Association Between the miR-146a Rs2910164 Polymorphism and Childhood Acute Lymphoblastic Leukemia Susceptibility in an Asian Population

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Background: miR-146a has been demonstrated to be involved in normal hematopoiesis and the pathogenesis of many hematological malignancies by inhibiting the expression of its targets. Rs2910164(G>C) may modify the expression of the miR-146a gene, which might influence an individual’s predisposition to childhood acute lymphoblastic leukemia (ALL). However, inconsistent findings have been reported on the association between the rs2910164(G>C) polymorphism and the risk of childhood ALL.

Methods: A comprehensive meta-analysis was performed to accurately estimate the association between the miR-146a rs2910164 polymorphism and childhood ALL among four different genetic models.

Results: This meta-analysis included Asian studies with a total of 1,543 patients and 1,816 controls. We observed a significant difference between patients and controls for the additive model (CC vs. GG: OR = 1.598, 95% CI: 1.003–2.545, P = 0.049) using a random effects model. Meanwhile, there was a trend of increased childhood ALL risk in the dominant model (CC + CG vs. GG: OR = 1.501, 95% CI: 0.976–2.307, P = 0.065), recessive model (CC vs. GG + CG: OR = 1.142, 95% CI: 0.946–1.380, P = 0.168) and allele model (C vs. G: OR = 1.217, 95% CI: 0.987–1.500, P = 0.066) between patients and controls.

Conclusions: Our findings suggest that the miR-146a rs2910164 CC genotype was significantly associated with childhood ALL susceptibility.

Keywords: childhood acute lymphoblastic leukemia, miR-146a, rs2910164, Asian population, meta-analysis
INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a very common malignancy among children, accounting for ∼75% of leukemia cases among children (Pui et al., 2015). The incidence of this disease has continued to increase worldwide over the past several decades (Terracini, 2011). ALL is a clonal malignant disease that is characterized by an uncontrolled proliferation of immature cells, but its etiology remains unknown. MiRNAs are small non-coding RNAs that monitor gene expression post-transcriptionally. Previous studies have shown that miRNAs may play an important role in leukemogenesis (Schotte et al., 2010; Bottoni and Calin, 2013; Yan et al., 2013; Yin et al., 2014).

miR-146a has been identified as a modulator of cell differentiation and innate and adaptive immunity (Boldin et al., 2011; Rusca and Monticelli, 2011; Ghani et al., 2012; Labbaye and Testa, 2012). The abnormal expression of miR-146a is frequently observed in human diseases, such as inflammatory disorders and cancers (He et al., 2005; Iriyama et al., 2012; Petrovic et al., 2017; Shomali et al., 2017; Tan et al., 2018). Previous studies have reported that miR-146a is significantly increased in the peripheral blood samples of pediatric patients with ALL (Duyu et al., 2014; Yan et al., 2017), thus providing valuable insights into potential diagnostic or prognostic biomarkers. Lin showed that the absence of miR-146a can lead to leukemia in mice (Lin et al., 2015), which indicated that miR-146a might act as a...
In the rs2910164 polymorphism, which is located in pre-
miR-146a, the nucleotide substitution from G to C leads to a
transformation from a G:U pair to a C:U mismatch in the stem
structure of the miR-146a precursor and results in a reduced
amount of mature miR-146a (Yue et al., 2011; Palmieri et al.,
2014). Jazdzewski found that mature miR-146a with the C allele is
less able to inhibit the target genes IRAK1 and TRAF6 than the G
allele (Jazdzewski et al., 2008), which seems to be associated with
the development of ALL.

A significant association of miR-146a rs2910164 with
childhood ALL has been reported in an Iranian population
(Hasani et al., 2014). This result was successfully replicated in
two Chinese case-control studies (Liu et al., 2018; Pei et al.,
2020). In contrast, three studies from Thailand, India and
China failed to replicate the results (Chansing et al., 2016;
Devanandan et al., 2019; Xue et al., 2019). Considering the
conflicting results, whether miR-146a rs2910164 is associated
with childhood ALL in Asian populations remains to be
elucidated. In this study, we performed a meta-analysis
to estimate the association of miR-146a rs2910164 with
childhood ALL among four different genetic models in an
Asian population.

