Association of TLX1 gene polymorphisms with the risk of acute lymphoblastic leukemia and B lineage acute lymphoblastic leukemia in Han Chinese children

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Abstract
Background: Studies on gene polymorphism association are centered on childhood acute lymphoblastic leukemia (ALL), a common hematological malignancy in children younger than 16 years. Single-nucleotide polymorphisms (SNPs) in some genes, such as ARID5B and CDKN2B, are associated with the risk of childhood ALL. T-cell leukemia homeobox 1 (TLX1), a member of the HOX gene family, was identified based on its abnormal expression in T-lineage leukemia. This study aimed to determine whether TLX1 is associated with B-ALL and which SNP plays a significant role in ALL.

Methods: A total of 217 cases of ALL and 241 controls were included in this study. Six tag SNPs (rs75329544, rs946328, rs12415670, rs2075879, rs17113735, and rs1051723) were selected, and genotyping was carried out on Sequenom MassARRAY platform.

Results: Rs17113735 was possibly the risk locus associated with increased risk for ALL, whereas rs946328 was possibly associated with decreased risk for ALL. Moreover, rs17113735 was likely to be the risk locus for B-cell ALL (B-ALL), and rs2075879 was associated with decreased risk for B-ALL (P < .05). All SNPs in the two sample types (ALL and B-ALL samples) demonstrated linkage disequilibrium except between rs75329544 and rs2075879. Haplotype analysis showed no significant difference between the cases and controls in the two sample types.

Conclusion: TLX1 gene polymorphisms are associated with ALL (rs17113735 and rs946328) and possibly play a significant role in B-ALL (rs17113735 and rs2075879). This work provides a reference for the diagnosis and therapy of this disease.

Keywords
acute lymphoblastic leukemia, B-cell acute lymphoblastic leukemia, single-nucleotide polymorphism, T-cell leukemia homeobox 1
1 INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a common hematological malignancy that results from the disorder of lymphoid progenitor cells. The fastigium of ALL occurs between the ages of 2 and 5 years, although it also occurs in children and adults. The two cancer types of ALL are T-cell ALL (T-ALL) and B-cell ALL (B-ALL); the former is less common than the latter but is more aggressive. Specific gene mutations are possibly associated with abnormalities in the signaling pathway, whose abnormal activation could propel oncogenic alterations in ALL. Chromosomal rearrangement induces the formation of fusion genes, such as BCR-ABL and ETV6-RUNX1, which are oncogenes that cause ALL.

T-cell leukemia homeobox 1 (TLX1)/HOX11, a member of the HOX gene family, is identified through its abnormal expression in T-lineage leukemia; it is a DNA-binding homeodomain protein, but its function remains poorly understood. TLX1 could be aberrantly activated through the translocation of either t(7;10) or t(10;14), and it usually synergizes with NOTCH1 activation during malignant T-cell transformation. The aberrant expression of TLX1 in T-cell progenitors not only influences the development of normal T-cells but also contributes to the development of aneuploidy during T-cell transformation, and the disruption of the mitotic checkpoint in TLX1-induced tumors may be linked to the acquisition of secondary genetic alterations in T-ALL. In the mouse model from Keersmaecker's study, a typical aneuploid and apparent imperfection in the activation of the mitotic checkpoint were observed in TLX1 tumors. Moreover, it was demonstrated that STAT5, a downstream effector of BUP214-ABL1, can co-bind the poised enhancer region with TLX1, thereby activating the expression of crux proto-oncogenes, such as MYC and BCL2, and driving the development of T-ALL.

Analysis of single-nucleotide polymorphism (SNP) predicts the risk of ALL. The SNPs of ARID5B were confirmed to be significant determinants of the susceptibility and treatment outcomes of childhood ALL, and contributed to racial disparities in this cancer. Also, confirmed the association of 5 SNPs (rs7073837, rs10994982, rs10740055, rs10821936, and rs7089424) in the ARID5B gene with childhood acute lymphoblastic leukemia. Identified as novel locus, PIP4K2A SNPs (rs7088318 and rs10828317) are significantly associated with ALL susceptibility. On the basis of functional analysis, Hungate et al. discovered that rs662463 could adjust CDKN2B expression through CEBPB signaling to affect the risk of BCP-ALL.

