	38771460	38771460
22	14	S	25510923	qter	81798717
23	9	S	pter	29470565	29470565
24	1	W	pter	qter	
24	7	W	pter	qter	
24	11	W	pter	qter	
Adults					
25	16	W	pter	qter	
26	9	S	pter	39217322	39217322
27	9	S	19635062	32632532	12997470
28	6	S	pter	43019435	43019435
28	19	S	pter	21233406	21233406
29	3	W	pter	qter	
29	11	W	pter	qter	
30	9	S	pter	36805874	36805874
31	6	S	pter	26172219	26172219
32	3	W	pter	qter	
32	4	W	pter	qter	
32	5	W	pter	qter	
32	7	W	pter	qter	
32	9	W	pter	qter	
32	13	W	pter	qter	
32	15	W	pter	qter	
32	16	W	pter	qter	
32	17	W	pter	qter	
32	20	W	pter	qter	

BCP ALL, B-cell precursor acute lymphoblastic leukemia; bp, base pair; Chr, chromosome; FAS pos, first abnormal single nucleotide polymorphism position; LAS pos, last abnormal single nucleotide polymorphism position; pter, terminal of p-arm; qter, terminal of q-arm; S, segmental; UPID, uniparental isodisomy; W, whole chromosome.

[a]Data on wUPIDs and sUPIDs were also included, together with all copy number alterations, in supporting information tables in Olsson et al. (2014) and Safavi et al. (2015).

[b]Size is only given for sUPIDs and are approximate for sUPIDs with centromeric and/or terminal breakpoints.

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Supporting Information Table 5. Genomic Positions and Sizes for Constitutional UPIDs Detected in 155 Children and 43 Adults

Case No.	Chr. arm	FAS pos (bp)	LAS pos (bp)	Size (bp)[a]
Children				
1	12q	106755078	114962159	8207081
1	14q	83348722	89696915	6348193
2	11p	45586902	56046681	10459779
3	4q	66740703	80977078	14236375
3	8q	101671045	112410638	10739593
3	12q	74688745	94141536	19452791
33	12q	44568848	50223077	5654229
34	14q	39517925	48387621	8869696
35	3p	88176189	97759540	9583351
36	5q	56159171	65269795	9110624
37	12q	78356898	83396224	5039326
38	1q	220914920	237430682	16515762
38	5q	167543549	174130944	6587395
38	6p	33244716	43737831	10493115
38	6q	88051052	106795332	18744280
38	9p	4651478	23666653	19015175
38	10p	pter	10780896	10780896
38	11q	116130782	128078650	11947868
38	12p	21816382	29559676	7743294
38	18q	23407436	43085253	19677817
38	20p	7233257	15746342	8513085
39	7q	96737576	105581449	8843873
Adults				
25	3p	47660796	53599972	5939176
25	7p	56742179	66785634	10043455
26	11p	45837152	57468022	11630870
26	19p	22764877	29724184	6959307
40	7q	106033380	136553754	30520374
40	10q	123886277	130289885	6403608

40	14q	36454290	49256593	12802303
40	Xp	2625097	16564795	13939698
41	1p	71210705	84958504	13747799
41	3q	129102247	135112479	6010232
41	6p	3450266	18020604	14570338
41	7q	131679624	147195953	15516329
41	12q	43131848	52567434	9435586
41	14q	101976243	qter	5333397
41	16q	59919300	66116429	6197129
42	3p	26008272	38367942	12359670
43	3p	46824554	52436267	5611713
43	5q	88149648	93792823	5643175
44	12q	97368383	103184056	5815673
45	Xp	55566924	65141765	9574841
46	12q	115693895	125955294	10261399
47	22q	38678564	45871468	7192904

bp, base pair; Chr, chromosome; FAS pos, first abnormal single nucleotide polymorphism position; LAS pos, last abnormal single nucleotide polymorphism position; pter, terminal of p-arm; qter, terminal of q-arm; UPID, uniparental isodisomy.

[a]Sizes for sUPIDs with terminal breakpoints are approximate.

Supporting Information Table 6. Constitutional sUPIDs in Relation to Age and Gender

	Children ***n*** **= 155**	**Adults** ***n*** **= 43**	***P***
No. of sUPIDs/case	0.14	0.51	0.09[a]
No. of cases with sUPID (%)	10 (6.5)	10 (23)	**0.003**[b]
No. of terminal sUPIDs/all sUPIDs (%)	1/22 (4.5)	1/22 (4.5)	1.00[c]
	Males ***n*** **= 112**	**Females** ***n*** **= 86**	***P***
No. of sUPIDs/case	0.30	0.12	0.50[a]
No. of cases with sUPID (%)	14 (13)	6 (7.0)	0.30[b]
No. of terminal sUPIDs/all sUPIDs (%)	2/34 (5.9)	0/10 (0.0)	1.00[c]

sUPID, segmental uniparental isodisomy.

[a]Mann-Whitney test.

[b]Chi-square with Yates' correction. Significant *P* value is indicated in bold.

[c]Fisher exact probability test.