Potentially Functional Polymorphism in IL-23 Receptor and Risk of Acute Myeloid Leukemia in a Chinese Population

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Abstract

The interleukin-23 (IL-23) and its receptor (IL-23R) mediate the direct antitumor activities in human hematologic malignancies including pediatric acute leukemia. Two potentially functional genetic variants (IL-23R rs1884444 T>G and rs6682925 T>G) have been found to contribute to solid cancer susceptibility. In this study, we conducted a case-control study including 545 acute myeloid leukemia (AML) patients and 1,146 cancer-free controls in a Chinese population to assess the association between these two SNPs and the risk of AML. We found that IL-23R rs1884444 TG/GG and rs6682925 TC/CC variant genotypes were associated with significantly increased risk of AML (rs1884444: adjusted odds ratio (OR) = 1.28, 95% confidence interval (CI) = 1.01–1.62; rs6682925: adjusted OR = 1.30, 95% CI = 1.01–1.67), compared to their corresponding wild-type homozygotes, respectively. These findings indicated that genetic variants in IL-23R may contribute to AML risk in our Chinese population.

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Introduction

Acute myeloid leukemia (AML), a cancer of the myeloid line of blood cells, is the most common acute leukemia affecting adult [1]. The abnormal white blood cells accumulate in the bone marrow, thus interfering with the production of normal blood cells. Although most cases of AML have no obvious cause, it is considered that several factors may play a role in the increased occurrence of AML, including chemical exposure [2,3], ionizing radiation [4], and genetics [5].

Interleukin (IL)-23 is a heterodimeric proinflammatory cytokine composed of a p19 subunit and a p40 subunit, which is also part of IL-12 [6,7]. IL-23 is predominantly produced by antigen-presenting cells in response to microbial or host immune stimuli and is involved in the regulation of immune responses against infections and tumor development through the engagement of the IL-23 receptor (IL-23R) [8]. Recent studies also showed the direct antitumor activities of IL-23/IL-23R in human hematologic malignancies, i.e., pediatric acute leukemia, and IL-23 directly dampens tumor growth in vitro and in vivo through the inhibition of tumor cell proliferation and induction of apoptosis [9,10]. The IL-23R gene located on chromosome 1p31 encodes one subunit of the IL-23R [11]. Two potentially functional common variants of IL-23R, rs6882925 (T>C) located at 907-bp upstream of the transcriptional start position, and rs1884444 (T>G) located at codon 3 with amino acid His substituted by Gln in exon 2, have been shown to have association with risk of several solid cancers [12–14]. Here, we hypothesized these two single-nucleotide polymorphisms (SNPs) may also be associated with risk of AML.

Results

Of the 545 AML cases, 291 (53.4%) were males and the mean age at diagnosis was 44.1 ± 17.2 years old, while among the 1146 cancer-free controls, 820 (71.5%) were males and the mean age was 59.0 ± 9.7 years old. The clinical and cytogenetic characteristics of the AML cases are summarized in Table 1. The observed genotype frequencies for both rs1884444 TG/GG and rs6682925 TC/CC distributions of these two variants between the cases and controls are shown in Table 2. The observed genotype frequencies for both SNPs were in Hardy-Weinberg equilibrium among the controls (P = 0.829 for rs1884444 and P = 0.686 for rs6682925). Multivariate logistic regression analysis showed that the rs1884444 TG and combined genotypes TG/GG were associated with a significantly increased risk of AML (adjusted OR = 1.34, 95% CI = 1.04–1.72 for TG; adjusted OR = 1.28, 95% CI = 1.01–1.62 for TG/GG),
was no significant associations between AML1/ETO or PML/RARα and SNPs of M3 AML, we then investigated the association of these two genes accounted for the majority of molecular subtypes of M2 AML and respectively.

for rs6682925. For rs1884444, the increased risk of combined and age on AML risk (P = 0.030). However, there was no interaction between rs1884444 with human diseases in non-Chinese population [25–27], and none of them were involved in leukemia. Additionally, there haven’t been any studies focused on rs6682925 in other population except Chinese. So we could not evaluate the presence of these SNPs in non-Chinese population.