This study aimed to determine whether TLX1 is associated with B-ALL and which SNP plays a significant role in ALL. The SNPs of TLX1 in ALL and B-ALL were examined to explore TLX1 susceptibility in this disease and provide a reference for diagnosis and therapy.

2 MATERIALS AND METHODS

2.1 Case and control groups

The case group consisted of patients diagnosed with ALL at the Children’s Hospital of Zhejiang University School of Medicine from 2014 to 2016. Every diagnosis of ALL was based on MICM. All patients diagnosed with ALL exhibited a change in blood and bone marrow, which met the French-American-British (FAB) classification. A total of 241 healthy children from the same hospital were studied under the control group. All children involved were of Chinese Han ethnicity. Data of these children were collected from the above-mentioned children’s hospital and are shown in Table 1. The sample size for this study was set to 217 because the immunophenotype of the two cases is unknown. This study was approved by the Ethical Committee of the School of Life Sciences and Medicine, Zhejiang Sci-Tech University. The ethical number of this study is 1601-05. All the families of patients and controls provided an informed consent to genetic analysis for investigational studies.

2.2 SNP prediction and genomic DNA extraction

TLX1 SNPs were predicted using Haploview. Six tag SNPs (rs75329544, rs946328, rs12415670, rs2075879, rs17113735, and rs1051723) were selected, and their MAF was higher than 0.05. DNA was extracted from EDTA-anticoagulated blood samples by using a DNA extraction kit (Sangon Biotech Co. Ltd.) following the manufacturer’s instructions and then stored at -80°C.

2.3 SNP genotyping

The primers for the six SNPs are shown in Table 2. SNP genotyping was carried out on Sequenom MassARRAY platform (Sequenom) by applying a 384-well plate format. Genotype calling was conducted in real time on MassARRAY RT software version 3.0.0.4. The results were analyzed via MassARRAY Typer software version 3.4 (Sequenom).

2.4 Statistical analysis

Data were statistically analyzed using chi-square (χ²) test to ascertain differences in alleles, genotype, the haplotype frequencies, and the Hardy-Weinberg equilibrium between the case and control groups. The odds ratio (OR) and 95% confidence interval (CI) were calculated for comparison. Logistic regression analysis was conducted to test the association between the risk of ALL and TLX1 polymorphisms. All statistical analyses were performed using SPSS software version 22.0 (SPSS Inc.). Haploview 4.2 software was utilized to calculate the haplotype block and linkage disequilibrium (LD).

3 RESULTS

3.1 ALL Association

Six TLX1 SNPs (rs75329544, rs946328, rs12415670, rs2075879, rs17113735, and rs1051723) in the ALL and control groups were
**TABLE 1** Demographics and clinical characteristics of patients with ALL and controls

| Characteristics          | Cases  (n = 219) | Controls  (n = 241) | P     |
|--------------------------|------------------|---------------------|-------|
| Age (years), mean ± SD   | 6.39 ± 3.93      | 3.61 ± 3.50         | .051  |
| Range                    | 0-16             | 0-14                | .319  |
| Gender (male/female)     | 142/77           | 145/96              | .051  |
| Immunophenotype          |                  |                     |       |
| B-ALL                    | 173              |                     |       |
| T-ALL                    | 17               |                     |       |
| Pre-B-ALL                | 17               |                     |       |
| Pro-B-ALL                | 7                |                     |       |
| Early Pre-T-ALL          | 2                |                     |       |
| Pre-T-ALL                | 1                |                     |       |
| No Date                  | 2                |                     |       |
| Risk                     |                  |                     |       |
| Low                      | 55               |                     |       |
| Middle                   | 80               |                     |       |
| High                     | 83               |                     |       |
| No Date                  | 1                |                     |       |
| Classification           |                  |                     |       |
| L1                       | 13               |                     |       |
| L2                       | 182              |                     |       |
| L3                       | 15               |                     |       |
| No Date                  | 9                |                     |       |
| MRD                      |                  |                     |       |
| Low                      | 59               |                     |       |
| Middle                   | 81               |                     |       |
| High                     | 71               |                     |       |
| No Date                  | 8                |                     |       |
| Chromosomal type         |                  |                     |       |
| Normal                   | 155              |                     |       |
| Hypodiploid              | 9                |                     |       |
| Hyperdiploid             | 17               |                     |       |
| High hyperdiploid        | 37               |                     |       |
| No Date                  | 1                |                     |       |
| Relapse                  | 13               |                     |       |

