Genetic polymorphisms of CYP1A1 and risk of leukemia: a meta-analysis

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Abstract: The associations between CYP1A1 polymorphisms and risk of leukemia have been studied extensively, but the results have been inconsistent. Therefore, in this study, we performed a meta-analysis to clarify associations of three CYP1A1 polymorphisms (T3801C, A2455G, and C4887A) with the risks of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). Medline, EMBASE, and China National Knowledge Infrastructure databases were searched to collect relevant studies published up to April 20, 2015. The extracted data were analyzed statistically, and pooled odds ratios with 95% confidence intervals were calculated to quantify the associations. Overall, 26 publications were included. Finally, T3801C was associated with an increased risk of AML in Asians under the dominant model. For A2455G, the risk of ALL was increased among Caucasians in the recessive model and the allele-contrast model; A2455G was also associated with an increased risk of CML among Caucasians under the recessive model, dominant model, and allele-contrast model. For C4887A, few of the included studies produced data. In conclusion, the results suggest that Asians carrying the T3801C C allele might have an increased risk of AML and that Caucasians with the A2455G GG genotype might have an increased risk of ALL. Further investigations are needed to confirm these associations.

Keywords: CYP1A1, ALL, AML, CML, polymorphism

Background
Leukemia is a malignant tumor of the hematopoietic system.1 There are four common types of leukemia: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphoblastic leukemia, and chronic myeloid leukemia (CML). Environmental exposures and genetic susceptibility play roles in the etiology of leukemia.2 For environmental exposures, benzene, ionizing radiation, and cytotoxic therapy are some of the proposed causes of acute leukemia; for genetic susceptibility, the most common type is the single nucleotide polymorphism (SNP) that consists of a variation at a single base pair. Depending on where it is located, SNPs can interfere with a gene’s function, affecting metabolic pathways and further affecting the course of the disease and its progress. SNPs in xenobiotic system, DNA repair system, and cell regulation have been identified as risk factors in childhood leukemia.3,4

CYP1A1 and leukemia
Cytochrome P450 (CYP) enzyme catalyzes the phase I metabolism reaction. The CYP1A1 gene (CYP1A1) is a member of the CYP family that participates in the metabolism of xenobiotics and endogenous compounds, particularly polycyclic aromatic hydrocarbons such as benzo[a]pyrene.5 Genetic polymorphisms have been reported for CYP1A1 that may alter the function of enzyme and thus influence the ability of enzymes to metabolize the chemical carcinogens and mutagens,6,7 which
may influence how susceptible individuals are to contracting leukemia.8

**SNPs in CYP1A1**

The most commonly studied SNP in *CYP1A1* is the T3801C polymorphism (also referred to as *CYP1A1*+2A, m1, or rs4646903). This SNP was localized to chromosome 15q22 and is characterized by a T to C mutation at nucleotide 3,801 in the 3′-flanking region of *CYP1A1*. Some studies have indicated that the T3801C polymorphism can alter the level of gene expression or the stability of messenger RNA (mRNA), resulting in the enzyme exhibiting highly inducible activity.10 Another common genetic mutant site is A2455G (also referred to as *CYP1A1*+2C, m2 allele, or rs1048943), which has been widely examined with regard to cancer susceptibility.11-13 This SNP is characterized by an A to G mutation at nucleotide 2,455 in the region of *CYP1A1*.14 The C4887A mutation (*CYP1A1*+4 allele) is also an important mutant site, which results in the replacement of Thr by Asn in codon 461, near the site of the A2455G mutation.15 Previous research has shown that this polymorphism can alter the level of gene expression or the stability of mRNA, resulting in the enzyme exhibiting highly inducible activity. In other words, certain variant genotypes of *CYP1A1* that change the enzymatic activity appear to crucially influence the risk of leukemia.16

**Aim of this study**

Previous studies of the relationships between *CYP1A1* polymorphisms and risk of leukemia have generated controversial results, and so whether *CYP1A1* polymorphisms are a risk factor for leukemia remains uncertain. In this study, we performed a quantitative meta-analysis with the aim of generating more reliable results by applying an analysis with greater statistical power.

**Materials and methods**

**Search strategy**

We searched Medline (PubMed), EMBASE, and CNKI (China National Knowledge Infrastructure) databases for publications written in English or Chinese up to April 20, 2015. The search was based on the following Boolean combination of keywords: “*CYP1A1*” (“Cytochrome P450 1A1”) AND (“ALL” (“acute lymphocytic leukemia” OR “acute lymphoblastic leukemia”) OR “AML” (“acute myeloid leukemia” OR “acute myeloblastic leukemia” OR “acute myelocytic leukemia”) OR “CML” (“chronic myeloid leukemia” OR “chronic myeloblastic leukemia”) OR “leukemia” (“leucocythemia”)). All searched studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were searched manually to find additional eligible studies.

**Inclusion criteria**

Published studies were included if they fulfilled the following criteria:
1) Use of a case-control design.
2) Providing sufficient data on the distribution of *CYP1A1* polymorphisms in leukemia and in controls or sufficient information for such data to be calculated.
3) Focusing on the associations between *CYP1A1* polymorphisms and the risk of AML, ALL, and/or CML.

