**Supplemental Figure 1.** Schematic representation of five haplotypes (*1 to *5) of four coding variants in *NUDT15*.

**Supplemental Figure 2.** Association of types of fusion with the log IC50 (day 7) values of 6MP in the 83 BCP-ALL cell lines. Gray circles indicate *BCR/ABL1*-like cell lines. P-values in Mann-Whitney analysis are indicated, when significant (p<0.05).

**Supplemental Figure 3.** Comparison of the log IC50 (day 7) values of 6MP between 29 BCP-ALL cell lines established at diagnosis and 46 BCP-ALL cell lines established at relapse. P-value in Mann-Whitney analysis is indicated, when significant (p<0.05).
Supplemental Figure 3. 

![Supplemental Figure 3](image-url)

**Supplemental Figure 4.** Sequence of genomic PCR products of exon 1 in representative cell lines.

**Supplemental Figure 4**

![Supplemental Figure 4](image-url)

**Supplemental Figure 5.** Sequence of genomic PCR products of exon 3 in representative cell lines.

**Supplemental Figure 5**

![Supplemental Figure 5](image-url)

**Supplemental Figure 6.** Sequence of NT5C2 mutations in four cell lines.
Supplemental Figure 6

|            | Forward     | Reverse    |
|------------|-------------|------------|
| YAMN73 V212G exon 8 | AGAC TGGAA | TGG ACTGT |
| P30/OHK G231fs exon 9 | GAGA TCTGC | GTTT TCCAT |
| 697 R238W exon 9 | GAGC TGGAT | ATGC AGTCC |
| KOPN32 R367Q exon 13 | TGGC TACCT | AGTT TGGCA |

Supplemental Figure 7. Sequence of PRPS1 mutation in KOPN72bi.

Supplemental Figure 7

|            | Wild type   | Anti-sense |
|------------|-------------|------------|
| V208A      | TCTCCCAAGCAACCAT | ctttgtggga |
| KOPN72bi   | TCTCCCGCAGCACCAT | Leu Val gly |

Supplemental Figure 8. Association of NUDT15 genotype with the log IC50 (day 3) values of 6MP (left) and 6TG (right) in the 84 BCP-ALL cell lines. P-value in Mann-Whitney analysis is indicated.

Supplemental Figure 8

|            | (µM) | (µg/ml) |
|------------|------|---------|
| NUDT15 WT  | WT   | Homo    |
|            | 0.05 | 0.25    |
|            | 0.50 | 0.40    |
|            | 1.00 | 2.00    |

Supplemental Figure 9. Association of NT5C2 (open circles) and PRPS1 (open rectangle) mutations with the log IC50 (day 3) values of 6MP (left) and 6TG (right) in the 83 BCP-ALL cell lines.
lines. P-value in Mann-Whitney analysis is indicated.

Supplemental Figure 9

Supplemental Figure 10. Association of NUDT15 genotype (left) and NT5C2 and PRPS1 mutations (right) with log IC50 (day 7) values of 6MP in the 46 BCP-ALL cell lines established at relapse. P-value in Mann-Whitney analysis is indicated.

Supplemental Figure 11. Comparison of the log IC50 (day 7) values of 6MP between 35 ALL cell lines established at diagnosis and 63 ALL cell lines established at relapse. P-value in Mann-Whitney analysis is indicated, when significant (p<0.05).
Supplemental Figure 1. Association of NUDT15 genotype (left) and NT5C2 and PRPS1 mutations (right) with log IC50 (day 7) values of 6MP in the 63 ALL cell lines established at relapse. P-value in Mann-Whitney analysis is indicated.

Supplemental Figure 12. Association of NUDT15 genotype (left) and NT5C2 and PRPS1 mutations (right) with log IC50 (day 7) values of 6MP in the 63 ALL cell lines established at relapse. P-value in Mann-Whitney analysis is indicated.