Thus far, it is challenging to know the exact mechanisms of these two variants on AML carcinogenesis. The SNP rs1884444 locates on exon 2 of IL-23R, which is responsible for the signal peptide of IL-23R [28]. According to the web-based prediction tool of PupaSuite2 (http://pupasuite.bioinfo.cipf.es/) [29], the T-to-G base change of rs1884444 may disrupt an exonic splicing enhancer, resulting in exon skipping, malformation, or transcript alternative splicing. Another possible explanation is that rs1884444 resulted in amino acid change (His>Gln), which may influence the ligand-receptor binding specificity and affinity, and thus modulate the proinflammatory effect by Th17 cell and get involved in the development of AML [14]. The SNP rs6682925 locates at 907-bp upstream from the transcriptional start position of IL-23R. The web-based tool of TFSSEARCH 1.3 (http://www.chrc.jp/research/db/TFSSEARCH.html) [12] showed that the T-to-G base change of rs6682925 might affect a predicted GATA-X transcription factor binding, which may be involved in tumor differentiation and other carcinogenesis-related pathways [30,31]. Xu et al. found that the C allele (G allele in antisense strand) of rs1884444 resulted in amino acid change (His>Gln), which may influence the ligand-receptor binding specificity and affinity, and thus modulate the proinflammatory effect by Th17 cell and get involved in the development of AML [14]. The SNP rs6682925 locates at 907-bp upstream from the transcriptional start position of IL-23R. The web-based tool of TFSSEARCH 1.3 (http://www.chrc.jp/research/db/TFSSEARCH.html) [12] showed that the T-to-G base change of rs6682925 might affect a predicted GATA-X transcription factor binding, which may be involved in tumor differentiation and other carcinogenesis-related pathways [30,31]. Xu et al. found that the C allele (G allele in antisense strand) of rs6682925 may increase the promoter activity of IL-23R by luciferase assay, which was consistent with the web-based prediction [12].

There are a few biases that may lead to spurious findings. Firstly, cases and controls were not matched on age and gender, but we used further statistical adjustment to minimize potential biases. Secondly, some risk predictors of AML, such as exposure to carcinogens and development of myelodysplasia, were not

| Characteristics | AML (n = 545) |
|-----------------|--------------|
| No. (%)         |              |
| **Lineage**     |              |
| Myeloid         | 378          | 69.4         |
| Myeloid and Lymphoid | 157 | 28.8         |
| Myeloid and Monocytic | 10  | 1.8          |
| **Classification of diagnosis** | |
| M0              | 3            | 0.6          |
| M1              | 103          | 18.9         |
| M2              | 175          | 32.1         |
| M3              | 90           | 16.5         |
| M4              | 58           | 10.6         |
| M5              | 89           | 16.3         |
| Unknown         | 27           | 5.0          |
| **Karyotype**   |              |
| Aberrant        | 246          | 45.1         |
| t(9;22)         | 11           | 2.0          |
| t(8;21)         | 48           | 8.8          |
| t(15;17)        | 64           | 11.7         |
| complex         | 114          | 20.9         |
| others          | 9            | 1.7          |
| Normal          | 235          | 43.1         |
| Unknown         | 64           | 11.8         |
| **Molecular subtype** | |
| Common fusion gene transcripts | 187 | 34.3 |
| PML/RARα        | 77           | 14.1         |
| BCR/ABL         | 13           | 2.4          |
| AML1/ETO        | 54           | 9.9          |
| CBFβ2/MYH11     | 10           | 1.8          |
| MLL rearrangement | 15  | 2.8          |
| WT1             | 11           | 2.0          |
| Others          | 7            | 1.3          |
| No common fusion gene transcrspts | 303 | 55.6 |
| Unknown         | 55           | 10.1         |

Table 1. Clinical Characteristics of AML Patients.