**Data extraction**

Two investigators independently carried out an eligibility evaluation and data abstraction for each potentially eligible study. Any disagreements were further discussed and resolved by consensus. The following data were abstracted from each of the included studies: name of the first author, year of publication, race distribution of the study population, genotype distributions of the cases and controls, and numbers of cases and controls. We also checked that the distribution of the genotypes in controls conformed with Hardy–Weinberg equilibrium (HWE).

**Statistical analysis**

The meta-analysis examined the overall associations under the recessive model (CC versus TT for T3801C, GG versus AG + AA for A2455G, and CC versus AC + AA for C4887A), the dominant model (CC + TC versus TT for T3801C, GG + AG versus AA for A2455G, and CA + AA versus CC for C4887A), and the allele-contrast model (C allele versus T allele for T3801C, G allele versus A allele for A2455G, and A allele versus C for C4887A).

The raw data for genotype distribution were used to calculate the study-specific estimates of odds ratio (OR) and 95% confidence interval (CI). Review Manager (version 5.3) software (The Nordic Cochrane Centre, Copenhagen, Denmark) was used to implement the meta-analysis. The presence of heterogeneity was assessed using Cochran’s *Q* statistic and quantified using the *I²* statistic, where a value above 50% indicates the presence of a very high degree of heterogeneity.17

ORs and 95% CIs were calculated using the Z-test to assess the associations between the *CYP1A1* SNPs and risk of leukemia. The threshold for statistical significance was
set at $P<0.05$. The fixed effects model was used when no significant clinical or statistical heterogeneity was present ($I^2\leq50\%$), whereas the random effects model was used when there was substantial heterogeneity ($I^2>50\%$).

When substantial heterogeneity was present, sensitivity analysis was performed by excluding individual studies; outlying studies were identified and excluded, and the $I^2$ estimates for these different sets of studies were examined.

Potential publication bias was estimated by constructing funnel plots. If most of the data appeared at the top of a funnel plot and were distributed approximately symmetrically, this was considered to indicate the absence of obvious publication bias and vice versa. Funnel plots were not constructed when there were too few analyzed studies.

Results
Overview of the characteristics of the included studies

The flow chart for the study selection process is depicted in Figure 1. We selected 217 articles identified by the Boolean combination of the 5 keywords listed in the “Search strategy” section. Checking for duplicates resulted in the removal of 118 articles. Of the remaining 99 articles, 45 did not report studies of the associations between $CYP1A1$ SNPs and leukemia, 6 did not focus on leukemia, 10 were review articles, and 11 did not provide enough data, and so all of these articles were also discarded. Moreover, the genotypes in controls did not conform with HWE in the study of Chen et al. Therefore, ultimately only 26 studies related to the

Figure 1 Flow chart of study selection.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism.
relationships between \textit{CYP1A1} SNPs and the risk of leukemia remained in this meta-analysis, among which 13, 5, and 2 related to ALL, AML, and CML, respectively, 5 articles related to both ALL and AML, and 1 article related to all three disease types.

\textbf{Study characteristics}

The basic data of the 26 articles included in the meta-analysis were extracted and are listed in Table 1. In the study of Majumdar et al,\textsuperscript{21} the distributions of the A2455G and C4887A genotypes in controls did not conform with HWE (although the T3801C genotypes did), and so this study was excluded when we analyzed the roles of the \textit{CYP1A1} A2455G and C4887A polymorphisms. Overall, the meta-analysis included the following studies:

1) Three studies involving 272 cases and 402 controls related to the role of the A2455G polymorphism in the risk of CML.
2) Four studies involving 846 cases and 2,201 controls related to the role of the A2455G polymorphism in the risk of AML.
3) Ten studies involving 1,330 cases and 3,688 controls related to the role of the T3801C polymorphism in the risk of AML.
4) One study involving 193 cases and 273 controls related to the role of the C4887A polymorphism in the risk of AML.