**MATERIALS AND METHODS**

This study was pursuant to the Preferred Reporting Items for
Systematic Reviews and Meta-analyses (PRISMA) guidelines.
The PRISMA checklist is provided in Supplementary Table 1.

**Literature Search**

The PubMed, Google Scholar, WanFang and Chinese National
Knowledge Infrastructure databases were systematically searched
for relevant studies using the words “miR-146a or microRNA-
146a” “rs2910164” “leukemia” with no language or time
restrictions. All studies were assessed by reading the title and
abstract and irrelevant studies were excluded. Then, the full
texts of the remaining studies were assessed to determine
their eligibility.

**Inclusion and Exclusion Criteria**

The study inclusion criteria were as follows: (a) case-control
or cohort studies that assessed the association between the
miR-146a rs2910164 polymorphism and the risk of childhood
ALL; (b) studies in which all patients had been diagnosed
with ALL by morphology, immunology, cytogenetic and
molecular biology (MICM) in accordance with one of the
following criteria: (i) bone marrow morphology standard:
according to the 2016 WHO diagnostic criteria, the original
and immature lymphocytes in bone marrow are not <20%,
(ii) if the original and immature lymphocytes were <20%, a
molecular diagnosis method was used to determine whether
ALL pathogenic genes existed; (c) studies with data that could
be used to estimate odds ratios (ORs) with corresponding 95%
confidence intervals (CIs); and (d) studies published before
April 30, 2020.

The exclusion criteria were as follows: (a) the study was
not a case–control study; (b) the study was not related
to acute lymphoblastic leukemia or 146a rs2910164; (c) the
study lacked particular genotype data; (d) the genotype
distribution of the control subjects was not in a Hardy–Weinberg
equilibrium (HWE).

**Data Extraction**

The following data were independently extracted from included
studies and entered into a database to ensure the veracity of the
data: first author’s name, year of publication, population,
genotyping techniques, number of patients and controls,
genotype distribution, allele distribution, HWE and other
information. Studies were excluded if they did not provide the
above information.

**Statistical Analysis**

The Hardy-Weinberg equilibrium was examined by Pearson’s
chi-squared test. Four genetic models were used in the study:
the dominant model (CC + CG vs. GG), the recessive model
(CC vs. GG + CG), the additive model (CC vs. GG) and the
allele model (C vs. G). Genetic heterogeneity was evaluated
using the Q-test and I²-test. I² statistics range from 0 to 100%.
Significant heterogeneity was defined as P < 0.01 and I² >
50%. ORs with corresponding 95% CIs were calculated using
the fixed effects model (Mantel-Haenszel) when no significant
heterogeneity was observed; otherwise, a random effects model
was used. The Z-test was used to test the significance of
the ORs. To check the stability of our results, sensitivity
analyses for the overall effect were conducted by excluding one
study at a time. Additionally, Egger’s and Begg’s tests were
used to assess publication bias. The statistical analyses were
performed using the STATA v.16.0 software (Stata Corporation,
Texas, USA), Review Manager 5.0.24 (The Nordic Cochrane
Center, Denmark), R version 3.6.2 (R Core Team, Vienna.

**TABLE 2 | Heterogeneity analysis with random-effect model.**

| Genetic model | N   | OR  | 95%-CI    | Q    | I² |
|---------------|-----|-----|-----------|------|----|
| CC + CG vs. GG| 6   | 1.2828 | [0.8669; 1.8883] | 19.93 | 74.90% |
| CC vs. GG + CG| 6   | 0.9959 | [0.6870; 1.4435] | 16.61 | 78.90% |
| CC vs. GG    | 6   | 1.2635 | [0.7010; 2.2776] | 27.16 | 81.60% |
| C vs. G      | 6   | 1.0965 | [0.8423; 1.4249] | 24.37 | 79.50% |

OR, odds ratio; CI, confidence interval; I², measure to quantify the degree of heterogeneity in meta-analyses.
Austria) and RStudio version 1.2.1 (Certified B Corporations, Boston, USA).