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compared with the rs1884444 wild-type TT, respectively. Similarly, compared to the wild TT genotype, rs6682925 CC and combined TC/CC genotypes contributed to AML risk by 1.48-fold (95% CI = 1.03–2.13) and 1.30-fold (95% CI = 1.01–1.67), respectively.

Stratified analyses of these two SNPs are summarized in Table 3. No significant heterogeneity between the subgroups was detected for rs6682925. For rs1884444, the increased risk of combined TG/GG genotypes was more significant in older patients (more than 45 years old at diagnosis), and P value for the heterogeneity was 0.030. However, there was no interaction between rs1884444 and age on AML risk (P = 0.097).

As the fusion gene AML1/ETO and PML/RARα respectively accounted for the majority of molecular subtypes of M2 AML and M3 AML, we then investigated the association of these two genes and SNPs of IL-23R in M2 AML and M3 AML. However, there was no significant associations between AML1/ETO or PML/RARα and IL-23R variants in M2 and M3 AML, respectively, as shown in Table 4.

Discussion

IL-23 is a proinflammatory heterodimeric cytokine sharing common subunits with IL-12 [6,7], which could directly inhibit human acute myeloid leukemia cell growth [15]. With the similar structures and biological activities of IL-12, IL-23 may also have some effects on human malignancies, whereas its antitumor activity remains controversial. Some groups held the opinion that IL-23 can impair CD8+ T-lymphocyte-mediated immune surveillance and promote de novo carcinogenesis and tumor neovascularization [16–18]. In contrast, other groups have shown that IL-23 exerts antitumor activity through stimulation of T cells and NK cells [19–24]. IL-23 mediates these cancer-related effects through IL-23R. Cocco et al. demonstrated that IL-23/IL-23R acts as antitumor agent on hematologic malignancies including childhood acute leukemia [9,10]. Recently, several studies evaluated the association between two variants (rs1884444 and rs6682925) of IL-23R polymorphisms and risk of solid cancers in Chinese population [12–14]. Xu et al. [12] reported that the variant alleles of rs6682925 and rs1884444 both increased the hepatocellular carcinoma risk. Chu et al. [13] found that rs6682925 TC/CC and rs1884444 TG/GG variant genotypes were associated with significantly increased risk of esophageal cancer. But Chen et al. [14] found the protective effect of rs1884444 G allele in gastric cancer. In this study, we found that the variant alleles of rs1884444 (T>G) and rs6682925 (T>C) were associated with an increased risk of AML in a Chinese population, although this type-specific association needs to be confirmed in other studies. However, up to date, only 3 studies focused on the association of rs1884444 with human diseases in non-Chinese population [25–27], and none of them were involved in leukemia. Additionally, there haven’t been any studies focused on rs6682925 in other population except Chinese. So we could not evaluate the presence of these SNPs in non-Chinese population.

Thus far, it is challenging to know the exact mechanisms of these two variants on AML carcinogenesis. The SNP rs1884444 locates on exon 2 of IL-23R, which is responsible for the signal peptide of IL-23R [28]. According to the web-based prediction tool of PupaSuite2 (http://pupasuite.bioinfo.cipf.es/) [29], the T-to-G base change of rs1884444 may disrupt an exonic splicing enhancer, resulting in exon skipping, malformation, or transcript alternative splicing. Another possible explanation is that rs1884444 resulted in amino acid change (His>Gln), which may influence the ligand-receptor binding specificity and affinity, and thus modulate the proinflammatory effect by Th17 cell and get involved in the development of AML [14]. The SNP rs6682925 locates at 907-bp upstream from the transcriptional start position of IL-23R. The web-based tool of TFSSEARCH 1.3 (http://www.chrc.jp/research/db/TFSSEARCH.html) [12] showed that the T-to-G base change of rs6682925 might affect a predicted GATA-X transcription factor binding, which may be involved in tumor differentiation and other carcinogenesis-related pathways [30,31]. Xu et al. found that the C allele (G allele in antisense strand) of rs6682925 may increase the promoter activity of IL-23R by luciferase assay, which was consistent with the web-based prediction [12].