\begin{table}[h]
\centering
\caption{Study characteristics}
\begin{tabular}{|l|l|l|l|l|l|}
\hline
Study & Ethnicity & Cases & SNP & Number of cases & Number of controls & $P_{\text{HWE}}$ in controls \\
\hline
Agha et al\textsuperscript{29} & Caucasian & ALL & T3801C, C4887A & 186 & 200 & 0.0577 \\
Aydin-Sayitoglu et al\textsuperscript{30} & Caucasian & ALL & T3801C & 249 & 140 & 0.3057 \\
Bolufer et al\textsuperscript{31} & Caucasian & ALL & T3801C & 443 & 454 & 0.151 \\
Bonaventure et al\textsuperscript{32} & Caucasian & ALL & T3801C & 493 & 549 & 0.2309 \\
Krajnovic et al\textsuperscript{37} & Caucasian & ALL & T3801C & 177 & 304 & 0.3941 \\
Ouerhani et al\textsuperscript{33} & Caucasian & ALL & T3801C & 100 & 106 & 0.5731 \\
Swinney et al\textsuperscript{12} & Caucasian & ALL & T3801C, A2455G & 258 & 646 & 0.1272 \\
Yamaguti et al\textsuperscript{13} & Caucasian & ALL & T3801C & 99 & 99 & 0.9485 \\
Selvin et al\textsuperscript{40} & Caucasian & ALL & T3801C & 175 & 175 & 0.9347 \\
Gao et al\textsuperscript{34} & Asian & ALL & T3801C & 78 & 112 & 0.1723 \\
Joseph et al\textsuperscript{35} & Asian & ALL & T3801C & 118 & 118 & 0.5939 \\
Lee et al\textsuperscript{36} & Asian & ALL & T3801C & 164 & 164 & 0.4015 \\
Suneetha et al\textsuperscript{37} & Asian & ALL & T3801C & 92 & 150 & 0.806 \\
Balta et al\textsuperscript{48} & Mixed & ALL & T3801C & 144 & 185 & 0.9097 \\
Canalle et al\textsuperscript{39} & Mixed & ALL & T3801C & 113 & 221 & 0.083 \\
Clavel et al\textsuperscript{49} & Mixed & ALL & T3801C & 219 & 105 & 0.081 \\
Galgos-Arreola et al\textsuperscript{50} & Mixed & ALL & T3801C & 210 & 228 & 0.7728 \\
Razmkhah et al\textsuperscript{51} & Mixed & ALL & A2455G & 85 & 94 & 0.4353 \\
Galgos-Arreola et al\textsuperscript{52} & Mixed & ALL & A2455G & 136 & 136 & 0.315 \\
D’Alo et al\textsuperscript{44} & Caucasian & AML & T3801C & 193 & 273 & 0.1604 \\
Jiang et al\textsuperscript{45} & Asian & AML & T3801C & 98 & 120 & 0.0527 \\
Kim et al\textsuperscript{46} & Asian & AML & T3801C & 415 & 1,700 & 0.7257 \\
Majumdar et al\textsuperscript{53} & Asian & AML & T3801C & 110 & 126 & 0.9415 \\
Yamaguti et al\textsuperscript{13} & Asian & AML & T3801C & 133 & 133 & 0.3451 \\
Al-Achkar et al\textsuperscript{54} & Caucasian & CML & A2455G & 126 & 172 & 0.3253 \\
Taspinar et al\textsuperscript{55} & Caucasian & CML & A2455G & 107 & 135 & 0.5889 \\
\hline
\end{tabular}
\end{table}

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; $P_{\text{HWE}}$, probability of adherence to the Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism.
5) Eight studies involving 1,734 cases and 2,194 controls related to the role of the A2455G polymorphism in the risk of ALL.
6) Sixteen studies involving 2,299 cases and 3,209 controls related to the role of the T3801C polymorphism in the risk of ALL.
7) One study involving 177 cases and 295 controls related to the role of the C4887A polymorphism in the risk of ALL.

Meta-analysis results
The main results of the meta-analysis are listed in Table 2.