RESULTS

Study Inclusion and Characteristics
A total of 113 potential studies were retrieved through the initial search. Twenty duplicates were excluded. Then, the titles and abstracts of 93 studies were screened and 73 studies were excluded. The full texts of the remaining 20 articles were evaluated; 6 were excluded because they were not case-control studies and 7 were excluded because they were not related to acute lymphoblastic leukemia or rs2910164 and 1 study was excluded because it did not provide sufficient data. A flow chart of the study selection process is shown in Figure 1. There were 6 potentially relevant papers, including 5 written in English and 1 written in Chinese. A total of 1,543 childhood ALL patients and 1,816 healthy controls were included in the meta-analysis. Table 1 shows the characteristics of each study. Power analysis was conducted with the total sample size and revealed a power of 94.6% using an OR of 1.2 for the risk allele and a MAF of 0.39 for the C allele.

Heterogeneity Analysis
The Cochran’s Q test and the $I^2$ statistics shown in Table 2 revealed that high heterogeneity among studies was detected in the CC + CG vs. GG ($I^2 = 74.9\%$), CC vs. GG + CG ($I^2 = 69.9\%$), CC vs. GG ($I^2 = 81.6\%$) and C vs. G ($I^2 = 79.5\%$).

| Genetic model | Study(n) | OR  | 95%-CI    | Q   | $I^2$  |
|---------------|----------|-----|-----------|-----|--------|
| CC + CG vs. GG| 5        | 1.5006 | [0.9760; 2.3072] | 11.94 | 66.50% |
| CC vs. GG + CG| 5        | 1.1413 | [0.9439; 1.3799] | 2.92  | 0.00%  |
| CC vs. GG     | 5        | 1.5977 | [1.0027; 2.5455] | 9.51  | 57.90% |
| C vs. G       | 5        | 1.2167 | [0.9873; 1.4995] | 8.74  | 54.30% |

OR, odds ratio; CI, confidence interval; $I^2$, measure to quantify the degree of heterogeneity in meta-analyses.

FIGURE 2 | Sensitivity analysis was performed by removing one study at a time. (A) Dominant model, CC + CG vs. GG. (B) Recessive model, CC vs. GG + CG. (C) Additive model, CC vs. GG. (D) Allele model, C vs. G.
models for the rs2910164 polymorphism. As high heterogeneity was observed, sensitivity analysis was performed to analyze the sources of heterogeneity.

**Sensitivity Analysis**

To estimate the influence of each study on the overall OR of the four genetic models and to analyze the sources of high heterogeneity, a sensitivity analysis was performed with a random effects model. The results are shown in Figure 2. Omitting Pei’s study effectively reduced heterogeneity, especially in the recessive model (CC vs. GG + CG: $I^2 = 0.0\%$, $P = 0.571$). The other three models showed a moderate degree of heterogeneity (CC + CG vs. GG: $I^2 = 66.5\%$, $P = 0.018$; CC vs. GG: $I^2 = 57.9\%$, $P = 0.050$; C vs. G: $I^2 = 54.3\%$, $P = 0.068$, respectively) (Table 3).

**Results of the Association Between miR-146a rs2910164 and Childhood ALL Meta-Analysis**

After one study was omitted, there was a moderate degree of heterogeneity among studies. A fixed effects model was used to analyze the recessive model; the dominant, additive and allele models were analyzed with a random effects model. The results showed a significant difference between childhood ALL patients and controls for the additive model (CC vs. GG: OR = 1.598, 95% CI: 1.003–2.645, $P = 0.049$) and a trend of increased childhood ALL risk for the dominant model (CC + CG vs. GG: OR = 1.501, 95% CI: 0.976–2.307, $P = 0.065$), recessive model (CC vs. GG + CG: OR = 1.142, 95% CI: 0.946–1.380, $P = 0.168$) and allele model (C vs. G: OR = 1.217, 95% CI: 0.987–1.500, $P = 0.066$) between patients and controls (Figures 3, 4).

**Publication Bias**

There was no significant publication bias in any of the genetic models according to Begg’s and Egger’s tests (all $P > 0.05$, data not shown) and the funnel plot was symmetrical, as the studies did not coagulate into one quadrant of the funnel (Figure 5).