Abbreviations: ALL, acute lymphoblastic leukemia; MRD, minimal residual disease; SD, standard deviation.

analyzed (Table 3). All SNPs were in HWE in the two groups (P > .05). The genotype A/A of rs17113735 in the case group was significantly higher than that in the control (OR 3.04, 95% CI 1.47-6.28, P = .006 < .01). Moreover, rs17113735 accorded with the recessive model (OR 2.95, 95% CI 1.32-6.65, P = .006 < .01) and log-additive model (OR 1.37, 95% CI 1.02-1.84, P = .038 < .05). The frequency of the mutation type (A allele) was distinctly higher in the ALL group (OR 1.37, 95% CI 1.02-1.84, P = .039 < .05) than in the control. The inherited models and allele analysis showed that the rs17113735 polymorphism possibly increased the risk for ALL. The rs946328 genotype C/T in the ALL group was significantly lower than that in the control group (OR 0.64, 95% CI 0.42-0.98, P = .039 < .05), and this locus was consistent with the overdominant model (OR 0.64, 95% CI 0.42-0.98, P = .037 < .05). These findings indicated that rs946328 might be associated with decreased risk for ALL. In this analysis, the rs17113735 and rs946328, which belong to TLX1, were significantly associated with ALL.

The B-ALL cases and controls were analyzed to determine the association of TLX1 SNPs with B-ALL (Table 4). Rs17113735 still conformed to the recessive model (OR 2.91, 95% CI 1.29-6.55, P = .007 < .01), and its genotype (allele A/A) was higher in the B-ALL group than in the control group (OR 2.94, 95% CI 1.29-6.72, P = .008 < .01) but not with the log-additive model. This finding showed that TLX1 possibly affected the morbidity of B-ALL, and rs17113735 could increase the risk of B-ALL. Moreover, rs2075879 decreased the risk for B-ALL because its genotype (Allele A/G) was higher in the healthy people group (OR 0.66, 95% CI 0.44-0.99, P = .044 < .05) than in the B-ALL group.

### 3.2 | LD and Haplotype

All SNPs in the two sample types (ALL and B-ALL samples) demonstrated LD except between rs75329544 and rs2075879 in the block (Figure 1). The haplotype analysis indicated that both blocks for the two sample types (ALL and B-ALL samples) containing rs75329544, rs946328, rs12415670, rs2075879, s17113735, and rs1051723 showed no significant difference between the two groups (Table 5).

### 4 | DISCUSSION

TLX1 is a homeobox transcription factor oncogene of T-ALL in humans. TLX1 expression can be detected in mice during the embryonic phase and is significantly associated with the fate of splenic cells under normal conditions. However, the specific mechanisms remain unclear, especially in T-ALL. Bergeron showed that T-ALLs with high expression of TLX1 harbor molecular TLX1 locus abnormalities, whereas T-ALLs that express TLX1 at low levels do not share these characteristics. In the cell cycle, the variation in TLX1 might contribute to the abnormal proliferation of lymphocytes and promote the development of ALL. TLX1 can alter the cell cycle, including that of G1/S and G2/M, by interacting with PP2A. Integrative genomics was used by Durinck et al to study the role of TLX1 in T-ALL; the results showed that ectopic TLX1 expression inhibits T cell–specific enhancers and mediates an unexpected transcriptional antagonism with NOTCH1 at critical target genes, including IL7R and NOTCH3. Riz et al found that TLX1 and NOTCH cooperate to regulate the transcription in T-ALL, and the TLX1/NOTCH/MYC transcriptional network coregulates genes involved in T-cell development. Heidari et al utilized whole-genome PCR and found that the TLX1 protein interacts with pericentromeric human satellite 2 DNA sequences, which could be related to its roles...
### TABLE 2  Primers of the six tag SNPs