There are a few biases that may lead to spurious findings. Firstly, cases and controls were not matched on age and gender, but we used further statistical adjustment to minimize potential biases. Secondly, some risk predictors of AML, such as exposure to carcinogens and development of myelodysplasia, were not
### Table 2. Distribution of Alleles and Genotypes of IL-23R Variants and Their Association with AML Risk.

|                   | AML (n = 545) | Controls (n = 1146) | OR (95%CI)a | p^ | OR (95%CI)b | p^ |
|-------------------|--------------|---------------------|-------------|----|-------------|----|
|                   | N  | %  | N  | %  |          |    |
| rs1884444 T>Gc    |    |    |    |    |          |    |
| TT               | 223 | 41.5 | 519 | 45.7 | 1.00 | 1.00 |
| TG               | 254 | 47.3 | 496 | 43.6 | 1.19(0.96, 1.48) | 0.115 | 1.34(1.04, 1.72) | 0.024 |
| GG               | 60  | 11.2 | 122 | 10.7 | 1.15(0.81, 1.62) | 0.445 | 1.05(0.70, 1.57) | 0.814 |
| TG/GG            | 314 | 58.5 | 618 | 54.3 | 1.18(0.96, 1.46) | 0.113 | 1.28(1.01, 1.62) | 0.047 |
| G allele         | 34.8% | 32.5% | 1.11(0.95, 1.29) | 0.189 | 1.12(0.94, 1.34) | 0.214 |
| rs6682925 T>Cd   |    |    |    |    |          |    |
| TT               | 184 | 35.0 | 452 | 40.5 | 1.00 | 1.00 |
| TC               | 247 | 47.1 | 522 | 46.7 | 1.16(0.93, 1.46) | 0.197 | 1.25(0.96, 1.62) | 0.103 |
| CC               | 94  | 17.9 | 143 | 12.8 | 1.62(1.18, 2.21) | 0.003 | 1.48(1.03, 2.13) | 0.033 |
| TC/CC            | 341 | 65.0 | 665 | 59.5 | 1.26(1.02, 1.56) | 0.036 | 1.30(1.01, 1.67) | 0.039 |
| C allele         | 41.4% | 36.2% | 1.25(1.07, 1.45) | 0.004 | 1.22(1.01, 1.45) | 0.022 |

*aCrude odds ratio (OR), 95% confidence interval (CI) and corresponding P value.
bAdjusted for age and gender.
cGenotypes were unavailable in 8 cases and 9 controls.
dGenotypes were unavailable in 20 cases and 29 controls.
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### Table 3. Stratification Analysis of rs1884444 and rs6682925 Genotypes by Selected Variables in AML Patients and Controls.