Table 2 ORs and heterogeneity results for CYP1A1 meta-analysis

| SNP   | Cancer | Ethnicity | n   | Genetic model | I²   | Contrast model | P    | ORs (95% CIs) |
|-------|--------|-----------|-----|---------------|------|----------------|------|---------------|
|       |        |           |     |               |      |                |      |               |
| T3801C| ALL    | Caucasian | 8   | Recessive      | 26%  | Fixed effects  | 0.28 | 1.31 (0.81, 2.12) |
|       |        |           |     | Dominant       | 61%  | Random effects | 0.10 | 1.30 (0.95, 1.79) |
|       |        |           |     | Allele contrast | 32%  | Fixed effects  | 0.05 | 1.18 (1.00, 1.39) |
|       |        | Asian     | 4   | Recessive      | 63%  | Random effects | 0.73 | 1.14 (0.54, 2.39) |
|       |        |           |     | Dominant       | 68%  | Random effects | 0.06 | 1.64 (0.98, 2.73) |
|       |        |           |     | Allele contrast | 80%  | Random effects | 0.19 | 1.35 (0.86, 2.14) |
|       |        | Mix       | 4   | Recessive      | 76%  | Random effects | 0.21 | 2.68 (0.57, 12.62) |
|       |        |           |     | Dominant       | 82%  | Random effects | 0.32 | 1.34 (0.75, 2.39) |
|       |        |           |     | Allele contrast | 92%  | Random effects | 0.34 | 1.42 (0.69, 2.91) |
| A2455G| ALL    | Caucasian | 4   | Recessive      | 0%   | Fixed effects  | 0.002 | 2.23 (1.36, 3.68) |
|       |        |           |     | Dominant       | 39%  | Fixed effects  | 0.12 | 1.22 (0.95, 1.58) |
|       |        |           |     | Allele contrast | 41%  | Fixed effects  | 0.010 | 1.31 (1.00, 1.39) |
|       |        | Asian     | 3   | Recessive      | 11%  | Fixed effects  | 0.14 | 1.57 (0.87, 2.83) |
|       |        |           |     | Dominant       | 72%  | Random effects | 0.29 | 1.40 (0.76, 2.59) |
|       |        |           |     | Allele contrast | 0%   | Fixed effects  | 0.89 | 1.02 (0.80, 1.29) |
|       |        | Mix       | 1   | Recessive      | 0%   | Fixed effects  | 0.94 | 1.03 (0.45, 2.34) |
|       |        |           |     | Dominant       | 0%   | Fixed effects  | 0.94 | 1.03 (0.47, 2.26) |
|       |        |           |     | Allele contrast | 0%   | Fixed effects  | 0.22 | 0.65 (0.33, 1.30) |
| C4887A| ALL    | Caucasian | 1   | Recessive      | 0%   | Fixed effects  | 0.26 | 1.74 (0.66, 4.55) |
|       |        |           |     | Dominant       | 0%   | Fixed effects  | 0.16 | 0.82 (0.62, 1.08) |
|       |        |           |     | Allele contrast | 0%   | Fixed effects  | 0.22 | 0.65 (0.33, 1.30) |
| T3801C| AML    | Caucasian | 4   | Recessive      | 0%   | Fixed effects  | 0.26 | 1.74 (0.66, 4.55) |
|       |        |           |     | Dominant       | 47%  | Fixed effects  | 0.16 | 0.82 (0.62, 1.08) |
|       |        |           |     | Allele contrast | 59%  | Random effects | 0.63 | 0.90 (0.59, 1.37) |
|       |        | Asian     | 3   | Recessive      | 0%   | Fixed effects  | 0.60 | 0.93 (0.71, 1.22) |
|       |        |           |     | Dominant       | 0%   | Fixed effects  | 0.03 | 1.26 (1.02, 1.55) |
|       |        |           |     | Allele contrast | 0%   | Fixed effects  | 0.23 | 1.09 (0.95, 1.26) |
| Mix   | AML    | Caucasian | 4   | Recessive      | 0%   | Fixed effects  | 0.72 | 1.19 (0.46, 3.05) |
|       |        |           |     | Dominant       | 74%  | Random effects | 0.65 | 1.24 (0.48, 3.22) |
|       |        |           |     | Allele contrast | 72%  | Random effects | 0.81 | 1.11 (0.48, 2.55) |
| A2455G| AML    | Caucasian | 1   | Recessive      | 0%   | Fixed effects  | 0.47 | 0.78 (0.39, 1.53) |
|       |        |           |     | Dominant       | 48%  | Fixed effects  | 0.48 | 0.78 (0.40, 1.53) |
|       |        |           |     | Allele contrast | 39%  | Fixed effects  | 0.39 | 0.79 (0.47, 1.35) |
|       |        | Asian     | 1   | Recessive      | 0%   | Fixed effects  | 0.50 | 1.64 (0.39, 6.92) |
|       |        |           |     | Dominant       | 0%   | Fixed effects  | 0.0009 | 1.96 (1.32, 2.90) |
|       |        |           |     | Allele contrast | 0%   | Fixed effects  | 0.002 | 1.72 (1.22, 2.43) |
| C4887A| AML    | Caucasian | 1   | Recessive      | 0%   | Fixed effects  | 0.39 | 2.85 (0.26, 31.63) |
|       |        |           |     | Dominant       | 0%   | Fixed effects  | 0.005 | 2.16 (1.27, 3.69) |
|       |        |           |     | Allele contrast | 0%   | Fixed effects  | 0.004 | 2.08 (1.26, 3.44) |
| A2455G| CML    | Caucasian | 2   | Recessive      | 17%  | Fixed effects  | 0.004 | 19.61 (2.62, 146.76) |
|       |        |           |     | Dominant       | 69%  | Random effects | 0.0010 | 3.93 (1.74, 8.87) |
|       |        |           |     | Allele contrast | 1%   | Fixed effects  | 0.000001 | 3.92 (2.61, 5.90) |
| Mix   | AML    | Caucasian | 1   | Recessive      | 0%   | Fixed effects  | 0.89 | 0.80 (0.03, 20.00) |
|       |        |           |     | Dominant       | 0%   | Fixed effects  | 0.79 | 0.88 (0.34, 2.29) |
|       |        |           |     | Allele contrast | 0%   | Fixed effects  | 0.70 | 0.84 (0.34, 2.07) |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CML, chronic myeloid leukemia; OR, odds ratio; SNP, single nucleotide polymorphism.
CYP1A1 T3801C was not associated with ALL risk in Caucasians or Asians

In the meta-analysis of 16 studies that involved data from 2,299 cases and 3,209 controls and investigated the effect of the T3801C polymorphism on the risk of ALL, a high degree of heterogeneity was observed under the recessive model ($I^2=76\%$, $P=0.00001$), dominant model ($I^2=68\%$, $P<0.00001$), and allele-contrast model ($I^2=80\%$, $P<0.00001$). A sensitivity analysis was conducted since $I^2$ exceeded 50% for all three models. However, removing any particular article from the analysis did not reduce the degree of heterogeneity, and so the random effects model was used. This identified an association between the T3801C SNP and the risk of ALL under any contrast model ($P=0.002$, OR $=2.23$, 95% CI $=1.36–3.68$) and the allele-contrast model ($P=0.010$, OR $=1.31$, 95% CI $=1.07–1.61$), but not under the dominant model ($P=0.12$, OR $=1.22$, 95% CI $=0.95–1.58$) (Figure 3).

CYP1A1 C4887A was not associated with ALL risk in Caucasians

In the meta-analysis of the single study that involved 177 cases and 295 controls (all of whom were Caucasians) and investigated the effect of the C4887A polymorphism on the risk of ALL, no association was found between the CYP1A1 C4887A SNP and the risk of ALL under any contrast model when using the fixed effects model.