**DISCUSSION**

This meta-analysis included six Asian studies about the miR-146a rs2910164 loci and susceptibility to childhood ALL. Three studies reported an association between miR-146a rs2910164 and the risk of childhood ALL and the other three showed negative results. Moreover, the sample sizes of the individual studies were small, making it difficult to identify the possible small effect of rs2910164 on childhood ALL. Thus, this study enabled us to more accurately determine the association between rs2910164 and childhood ALL susceptibility due to the increased sample size and statistical power of the meta-analysis.

In this study, a total of 1,543 ALL patients and 1,816 controls were investigated to provide an overall evaluation of the association between the miR-146a rs2910164 polymorphism and childhood ALL. We conducted heterogeneity analysis and the results revealed that high heterogeneity among studies was detected in the four genetic models. Therefore, we explored the source of this heterogeneity via sensitivity analysis by omitting one study at a time. The results showed that omitting Pei’s study could effectively reduce heterogeneity, especially in the recessive model and the other three models showed a moderate degree of heterogeneity. The most likely reasons for this heterogeneity might involve ethnicity, geographical region and the selection of control groups. The minor allele frequencies (MAFs) ranged from 0.395 to 0.495 in each study (Table 1).
In Pei, Liu and Hasanis' studies, the MAF was higher than the NCBI SNP database in Asian populations. However, Pei's study sample sizes are larger than those of Liu and Hasanis. This is why Pei's study has a strong influence on heterogeneity.

In addition, the populations of the control groups were not uniform. Individuals in the control group in Pei's study were determined to be cancer-free in accordance with the criteria set by the International Classification of Disease (ninth revision, defined by World Health Organization), but other studies did not explain the diagnostic criteria of the control groups. Thus, after omitting Pei's study, a fixed effects model was used to analyze the recessive model; the dominant, additive and allele models were analyzed with a random effects model. The results showed a significant difference between childhood ALL patients and controls for the additive model. Interestingly, there was a trend of increased childhood ALL risk in the other three modalities between patients and controls. These results showed that miR146a rs2910164 (G>C) was significantly associated with childhood ALL susceptibility.

In recent years, an increasing amount of data have demonstrated that miR-146a is related to normal hematopoiesis and the pathogenesis of some hematological malignancies by inhibiting the expression of its targets (Hua et al., 2011). The miR146a rs2910164 polymorphism has been extensively tested in different cancers. The rs2910164 CG or GG genotype...
was linked to a significantly decreased risk for lung cancer compared to the CC genotype (Jeon et al., 2014). In addition, the rs2910164 CC genotype may be devoted to breast cancer susceptibility in Europeans (Lian et al., 2012). For childhood ALL, previous studies found that the rs2910164 CC or CG genotype significantly increased the risk of ALL (Hasani et al., 2014; Liu et al., 2018). The mir146a rs2910164 GG genotype was significantly related to a decreased susceptibility to childhood ALL (Pei et al., 2020). This study confirms that the mir146a rs2910164 polymorphism (G>C) contributes to childhood ALL susceptibility among Asians.

There are still some limitations in our study. Firstly, due to the limited examination of mir146a rs2910164 in childhood ALL, only six studies were included in the meta-analysis. Secondly, the current research only includes Asian studies and there is an urgent need to conduct research using large samples of other ethnic groups across the world. Thirdly, the complexity of ALL, which is the result of the interaction of genetic and environmental factors, may affect the results. Among individuals with the same genotype, their susceptibility to ALL may be different due to the geographical environment lifestyle and other factors of the diverse population (Garzon et al., 2010).

In conclusion, our work contributed important evidence regarding the association between the mir146a rs2910164 CC genotype and susceptibility to childhood ALL in an Asian population. Given the relatively small sample size of this study, more large-sample studies including different ethnic populations are needed to validate these results.

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DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

AUTHOR CONTRIBUTIONS

DZ, JY, ZY, and QZ were responsible for the statistical analysis, study design, and manuscript preparation. DZ and CT managed the literature searches and analyses. This study was supervised by YW, QC, and RC. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2020.00886/full#supplementary-material
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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