Supplemental Figure 13. Association between % mutated sequence and IC50 (day 7) values of 6MP in the 7 ALL cell lines with NT5C2 and PRPS1 mutations.
| Cell line | Japanese | ChubNod age | EBV Envelopment | Fusion | NUDT76 genotype | MT6210 mutation | MAPK mutation |
|-----------|-----------|-------------|----------------|--------|----------------|----------------|--------------|
| YAKYO     | Yes       | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| KOPN7b1   | Yes       | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| SKA       | No        | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| KOPN4bi   | Yes       | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| KOPN5bi   | Yes       | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| KOPN6bi   | Yes       | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| KOPN7b1   | Yes       | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| SU-PF2    | No        | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| KOPN5bi   | Yes       | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| KOPN6bi   | Yes       | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| KOPN7b1   | Yes       | Yes         | Diagnosis      | BCP-ABL2 | V219G         | No             | No           |
| KCB1      | Yes       | Yes         | Diagnosis      | BCP-ABL2 | V219G         | No             | No           |
| YAKM91    | Yes       | Yes         | Diagnosis      | BCP-ABL2 | V219G         | No             | No           |
| RAK012     | Yes       | No          | Diagnosis      | BCP-ABL2 | V219G         | No             | No           |
| TCDY      | Yes       | No          | NA             | BCP-ABL2 | V219G         | No             | No           |
| KOPM40    | Yes       | Yes         | Relapse        | BCP-ABL2 | V219G         | No             | No           |
| YUJ86     | Yes       | Yes         | Diagnosis      | BCP-ABL2 | V219G         | No             | No           |
| KCL17     | Yes       | Yes         | Relapse        | ML2-fusion | V219G | No             | No           |
| KOPN35    | Yes       | Yes         | Relapse        | ML2-fusion | V219G | No             | No           |
| KCL16     | Yes       | Yes         | Relapse        | ML2-fusion | V219G | No             | No           |
| KCL15     | Yes       | Yes         | Relapse        | ML2-fusion | V219G | No             | No           |
| TRM       | Yes       | Yes         | Diagnosis      | ML2-fusion | V219G | No             | No           |
| KCL13     | Yes       | Yes         | Diagnosis      | ML2-fusion | V219G | No             | No           |
| YAC15     | No        | No          | Relapse        | ML2-fusion | V219G | No             | No           |
| KCL12     | Yes       | Yes         | Diagnosis      | ML2-fusion | V219G | No             | No           |
| KOPM20    | Yes       | Yes         | Diagnosis      | TCF1-PBX1 | V219G | No             | No           |
| YAKM20R     | Yes       | Yes         | Relapse        | TCF1-PBX1 | V219G | No             | No           |
| RCI-4      | No        | No          | Relapse        | TCF1-PBX1 | V219G | No             | No           |
| KOPM12     | Yes       | Yes         | Relapse        | TCF1-PBX1 | V219G | No             | No           |
| KOPM13     | Yes       | Yes         | Relapse        | TCF1-PBX1 | V219G | No             | No           |
| KOPM14     | Yes       | Yes         | Relapse        | TCF1-PBX1 | V219G | No             | No           |
| YUC93-B     | Yes       | Yes         | Diagnosis      | TCF1-PBX1 | V219G | No             | No           |
| TCF1-AP    | No        | Yes          | Diagnosis      | TCF1-PBX1 | V219G | No             | No           |
| Kasum2     | Yes       | Yes         | Relapse        | TCF1-PBX1 | V219G | No             | No           |
| SOEC-L2    | Yes       | Yes         | NA             | TCF1-PBX1 | V219G | No             | No           |
| YUC18     | Yes       | Yes         | Relapse        | TCF1-PBX1 | V219G | No             | No           |
| Endokan    | Yes       | Yes         | NA             | TCF1-RF | V219G | No             | No           |
| UC057      | No        | No          | Relapse        | TCF1-RF | V219G | No             | No           |
| HAL01      | Yes       | No          | NA             | TCF1-RF | V219G | No             | No           |
| KOPM18     | Yes       | Yes         | Relapse        | TCF1-RF | V219G | No             | No           |
| KOPM16     | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM15     | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM14     | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM13     | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM12     | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM11     | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM10     | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM9      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM8      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM7      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM6      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM5      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM4      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM3      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM2      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM1      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
| KOPM0      | Yes       | Yes         | Diagnosis      | TCF1-RF | V219G | No             | No           |
### Supplemental Table 2. List of T-ALL cell line