CYP1A1 T3801C was associated with AML risk in Asians

In the meta-analysis of ten studies that involved 1,330 cases and 3,688 controls and investigated the effect of the T3801C polymorphism on the risk of AML, a high degree of heterogeneity was observed under the recessive model ($I^2=62\%$, $P=0.010$), dominant model ($I^2=65\%$, $P=0.002$), and allele-contrast model ($I^2=72\%$, $P=0.0002$). A sensitivity analysis was therefore conducted, which revealed that the study of Majumdar et al\textsuperscript{11} was an outlier. Removing their data from the analysis reduced the degree of heterogeneity. Under the allele-contrast model, the degree of heterogeneity was still high, and so a random effects model was applied. No association was found between the T3801C SNP and the risk of AML under the recessive model ($P=0.91$, OR $=0.98$, 95% CI $=0.76–1.27$), the dominant model ($P=0.07$, OR $=1.15$, 95% CI $=0.99–1.34$), or the allele-contrast model ($P=0.71$, OR $=1.05$, 95% CI $=0.82–1.34$). The funnel plot did not reveal any obvious publication bias.

However, in subgroup analysis according to race, the risk was increased among Asians under the dominant model ($P=0.03$, OR $=1.26$, 95% CI $=1.02–1.55$), but not under the recessive model ($P=0.60$, OR $=0.93$, 95% CI $=0.71–1.22$) or the allele-contrast model ($P=0.23$, OR $=1.09$, 95% CI $=0.95–1.26$) (Figure 4).

CYP1A1 A2455G was not associated with AML risk in Caucasians or Asians

The meta-analysis of four studies that involved 846 patients and 2,201 controls – one study involved Caucasians, one study involved Asians, and two studies involved mixed races – found no association between the A2455G SNP and the risk of AML under any contrast model.

CYP1A1 A2455G was associated with ALL risk in Caucasians

In the meta-analysis of eight studies that involved the data from 1,734 patients and 2,194 controls and investigated the effect of the A2455G polymorphism on the risk of ALL, the forest plot revealed no heterogeneity under the recessive model ($I^2=0\%$, $P=0.49$), dominant model ($I^2=44\%$, $P=0.09$), and allele-contrast model ($I^2=20\%$, $P=0.27$). The fixed effects model was therefore used for these three contrast models, which revealed an association between the A2455G polymorphism and the risk of ALL under the recessive model ($P=0.0007$, OR $=1.93$, 95% CI $=1.32–2.82$), the dominant model ($P=0.02$, OR $=1.25$, 95% CI $=1.03–1.52$), and the allele-contrast model ($P=0.04$, OR $=1.17$, 95% CI $=1.01–1.36$). The funnel plot did not reveal any obvious publication bias.
A

| Study or subgroup | ALL Events Total | Control Events Total | Weight | OR M-H, random, 95% CI | OR M-H, random, 95% CI |
|------------------|------------------|---------------------|--------|------------------------|------------------------|
| Caucasian        |                 |                     |        |                        |                        |
| Agha et al[29]   | 3 186 2         | 200                 | 5.6%   | 1.62 (0.27, 9.82)      |                        |
| Aydin-Sayitoglu et al[30] | 1 155 4 | 140                 | 4.6%   | 0.22 (0.02, 2.00)      |                        |
| Bolufer et al[2] | 0 92 2         | 403                 | 3.0%   | 0.87 (0.04, 18.23)     |                        |
| Bonaventure et al[22] | 5 430 7 | 548                 | 7.6%   | 0.91 (0.29, 2.88)      |                        |
| Krajnovic et al[27] | 1 170 2 | 299                 | 4.1%   | 0.88 (0.08, 9.76)      |                        |
| Ouerhani et al[23] | 2 100 0 | 106                 | 3.0%   | 5.41 (0.26, 114.00)    |                        |
| Swinney et al[22] | 15 60 19       | 173                 | 8.8%   | 2.70 (1.27, 5.74)      |                        |
| Yanimuku et al[13] | 3 99 6       | 99                  | 6.7%   | 0.48 (0.12, 1.99)      |                        |
| Subtotal (95% CI) | 1,292          | 1,968               | 43.4%  | 1.19 (0.61, 2.30)      |                        |
| Total events     | 30              | 42                  |        |                        |                        |
| Heterogeneity: $r^2=0.22; \chi^2=9.40, df=7 (P=0.23); I^2=26\%$ | Test for overall effect: $Z=0.51 (P=0.61)$ |
| Asian            |                 |                     |        |                        |                        |
| Gao et al[34]    | 15 78 15       | 112                 | 8.8%   | 1.54 (0.70, 3.37)      |                        |
| Joseph et al[32] | 9 118 2        | 118                 | 6.3%   | 4.79 (1.01, 22.66)     |                        |
| Lee et al[32]    | 12 102 32      | 162                 | 9.0%   | 0.54 (0.26, 1.11)      |                        |
| Suneetha et al[31] | 9 91 17       | 150                 | 8.5%   | 0.86 (0.37, 2.02)      |                        |
| Subtotal (95% CI) | 389            | 542                 | 32.5%  | 1.14 (0.54, 2.39)      |                        |
| Total events     | 45              | 66                  |        |                        |                        |
| Heterogeneity: $r^2=0.35; \chi^2=8.02, df=3 (P=0.05); I^2=63\%$ | Test for overall effect: $Z=0.34 (P=0.73)$ |
| Mixed            |                 |                     |        |                        |                        |
| Balta et al[30]  | 1 105 7        | 145                 | 4.8%   | 0.19 (0.02, 1.56)      |                        |
| Canaile et al[30] | 6 113 3       | 221                 | 6.8%   | 4.07 (1.00, 16.61)     |                        |
| Clavel et al[30] | 3 190 0        | 105                 | 3.1%   | 3.94 (0.20, 76.99)     |                        |
| Gallegos-Arreola et al[31] | 88 210 18 | 228                 | 9.4%   | 8.42 (4.84, 14.64)     |                        |
| Subtotal (95% CI) | 618            | 699                 | 24.0%  | 2.68 (0.57, 12.62)     |                        |
| Total events     | 98              | 28                  |        |                        |                        |
| Heterogeneity: $r^2=1.72; \chi^2=12.50, df=3 (P=0.006); I^2=76\%$ | Test for overall effect: $Z=1.25 (P=0.21)$ |
| Total (95% CI)   | 2,299           | 3,209               | 100.0% | 1.43 (0.76, 2.70)      |                        |
| Total events     | 173             | 136                 |        |                        |                        |
| Heterogeneity: $r^2=1.04; \chi^2=61.24, df=15 (P=0.00001); I^2=76\%$ | Test for overall effect: $Z=1.11 (P=0.27)$ |
| Test for subgroup differences: $\chi^2=1.01, df=2 (P=0.60); I^2=0\%$ | |