| Characteristics | rs1884444 | rs6682925 |
|-----------------|-----------|-----------|
|                 | Case      | Control   | OR(95%CI) | p^ | Case      | Control   | OR(95%CI) | p^ |
|                 | TT | TG/GG | TT | TG/GG |          |    | TT | TC/CC | TT | TC/CC |          |    |
| gender          |    |       |    |       |          |    |    |       |    |       |          |    |
| Male            | 115 | 172   | 365 | 448   | 1.30(0.95, 1.78) | 0.848 | 98  | 183   | 318 | 483   | 1.26(0.91, 1.74) | 0.745 |
| Female          | 108 | 142   | 154 | 170   | 1.24(0.86, 1.80) | 0.197 | 86  | 158   | 134 | 182   | 1.37(0.93, 2.01) | 0.890 |
| Age at diagnosis, year |    |       |    |       |          |    |    |       |    |       |          |    |
| ≤45             | 134 | 159   | 48  | 67    | 0.85(0.55, 1.32) | 0.030 | 109 | 179   | 41  | 74    | 0.91(0.58, 1.43) | 0.062 |
| >45             | 89  | 155   | 471 | 551   | 1.52(1.14, 2.04) | 0.004 | 75  | 162   | 411 | 591   | 1.53(1.13, 2.08) | 0.022 |
| Lineage         |    |       |    |       |          |    |    |       |    |       |          |    |
| Myeloid         | 158 | 215   | 519 | 618   | 1.21(0.93, 1.59) | 0.985 | 131 | 234   | 452 | 665   | 1.25(0.94, 1.65) | 0.890 |
| Myeloid and Lymphoid | 61  | 93    | 519 | 618   | 1.26(0.86, 1.83) | 0.095 | 49  | 101   | 452 | 665   | 1.32(0.89, 1.95) | 0.523 |
| Myeloid and Monocytic | 4   | 6     | 519 | 618   | 1.20(0.34, 4.30) | 0.469 | 4   | 6     | 452 | 665   | 0.96(0.27, 3.44) | 0.900 |
| Karyotype       |    |       |    |       |          |    |    |       |    |       |          |    |
| t(8;21)         | 22  | 26    | 519 | 618   | 0.94(0.51, 1.73) | 0.726 | 15  | 31    | 452 | 665   | 1.29(0.67, 2.48) | 0.540 |
| t(15;17)        | 23  | 39    | 519 | 618   | 1.34(0.74, 2.42) | 0.017 | 21  | 42    | 452 | 665   | 1.26(0.69, 2.29) | 0.540 |
| Complex         | 53  | 60    | 519 | 618   | 0.93(0.61, 1.40) | 0.464 | 44  | 63    | 452 | 665   | 0.91(0.59, 1.39) | 0.356 |
| Others          | 8   | 11    | 519 | 618   | 1.05(0.41, 2.69) | 0.320 | 6   | 13    | 452 | 665   | 1.34(0.50, 3.63) | 0.090 |
| Normal          | 95  | 136   | 519 | 618   | 1.27(0.92, 1.74) | 0.173 | 78  | 148   | 452 | 665   | 1.31(0.94, 1.82) | 0.201 |
| Unknown         | 22  | 42    | 20  | 44    |          |    |    |       |    |       |          |    |
| Molecular subtype | 26  | 50    | 519 | 618   | 1.55(0.90, 2.69) | 0.167 | 23  | 51    | 452 | 665   | 1.37(0.78, 2.43) | 0.208 |
| PML/RARα        | 25  | 29    | 519 | 618   | 0.94(0.53, 1.66) | 0.372 | 19  | 33    | 452 | 665   | 1.10(0.60, 2.01) | 0.890 |
| AML1/ETO        | 24  | 32    | 519 | 618   | 1.08(0.61, 1.91) | 0.605 | 21  | 34    | 452 | 665   | 1.06(0.59, 1.90) | 0.900 |
| No common fusion gene transcripts | 126 | 170   | 519 | 618   | 1.17(0.88, 1.56) | 0.095 | 102 | 188   | 452 | 665   | 1.23(0.92, 1.65) | 0.022 |
| Unknown         | 22  | 33    | 19  | 35    |          |    |    |       |    |       |          |    |

*aAdjusted for age.
bAdjusted for gender.
cAdjusted for age and gender.
dAdjusted for age and gender.
^P value for heterogeneity test based on χ²-based Q test.
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Table 4. Association of AML1/ETO and IL-23R Variants in M2 AML, and Association of PML/RARα and IL-23R Variants in M3 AML.