| SNP          | Forward Primer                  | Reverse Primer                  |
|--------------|---------------------------------|---------------------------------|
| rs2075879    | 5′-ACGTTGGATTTGGAATGCCAGTGGTCTC-3′ | 5′-ACGTTGGATGACACGGACTCAGGCATC-3′ |
| rs12415670   | 5′-ACGTTGGATGTGCTGCTAGGCTAAGC-3′ | 5′-ACGTTGGATAGGGCAGCAAGCAGCGTCA-3′ |
| rs17113735   | 5′-ACGTTGGATAGTAAAGGAGCCACAGGG-3′ | 5′-ACGTTGGATGGGCTGTCATCTGAGCCTC-3′ |
| rs1051723    | 5′-ACGTTGGATGCTCTGTTGAGTTGCT-3′ | 5′-ACGTTGGATGGGCTGTCATCTGAGCCTC-3′ |
| rs946328     | 5′-ACGTTGGATGAGTTGCTGCTAGAGCT-3′ | 5′-ACGTTGGATGGGCTGTCATCTGAGCCTC-3′ |
| rs75329544   | 5′-ACGTTGGATGAGTTGCTGCTAGAGCT-3′ | 5′-ACGTTGGATGGGCTGTCATCTGAGCCTC-3′ |

### TABLE 3  Associations between TLX1 SNPs and ALL

| TLX1        | Control n = 241(n[%]) | ALL n = 217(n[%]) | OR (95% CI) | P     |
|-------------|-----------------------|-------------------|-------------|-------|
| rs75329544  |                       |                   |             |       |
| genotype    |                       |                   |             |       |
| T/T         | 210 (87.1%)           | 184 (84.8%)       | 1.00        | .546  |
| A/T         | 31 (12.9%)            | 32 (14.8%)        | 1.18 (0.69-2.01) | .286  |
| A/A         | 0 (0%)                | 1 (0.5%)          | NA (0.00–NA) | .286  |
| Dominant model |                  |                   |             |       |
| T/T         | 210 (87.1%)           | 184 (84.8%)       | 1.00        | .546  |
| A/T-A/A     | 31 (12.9%)            | 33 (15.2%)        | 1.21 (0.72-2.06) | .286  |
| Recessive model |                |                   |             |       |
| T/T-A/T     | 241 (100%)           | 216 (99.5%)       | 1.00        | .546  |
| A/A         | 0 (0%)                | 1 (0.5%)          | NA (0.00–NA) | .546  |
| Overdominant model |              |                   |             |       |
| T/T-A/A     | 210 (87.1%)           | 185 (85.2%)       | 1.00        | .546  |
| A/T         | 31 (12.9%)            | 32 (14.8%)        | 1.17 (0.69-1.99) | .546  |
| Log-additive model |        |                   |             |       |
| –           | –                     | –                 | 1.25 (0.74-2.09) | .546  |
| Allele      |                       |                   |             |       |
| T           | 451 (93.6%)           | 400 (92.2%)       | 1.00        | .546  |
| A           | 31 (6.4%)             | 34 (7.8%)         | 1.24 (0.75-2.05) | .546  |
| rs946328    |                       |                   |             |       |
| genotype    |                       |                   |             |       |
| C/C         | 161 (66.8%)           | 163 (75.1%)       | 1.00        | .546  |
| C/T         | 74 (30.7%)            | 48 (22.1%)        | 0.64 (0.42-0.98) | .546  |
| T/T         | 6 (2.5%)              | 6 (2.8%)          | 0.99 (0.31-3.13) | .546  |
| Dominant model |                |                   |             |       |
| C/C         | 161 (66.8%)           | 163 (75.1%)       | 1.00        | .546  |
| C/T-T/T     | 80 (33.2%)            | 54 (24.9%)        | 0.67 (0.44-1.00) | .546  |
| Recessive model |                |                   |             |       |
| C/C-C/T     | 235 (97.5%)           | 211 (97.2%)       | 1.00        | .546  |
| T/T         | 6 (2.5%)              | 6 (2.8%)          | 1.11 (0.35-3.51) | .546  |
| Overdominant model |        |                   |             |       |
| C/C-T/T     | 167 (69.3%)           | 169 (77.9%)       | 1.00        | .546  |
| C/T         | 74 (30.7%)            | 48 (22.1%)        | 0.64 (0.42-0.98) | .546  |