Figure 2 (Continued)
Figure 2 (Continued)
### Study or subgroup

|                  | ALL | Control |
|------------------|-----|---------|
|                  | Events | Total | Events | Total |

**Caucasian**

- Agha et al<sup>29</sup> 23 372 22 400 5.4% 1.13 (0.62, 2.07)
- Aydin-Saydoglu et al<sup>30</sup> 48 310 38 280 6.3% 1.17 (0.74, 1.85)
- Boulfer et al<sup>31</sup> 13 184 86 806 5.4% 0.62 (0.34, 1.14)
- Bonaventure et al<sup>32</sup> 85 860 101 1,096 7.2% 1.08 (0.80, 1.46)
- Krajnovic et al<sup>33</sup> 34 340 37 598 6.1% 1.68 (1.04, 2.74)
- Ouerhani et al<sup>34</sup> 22 200 11 212 4.6% 2.26 (1.07, 4.79)
- Swinnen et al<sup>35</sup> 54 120 128 346 6.5% 1.39 (0.91, 2.12)
- Yamaguchi et al<sup>36</sup> 41 198 39 198 6.1% 1.06 (0.65, 1.74)

**Subtotal (95% CI)** 2,584 3,936 47.8% 1.29 (0.97, 1.74)

**Total events** 320 464

Heterogeneity: $I^2=0.03$, $\chi^2=10.37$, $df=7$ ($P=0.17$); $P=32$

Test for overall effect: $Z=1.71$ ($P=0.09$)

**Asian**

- Gao et al<sup>37</sup> 80 156 91 224 6.6% 1.54 (1.02, 2.32)
- Joseph et al<sup>38</sup> 59 236 26 236 6.0% 2.69 (1.63, 4.45)
- Lee et al<sup>39</sup> 80 204 138 324 6.8% 0.87 (0.61, 1.24)
- Suneetha et al<sup>40</sup> 61 182 99 300 6.7% 1.02 (0.69, 1.51)

**Subtotal (95% CI)** 778 1,084 26.3% 1.35 (0.86, 2.14)

**Total events** 280 354

Heterogeneity: $I^2=0.17$, $\chi^2=14.90$, $df=3$ ($P=0.002$); $P=80$

Test for overall effect: $Z=1.30$ ($P=0.19$)

**Mixed**

- Baltas et al<sup>41</sup> 35 210 49 290 6.2% 0.98 (0.61, 1.58)
- Canalie et al<sup>42</sup> 46 226 77 442 6.6% 1.21 (0.81, 1.82)
- Gavel et al<sup>43</sup> 40 380 24 210 5.8% 0.91 (0.53, 1.56)
- Gallegos-Arreola et al<sup>44</sup> 238 420 125 456 7.3% 3.46 (2.61, 4.59)

**Subtotal (95% CI)** 1,236 1,398 26.0% 1.42 (0.89, 2.91)

**Total events** 359 275

Heterogeneity: $I^2=0.49$, $\chi^2=36.59$, $df=3$ ($P=0.00001$); $P=92$

Test for overall effect: $Z=0.96$ ($P=0.34$)

**Total (95% CI)** 4,598 6,418 100% 1.31 (1.02, 1.67)

**Total events** 959 1,093

Heterogeneity: $I^2=0.19$, $\chi^2=74.71$, $df=15$ ($P=0.00001$); $P=80$

Test for overall effect: $Z=2.15$ ($P=0.03$)

Test for subgroup differences: $\chi^2=0.38$, $df=2$ ($P=0.83$); $P=0$

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**Figure 2** Meta-analysis of the association between *CYP1A1* T3801C gene polymorphism and ALL risk under three models: (A) recessive, (B) dominant, and (C) allele contrast.

**Abbreviations:** ALL acute lymphoblastic leukemia; CI, confidence interval; M–H, Mantel-Haenszel type; OR, odds ratio; SE, standard error.
### Figure 3

Meta-analysis of the association between CYP1A1 A2455G gene polymorphism and ALL risk under three models: (A) recessive, (B) dominant, and (C) allele contrast.

**Abbreviations:** CML, chronic myeloid leukemia; CI, confidence interval; M–H, Mantel–Haenszel type; OR, odds ratio; ALL, acute lymphoblastic leukemia.