| Classification | Molecular subtype | rs1884444 | rs6682925 |
|---------------|------------------|-----------|-----------|
|               |                  | Case | Control | OR(95%CI)* | p | Case | Control | OR(95%CI)* | p |
| M2            | AML1/ETO         | TT   | TG/GG   | 1.04(0.59, 1.83) | 0.709 | TT   | TG/GG   | 1.21(0.67, 2.20) | 0.929 |
|               | No common        | 20   | 25      | 519 618     | | 14   | 29      | 452 665     | |
|               | fusion gene      | 51   | 55      | 519 618     | 0.91(0.60, 1.37) | 35   | 66      | 452 665     | 1.17(0.76, 1.81) |
|               | transcripts      |      |         |             | |      |         |             | |
| M3            | PML/RARα         | 26   | 49      | 519 618     | 1.51(0.87, 2.62) | 0.241 | 23   | 50      | 452 665     | 1.33(0.75, 2.37) |
|               | No common        | 5    | 4       | 519 618     | 0.64(0.17, 2.41) | 4    | 5       | 452 665     | 0.82(0.22, 3.10) |
|               | fusion gene      |      |         |             | |      |         |             | |
|               | transcripts      | 3    | 1       | 519 618     |      | 3    | 1       | 452 665     | |

*Adjusted for age and gender;

**P** value for heterogeneity test based on $\chi^2$-based Q test.

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Included in this analysis. Therefore, large population-based prospective studies with ethnically diverse populations are warranted to further elucidate the impact of IL-23R SNPs on AML susceptibility.

Materials and Methods

Ethics Statement

The study is in compliance with the Helsinki declaration, and was approved by the institutional review board of Nanjing Medical University. The informed written consent was obtained from all subjects.

Study Subjects

All of the cases and controls were unrelated ethnic Han Chinese. The 545 newly diagnosed AML patients were consecutively recruited between December 2007 and August 2011 from Wuxi people’s Hospital Affiliated to Nanjing Medical University. The informed written consent was obtained from all patients. The study is in compliance with the Helsinki declaration, and was approved by the institutional review board of Nanjing Medical University. The informed written consent was obtained from all subjects. There were no restrictions in terms of age, stage of disease, or histology preventing people from participating in the study. The study is in compliance with the Helsinki declaration, and was approved by the institutional review board of Nanjing Medical University. The informed written consent was obtained from all subjects. There were no restrictions in terms of age, stage of disease, or histology preventing people from participating in the study. All of the cases and controls were unrelated ethnic Han Chinese. The 545 newly diagnosed AML patients were consecutively recruited between December 2007 and August 2011 from Wuxi people’s Hospital Affiliated to Nanjing Medical University.

Laboratory Assays

Genomic DNA was extracted from a leukocyte pellet by traditional proteinase K digestion followed by phenol-chloroform extraction and ethanol precipitation. SNPs rs6682925 T>G and rs1884444 T>G were genotyped by using the TaqMan allelic discrimination assay on an ABI 7900 system (Applied Biosystems, Foster City, CA). The primers and probes for rs6682925 and rs1884444 were described previously [13]. Genotyping was performed without knowing the subjects’ case or control status. Two blank (water) wells in each 384-well plate were used for quality control and more than 10% samples were randomly selected to repeat, yielding a 100% concordant.

Statistical Analysis

The $\chi^2$ tests were used to evaluate differences in the distributions of genotypes of the two variants between the cases and controls. Hardy-Weinberg equilibrium was tested by a goodness-of-fit $\chi^2$ tests to compare the observed genotype frequencies to the expected ones among the control subjects. The associations between IL-23R SNPs and AML risks were estimated by computing the odds ratio (ORs) and their 95% confidence intervals (CIs) from both univariate and multivariate logistic regression analysis. Homogeneity test among different strata according to selected variables was assessed with the $\chi^2$-based Q tests. All the statistical analyses were performed with SAS 9.1.3 software (SAS Institute, Cary, NC). $P<0.05$ was the criterion of statistical significance, and all statistical tests were two sided.

Author Contributions

Conceived and designed the experiments: YFS ZBH. Performed the experiments: SYC GHY YP CYC XC Y. Zhu Y. Zhuang. Analyzed the data: XFO SYC YP. Contributed reagents/materials/analysis tools: XFQ SYC. Wrote the paper: XFQ SYC.

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