(Continues)
| rs12415670 | Allele  | Control n = 241(n[%]) | ALL n = 217(n[%]) | OR (95% CI) | P      |
|------------|---------|------------------------|-------------------|-------------|--------|
| Log-additive model | —       | —                      | —                 | 0.74 (0.52-1.06) | .097   |
| Allele     | T       | 86 (17.8%)             | 60 (13.8%)        | 1.00        |        |
|            | C       | 396 (82.2%)            | 374 (86.2%)       | 1.35 (0.95-1.94) | .254   |
| rs2075879  | Allele  | Control n = 241(n[%])  | ALL n = 217(n[%]) | OR (95% CI) | P      |
|------------|---------|------------------------|-------------------|-------------|--------|
| Log-additive model | —       | —                      | —                 | 1.13 (0.86-1.48) | .39   |
| Allele     | G       | 345 (71.6%)            | 299 (68.9%)       | 1.00        |        |
|            | A       | 137 (28.4%)            | 135 (31.1%)       | 1.14 (0.86-1.51) | .655   |

(Continues)
in transcriptional repression and T-cell immortalization. However, the relationship between TLX1 and B-ALL needs further researches because the studies on the association between TLX1 and B-ALL are limited and the pathogenic mechanism is unknown.

Single-nucleotide polymorphisms research on ALL has been conducted for many years, and some ALL-associated gene or SNPs have been extensively investigated. Papaemmanuil et al identified the risk locus for ALL at 7p12.2 (IKZF1, rs4132601, OR = 1.69, P < 0.001).

**TABLE 3** (Continued)

| TLX1 | Control n = 241[n(%)] | ALL n = 217[n(%)] | OR (95% CI) | P |
|------|-----------------------|-------------------|-------------|---|
|     |                       |                   |             |   |
| **rs17113735** |                       |                   |             |   |
| **genotype** |                       |                   |             |   |
| G/G  | 139 (57.7%)           | 113 (52.1%)       | 1.00        |   |
| A/G  | 93 (38.6%)            | 82 (37.8%)        | 1.08 (0.74-1.60) | .681 |
| A/A  | 9 (3.7%)              | 22 (10.1%)        | 3.01 (1.33-6.79) | .006 |
| **Dominant model** |                       |                   |             |   |
| G/G  | 139 (57.7%)           | 113 (52.1%)       | 1.00        |   |
| A/G-A/A | 102 (42.3%)        | 104 (47.9%)       | 1.25 (0.87-1.81) | .23  |
| **Recessive model** |                       |                   |             |   |
| G/G-A/G | 232 (96.3%)       | 195 (89.9%)       | 1.00        |   |
| A/A  | 9 (3.7%)              | 22 (10.1%)        | 2.91 (1.31-6.46) | .006 |
| **Overdominant model** |                       |                   |             |   |
| G/G-A/A | 148 (61.4%)       | 135 (62.2%)       | 1.00        |   |
| A/A  | 9 (3.7%)              | 22 (10.1%)        | 3.01 (1.33-6.79) | .006 |
| **Log-additive model** |                       |                   |             |   |
| G    | 371 (77.0%)           | 308 (71.0%)       | 1.37 (1.02-1.84) | .038 |
| A    | 111 (23.0%)           | 126 (29.0%)       | 1.37 (1.02-1.84) | .039 |
| **rs1051723** |                       |                   |             |   |
| **genotype** |                       |                   |             |   |
| C/C  | 169 (70.1%)           | 167 (77%)         | 1.00        |   |
| C/T  | 68 (28.2%)            | 47 (21.7%)        | 0.70 (0.46-1.07) | .102 |
| T/T  | 4 (1.7%)              | 3 (1.4%)          | 0.76 (0.17-3.44) | .720 |
| **Dominant model** |                       |                   |             |   |
| C/C  | 169 (70.1%)           | 167 (77%)         | 1.00        |   |
| C/T-T/T | 72 (29.9%)       | 50 (23%)          | 0.70 (0.46-1.07) | .098 |
| **Recessive model** |                       |                   |             |   |
| C/C-C/T  | 237 (98.3%)       | 214 (98.6%)       | 1.00        |   |
| T/T  | 4 (1.7%)              | 3 (1.4%)          | 0.83 (0.18-3.75) | .81  |
| **Overdominant model** |                       |                   |             |   |
| C/C-T/T | 173 (71.8%)       | 170 (78.3%)       | 1.00        |   |
| C/T  | 68 (28.2%)            | 47 (21.7%)        | 0.70 (0.46-1.08) | .11  |
| **Log-additive model** |                       |                   |             |   |
| T    | 76 (15.8%)            | 53 (12.2%)        | 0.73 (0.50-1.08) | .11  |
| C    | 406 (84.2%)           | 381 (87.8%)       | 1.35 (0.92-1.96) | .122 |

Note: Of the 217 ALL cases, 197 were B-ALL and 20 were T-ALL; significant values (P < .05) are in bold.