#### A: Recessive Model

| Study or subgroup | CML | Control | Weight | OR M–H, fixed, 95% CI | OR M–H, fixed, 95% CI |
|------------------|-----|---------|--------|----------------------|----------------------|
| Caucasian        |     |         |        |                      |                      |
| Al-Achkar et al[1] | 12  | 126     | 0      | 172                  | 22.6%                |
| Taspin et al[2] | 1   | 107     | 0      | 135                  | 25.8%                |
| Subtotal (95% CI) | 233 | 307     | 48.4%  | 18.61 (2.62, 146.76) |                      |
| Total events     | 13  | 0       |        |                      |                      |
| Heterogeneity    | χ²=1.20, df=1 (P=0.27); I²=17% |
| Test for overall effect: Z=2.90 (P=0.004) |                      |

| Mixed            |     |         |        |                      |                      |
| Subtotal (95% CI) | 39  | 95      | 51.6%  | 0.80 (0.03, 20.00)   |                      |
| Total events     | 0   | 1       |        |                      |                      |
| Heterogeneity    | Not applicable                        |
| Test for overall effect: Z=0.14 (P=0.99) |                      |

#### B: Dominant Model

| Study or subgroup | CML | Control | Weight | OR M–H, random, 95% CI | OR M–H, random, 95% CI |
|------------------|-----|---------|--------|------------------------|------------------------|
| Caucasian        |     |         |        |                        |                        |
| Al-Achkar et al[1] | 38  | 126     | 24     | 172                    | 36.4%                  |
| Taspin et al[2] | 40  | 107     | 12     | 135                    | 34.1%                  |
| Subtotal (95% CI) | 233 | 307     | 70.5%  | 3.93 (1.74, 8.87)      |                        |
| Total events     | 78  | 36      |        |                        |                        |
| Heterogeneity    | χ²=0.24, df=1 (P=0.67); I²=69% |
| Test for overall effect: Z=3.29 (P=0.0010) |                        |

| Mixed            |     |         |        |                        |                        |
| Subtotal (95% CI) | 7   | 39      | 95     | 29.5%                 | 0.88 (0.34, 2.29)      |
| Total events     | 7   | 19      |        |                        |                        |
| Heterogeneity    | Not applicable                        |
| Test for overall effect: Z=2.07 (P=0.09) |                        |

#### C: Allele Contrast Model

| Study or subgroup | CML | Control | Weight | OR M–H, random, 95% CI | OR M–H, random, 95% CI |
|------------------|-----|---------|--------|------------------------|------------------------|
| Caucasian        |     |         |        |                        |                        |
| Al-Achkar et al[1] | 50  | 252     | 24     | 344                    | 36.8%                  |
| Taspin et al[2] | 41  | 214     | 12     | 270                    | 33.9%                  |
| Subtotal (95% CI) | 466 | 614     | 70.7%  | 3.88 (2.57, 5.86)      |                        |
| Total events     | 91  | 36      |        |                        |                        |
| Heterogeneity    | χ²=0.00, df=1 (P=0.31); I²=1% |
| Test for overall effect: Z=6.45 (P<0.00001) |                        |

| Mixed            |     |         |        |                        |                        |
| Subtotal (95% CI) | 7   | 78      | 20     | 190                    | 29.3%                  |
| Total events     | 7   | 20      |        |                        |                        |
| Heterogeneity    | Not applicable                        |
| Test for overall effect: Z=0.38 (P=0.70) |                        |

| Total (95% CI)   | 544 | 804     | 100%   | 2.56 (1.05, 6.23)      |                        |
| Total events     | 98  | 56      |        |                        |                        |
| Heterogeneity    | χ²=0.49, df=2 (P=0.50); I²=80% |
| Test for overall effect: Z=2.20 (P=0.04) |                        |
| Test for subgroup differences: χ²=9.14, df=1 (P=0.002); I²=89.1% |                        |
### A

| Study or subgroup | AML Events | Control Events | Total | Weight | OR M–H, fixed, 95% CI | OR M–H, fixed, 95% CI |
|------------------|------------|----------------|-------|--------|----------------------|----------------------|
| **Caucasian**    |            |                |       |        |                      |                      |
| Aydin-Sayyoglu et al<sup>30</sup> | 5          | 94             | 140   | 2.5%   | 1.91 (0.50, 7.31)    |                      |
| Bolfer et al<sup>33</sup>          | 0          | 199            | 203   | 1.4%   | 0.40 (0.02, 8.42)    |                      |
| Bonaventure et al<sup>32</sup>     | 2          | 50             | 70    | 0.9%   | 3.22 (0.65, 15.93)   |                      |
| D’Alo et al<sup>41</sup>           | 0          | 178            | 178   |        | Not estimable        |                      |
| **Subtotal (95% CI)**              | **521**    |                | 1,359 | 4.8%   | 1.74 (0.66, 4.55)    |                      |
| **Total events**                   | 7          |                | 13    |        |                      |                      |
| Heterogeneity: $\chi^2=1.48$, $df=2$ ($P=0.48$); $I^2=0\%$ | | | | | | |
| Test for overall effect: $Z=1.12$ ($P=0.26$) | | | | | | |