| Cell line | Japanese | Childhood age<16 | Establishment | Fusion | NUDT15 genotype | TPM7 m1142345 | NT5C2 mutation | PRPS1 mutation |
|-----------|----------|------------------|--------------|--------|-----------------|----------------|----------------|----------------|
| DND-41    | NA       | Yes              | Diagnosis    | BCL11B-TLX3 | 1*/1*           | WT             | No             | No             |
| HPB-ALL   | Yes      | Yes              | Diagnosis    | BCL11B-TLX3 | 1*/1*           | WT             | No             | No             |
| KOP7-N1   | Yes      | Yes              | Relapse      | LM02-TGNG    | 1*/1*           | WT             | No             | No             |
| SUP-T13   | No       | Yes              | Relapse      | ML1-ENL      | 1*/1*           | WT             | No             | No             |
| SKW-3     | NA       | No               | Diagnosis    | MTC-TGNA     | 1*/1*           | WT             | No             | No             |
| Kasumi5   | Yes      | No               | Relapse      | NUP98-RAP1CGG | 1*/1*          | WT             | No             | No             |
| LOUCY     | No       | No               | Relapse      | SET-NUP214   | 1*/1*           | WT             | No             | No             |
| COCR-CEM  | No       | Yes              | Relapse      | STIL-TAL1    | 1*/1*           | WT             | No             | No             |
| HSZ2      | No       | Yes              | Relapse      | STIL-TAL1    | 1*/1*           | WT             | No             | No             |
| L-KAW     | Yes      | Yes              | Relapse      | STIL-TAL1    | 1*/1*           | WT             | No             | No             |
| MOLT-16   | NA       | Yes              | Relapse      | STIL-TAL1    | 1*/1*           | WT             | No             | No             |
| PFS82     | No       | Yes              | Relapse      | STIL-TAL1    | 1*/1*           | WT             | No             | No             |
| RPMI-8402 | No       | No               | Diagnosis    | STIL-TAL1    | 1*/1*           | WT             | No             | No             |
| ALL-SIL   | No       | No               | Relapse      | TLX1-TORO    | 1*/1*           | WT             | No             | No             |
| BE-13     | No       | Yes              | Relapse      | Others       | 1*/1*           | WT             | R29Q           | No             |
| JURKAT    | No       | Yes              | Relapse      | Others       | 1*/1*           | WT             | No             | No             |
| KOPT-6    | Yes      | Yes              | Relapse      | Others       | 1*/1*           | WT             | No             | No             |
| L-MAT     | Yes      | Yes              | Diagnosis    | Others       | 1*/1*           | A/G            | No             | No             |
| MOLT-13   | NA       | Yes              | Relapse      | Others       | 1*/1*           | WT             | No             | No             |
| MOLT-4    | NA       | No               | Relapse      | Others       | 1*/1*           | WT             | No             | No             |
| P12/RCK   | Yes      | Yes              | Diagnosis    | Others       | 1*/1*           | WT             | No             | No             |
| PCEH      | No       | Yes              | Relapse      | Others       | 1*/1*           | WT             | No             | No             |
| TALL-1    | Yes      | No               | Relapse      | Others       | 1*/1*           | WT             | No             | No             |

### Supplemental Table 3. List of NT5C2 and PRPS1 mutations

| Cell line | Lineage | Gene | Mutation | Amino acid change | Frequency (%) |
|-----------|---------|------|----------|-------------------|---------------|
| BE-13     | T       | NT5C2| c.86G>A  | p.R29Q           | 60.2          |
| YAMN73    | BCP     | NT5C2| c.656T>C  | p.V212G         | 49.8          |
| P32/OHK   | BCP     | NT5C2| c.693del | p.K231Nfs       | 44.9          |
| 697       | BCP     | NT5C2| c.712C>T  | p.R238W         | 38.8          |
| KOPN32    | BCP     | NT5C2| c.1100G>A | p.R367Q        | 46.6          |
| KOPN72bi  | BCP     | PRPS1| c.623T>C  | p.V208A        | 100           |
| RS4:11    | BCP     | PRPS1| c.866T>C  | p.V289A        | 28.1          |