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; OR, odds ratio; SNPs, single-nucleotide polymorphisms; TLX1, T-cell leukemia homeobox 1.
### TABLE 4  Associations between TLX1 SNPs and B-ALL

| TLX1 | Control n = 241(n[%]) | ALL n = 197(n[%]) | OR (95% CI) | P   |
|------|----------------------|-------------------|-------------|-----|
| rs75329544 genotype | | | | |
| T/T | 210 (87.1%) | 168 (85.3%) | 1.00 | |
| A/T | 31 (12.9%) | 28 (14.2%) | 1.13 (0.65-1.96) | .665 |
| A/A | 0 (0%) | 1 (0.5%) | NA (0.00–NA) | .264 |
| Dominant model | T/T | 210 (87.1%) | 168 (85.3%) | 1.00 | |
| A/T-A/A | 31 (12.9%) | 29 (14.7%) | 1.17 (0.68-2.02) | .57 |
| A/A | 0 (0%) | 1 (0.5%) | NA (0.00–NA) | .21 |
| recessive model | T/T-A/T | 241 (100%) | 196 (99.5%) | 1.00 | |
| A/A | 0 (0%) | 1 (0.5%) | NA (0.00–NA) | .21 |
| Overdominant model | T/T-A/A | 210 (87.1%) | 169 (85.8%) | 1.00 | |
| A/T | 31 (12.9%) | 28 (14.2%) | 1.12 (0.65-1.94) | .68 |
| A/A | 0 (0%) | 1 (0.5%) | NA (0.00–NA) | .21 |
| log-additive model | — | — | — | 1.21 (0.71-2.06) | .49 |
| Allele | T | 451 (93.6%) | 364 (92.4%) | 1.00 | |
| A | 31 (6.4%) | 30 (7.6%) | 1.20 (0.71-2.02) | .49 |
| rs946328 genotype | | | | |
| C/C | 161 (66.8%) | 145 (73.6%) | 1.00 | |
| C/T | 74 (30.7%) | 46 (23.4%) | 0.69 (0.45-1.06) | .091 |
| T/T | 6 (2.5%) | 6 (3%) | 1.11 (0.35-3.52) | .859 |
| Dominant model | C/C | 161 (66.8%) | 145 (73.6%) | 1.00 | |
| C/T-T/T | 80 (33.2%) | 52 (26.4%) | 0.72 (0.48-1.09) | .12 |
| recessive model | C/C-C/T | 235 (97.5%) | 191 (97%) | 1.00 | |
| T/T | 6 (2.5%) | 6 (3%) | 1.23 (0.39-3.88) | .72 |
| Overdominant model | C/C-T/T | 167 (69.3%) | 151 (76.7%) | 1.00 | |
| C/T | 74 (30.7%) | 46 (23.4%) | 0.69 (0.45-1.06) | .085 |
| log-additive model | — | — | — | 0.80 (0.55-1.14) | .21 |
| Allele | C | 396 (82.2%) | 336 (85.3%) | 1.00 | |
| T | 86 (17.8%) | 58 (14.7%) | 1.26 (0.87-1.80) | .215 |
| rs12415670 genotype | | | | |
| G/G | 126 (52.3%) | 96 (48.7%) | 1.00 | |
| A/G | 93 (38.6%) | 78 (39.6%) | 1.10 (0.74-1.64) | .639 |
| A/A | 22 (9.1%) | 23 (11.7%) | 1.37 (0.72-2.61) | .333 |

(Continues)
| **TLX1** | **Control** |        | **ALL** |        | **OR (95% CI)** | **P** |
|----------|-------------|--------|---------|--------|-----------------|------|
|          | n = 241(n[%]) | ALL n = 197(n[%]) |         |        |                 |      |
| Dominant model |             |         |         |        |                 |      |
| G/G      | 126 (52.3%) | 96 (48.7%) | 1.00    |       |                 |      |
| A/G-A/A | 115 (47.7%) | 101 (51.3%) | 1.15 (0.79-1.68) | .46 |
| Recessive model |             |         |         |        |                 |      |
| G/G-A/G | 219 (90.9%) | 174 (88.3%) | 1.00    |       |                 |      |
| A/A      | 22 (9.1%)  | 23 (11.7%) | 1.32 (0.71-2.44) | .38 |
| Overdominant model |             |         |         |        |                 |      |
| G/G-A/A | 148 (61.4%) | 119 (60.4%) | 1.00    |       |                 |      |
| A/G      | 93 (38.6%) | 78 (39.6%) | 1.04 (0.71-1.53) | .83 |
| Log-additive model |             |         |         |        |                 |      |
| —        | —           | —       | 1.15 (0.86-1.52) | .34 |
| Allele   |             |         |         |        |                 |      |
| G        | 345 (71.6%) | 270 (68.5%) | 1.00    |       |                 |      |
| A        | 137 (28.4%) | 124 (31.5%) | 1.16 (0.86-1.55) | .33 |
| rs2075879 genotype |             |         |         |        |                 |      |
| G/G      | 110 (45.6%) | 108 (54.8%) | 1.00    |       |                 |      |
| A/G      | 109 (45.2%) | 71 (36.0%) | 0.66 (0.44-0.99) | .044 |
| A/A      | 22 (9.1%)  | 17 (8.6%)  | 0.79 (0.40-1.56) | .493 |
| NA       | 1 (0.5%)   |          |          |        |                 |      |
| Dominant model |             |         |         |        |                 |      |
| G/G      | 110 (45.6%) | 108 (55.1%) | 1.00    |       |                 |      |
| A/G-A/A | 131 (54.4%) | 88 (44.9%)  | 0.68 (0.47-1.00) | .049 |
| Recessive model |             |         |         |        |                 |      |
| G/G-A/G | 219 (90.9%) | 179 (91.3%) | 1.00    |       |                 |      |
| A/A      | 22 (9.1%)  | 17 (8.7%)  | 0.95 (0.49-1.83) | .87 |
| Overdominant model |             |         |         |        |                 |      |
| G/G-A/A | 132 (54.8%) | 125 (63.8%) | 1.00    |       |                 |      |
| A/G      | 109 (45.2%) | 71 (36.2%) | 0.69 (0.47-1.01) | .057 |
| Log-additive model |             |         |         |        |                 |      |
| —        | —           | —       | 0.79 (0.59-1.06) | .11 |
| Allele   |             |         |         |        |                 |      |
| G        | 329 (68.3%) | 287 (73.2%) | 1.00    |       |                 |      |
| A        | 153 (31.7%) | 105 (26.8%) | 0.79 (0.59-1.06) | .11 |
| rs17113735 genotype |             |         |         |        |                 |      |
| G/G      | 139 (57.7%) | 105 (53.3%) | 1.00    |       |                 |      |
| A/G      | 93 (38.6%) | 72 (36.5%) | 1.02 (0.69-1.53) | .904 |
| A/A      | 9 (3.7%)   | 20 (10.2%) | 2.94 (1.29-6.72) | .008 |
| Dominant model |             |         |         |        |                 |      |
| G/G      | 139 (57.7%) | 105 (53.3%) | 1.00    |       |                 |      |
| A/G-A/A | 102 (42.3%) | 92 (46.7%)  | 1.19 (0.82-1.74) | .36 |
| Recessive model |             |         |         |        |                 |      |
| G/G-A/G | 232 (96.3%) | 177 (89.8%) | 1.00    |       |                 |      |

(Continues)
### TABLE 4  (Continued)

| TLX1 | Control n = 241(n[%]) | ALL n = 197(n[%]) | OR (95% CI) | P |
|------|-----------------------|-------------------|------------|---|
|      | A/A                  | 9 (3.7%)          | 20 (10.2%) | 2.91 (1.29-6.55) | .007 |
|      | G/G-A/A              | 148 (61.4%)       | 125 (63.5%) | 1.00 |
|      | A/G                  | 93 (38.6%)        | 72 (36.5%) | 0.92 (0.62-1.35) | .66 |
|      | Log-additive model   |                   |            |          |
|      |                     |                   |            |          |
|      | Allele               |                   |            |          |
|      | G                    | 371 (77.0%)       | 282 (71.6%) | 1.00 |
|      | A                    | 111 (23.0%)       | 112 (28.4%) | 1.33 (0.98-1.80) | .068 |
|      | rs1051723 genotype   |                   |            |          |
|      | C/C                  | 169 (70.1%)       | 149 (75.6%) | 1.00 |
|      | C/T                  | 68 (28.2%)        | 45 (22.8%) | 0.75 (0.49-1.16) | .197 |
|      | T/T                  | 4 (1.7%)          | 3 (1.5%) | 0.85 (0.19-3.86) | .834 |
|      | Dominant model       |                   |            |          |
|      | C/C                  | 169 (70.1%)       | 149 (75.6%) | 1.00 |
|      | C/T-T/T              | 72 (29.9%)        | 48 (24.4%) | 0.76 (0.49-1.16) | .2 |
|      | Recessive model      |                   |            |          |
|      | C/C-C/T              | 237 (98.3%)       | 194 (98.5%) | 1.00 |
|      | T/T                  | 4 (1.7%)          | 3 (1.5%) | 0.92 (0.20-4.14) | .91 |
|      | Overdominant model   |                   |            |          |
|      | C/C-T/T              | 173 (71.8%)       | 152 (77.2%) | 1.00 |
|      | C/T                  | 68 (28.2%)        | 45 (22.8%) | 0.75 (0.49-1.16) | .2 |
|      | Log-additive model   |                   |            |          |
|      |                     |                   |            |          |
|      | Allele               |                   |            |          |
|      | C                    | 406 (84.2%)       | 343 (87.1%) | 1.00 |
|      | T                    | 76 (15.8%)        | 51 (12.9%) | 1.26 (0.86-1.85) | .238 |

Note: Significant values (P < .05) are in bold.

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; OR, odds ratio; SNPs, single-nucleotide polymorphisms; TLX1, T-cell leukemia homeobox 1.

**FIGURE 1** Linkage disequilibrium (LD) structure and haplotype blocks of the six Single-nucleotide polymorphisms (SNPs) of the T-cell leukemia homeobox 1 (TLX1) gene. A, LD structure and haplotype blocks of the six SNPs of the TLX1 gene in ALL. B, LD structure and haplotype blocks of the six SNPs of the TLX1 gene in B-ALL.
10q21.2 (ARID5B, rs7089424, OR = 1.65, \(P = 6.69 \times 10^{-19}\)), and 14q11.2 (CEBPE, rs2239633, OR = 1.34, \(P = 2.88 \times 10^{-7}\)) by analyzing 907 ALL cases and 2,398 controls.

Ellinghaus studied 474 controls and 419 childhood ALL cases and identified rs17505102 belonging to TP63 as a novel, genome-wide significant risk locus (\(P_{\text{CMHT}} = 8.94 \times 10^{-9}, \text{OR} = 0.65\)).

In this study, the association between TLX1 and ALL was determined. The significance of rs75329544, rs946328, rs12415670, rs2075879, rs17113735, and rs1051723 polymorphisms in the susceptibility to ALL in Chinese children was studied. The results from SPSS and Haploview analysis revealed that the rs17113735 polymorphisms were a novel risk locus correlated with increased risk of ALL, whereas rs946328 prevented ALL in humans. Moreover, TLX1 was associated with B-ALL. Rs17113735 was a risk locus in the B-ALL samples, and rs2075879 might be associated with decreased risk of B-ALL. The LD analysis showed that all SNPs in the two sample types (ALL and B-ALL samples) demonstrated LD except between rs75329544 and rs2075879. Haplotype analysis found no significant difference between the two groups in both types.

### 5 | CONCLUSION

This study demonstrated that TLX1 rs17113735 could be the risk locus associated with increased risk for ALL, including B-ALL. Meanwhile, rs946328 might be associated with decreased risk for ALL. Rs2075879 was associated with decreased risk for B-ALL. These results indicate that TLX1 possibly plays a significant role in B-ALL. However, the results should be interpreted discretely due to the relatively small sample size and the homogeneous ethnic origin of the respondents. Further studies should employ larger sample sizes and multifarious populations to thoroughly investigate the association between TLX1 and ALL, especially B-ALL.

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