| **Asian**       |            |                |       |        |                      |                      |
| Jiang et al<sup>28</sup>           | 19         | 98             | 217   | 15.6%  | 0.87 (0.45, 1.69)    |                      |
| Kim et al<sup>26</sup>             | 61         | 415            | 476   | 73.0%  | 0.94 (0.70, 1.27)    |                      |
| Majumdar et al<sup>27</sup>        | 30         | 110            | 140   | 0.0%   | 4.88 (2.20, 10.82)   |                      |
| **Subtotal (95% CI)**              | **513**    |                | 1,820 | 88.6%  | 0.93 (0.71, 1.22)    |                      |
| **Total events**                   | 80         |                | 289   |        |                      |                      |
| Heterogeneity: $\chi^2=0.05$, $df=1$ ($P=0.83$); $I^2=0\%$ | | | | | | |
| Test for overall effect: $Z=0.53$ ($P=0.60$) | | | | | | |

| **Mixed**        |            |                |       |        |                      |                      |
| Baltas et al<sup>30</sup>          | 0          | 26             | 26    | 1.9%   | 0.35 (0.02, 6.29)    |                      |
| Clavel et al<sup>33</sup>           | 0          | 27             | 27    |        | Not estimable        |                      |
| Yamaguchi et al<sup>32</sup>       | 9          | 133            | 142   | 4.6%   | 1.54 (0.53, 4.44)    |                      |
| **Subtotal (95% CI)**              | **186**    |                | 383   | 6.5%   | 1.19 (0.46, 3.05)    |                      |
| **Total events**                   | 9          |                | 13    |        |                      |                      |
| Heterogeneity: $\chi^2=0.91$, $df=1$ ($P=0.34$); $I^2=0\%$ | | | | | | |
| Test for overall effect: $Z=0.36$ ($P=0.72$) | | | | | | |

**Figure 4 (Continued)**
## B

| Study or subgroup | AML Events | Control Events | Weight | OR M−H, fixed, 95% CI |
|-------------------|------------|----------------|--------|----------------------|
| **Caucasian**     |            |                |        |                      |
| Aydin-Saytioglu et al\(^\text{a}\) | 29         | 94             | 34     | 140                  |
| Bolufet et al\(^\text{a}\) | 31         | 199            | 86     | 403                  |
| Bonaventure et al\(^\text{a}\) | 9          | 50             | 94     | 548                  |
| D’Alo et al\(^\text{a}\) | 17         | 178            | 42     | 268                  |
| Subtotal (95% CI) | 521        |                |        | 1,359 36.4%          |
| **Asian**         |            |                |        |                      |
| Jang et al\(^\text{a}\) | 69         | 98             | 76     | 120                  |
| Kim et al\(^\text{a}\) | 280        | 415            | 1,064  | 1,700 44.9%          |
| Majumder et al\(^\text{a}\) | 69         | 110            | 60     | 126                  |
| Subtotal (95% CI) | 513        |                |        | 1,820 51.6%          |
| **Mixed**         |            |                |        |                      |
| Balata et al\(^\text{a}\) | 6          | 26             | 42     | 145                  |
| Olave et al\(^\text{a}\) | 5          | 27             | 24     | 105                  |
| Yamaguti et al\(^\text{a}\) | 68         | 133            | 38     | 133                  |
| Subtotal (95% CI) | 186        |                |        | 383 12.0%            |
| Total (95% CI)    | 1,220      | 3,562          | 100%   | 1.15 (0.99, 1.34)    |

Heterogeneity: \(\chi^2=5.70, df=3 (P=0.13); I^2=47\%

Test for overall effect: \(Z=1.42 (P=0.16)\)

Heterogeneity: \(\chi^2=0.11, df=1 (P=0.74); I^2=0\%

Test for overall effect: \(Z=2.12 (P=0.03)\)

Heterogeneity: \(\chi^2=7.69, df=2 (P=0.02); I^2=74\%

Test for overall effect: \(Z=2.63 (P=0.009)\)

Heterogeneity: \(\chi^2=23.22, df=8 (P=0.003); I^2=66\%

Test for overall effect: \(Z=1.78 (P=0.07)\)

Test for subgroup differences: \(\chi^2=10.17, df=2 (P=0.006); I^2=80.3\%

Figure 4 (Continued)
CYP1A1 Polymorphisms and Leukemia

| Study or subgroup | AML Events | Control Events | Weight OR | OR M–H, random, 95% CI |
|-------------------|------------|----------------|-------------|-------------------------|
| **Caucasian**     |            |                |             |                         |
| Aydin-Sayitoglu et al. | 34         | 188            | 38          | 280                     | 11.3% | 1.41 (0.85, 2.33) |
| Bolufer et al.    | 31         | 398            | 88          | 806                     | 13.0% | 0.69 (0.45, 1.06) |
| Bonaventure et al. | 11         | 100            | 101         | 1,096                   | 8.4%  | 1.22 (0.63, 2.35) |
| D’Alò et al.      | 17         | 356            | 42          | 536                     | 9.8%  | 0.59 (0.33, 1.05) |
| **Subtotal (95% CI)** | **1,042** | 2,718          |             |                         |       | **0.90 (0.59, 1.37)** |
| Total events      | 93         | 269            |             |                         |       |                 |
| Heterogeneity: $\chi^2=0.11, df=3 (P=0.66); I^2=59\%$ Test for overall effect: $Z=0.48 (P=0.63)$ |

| **Asian**         |            |                |             |                         |
| Jang et al.       | 88         | 196            | 102         | 240                     | 14.2% | 1.10 (0.75, 1.61) |
| Kim et al.        | 341        | 830            | 1,327       | 3,400                   | 20.0% | 1.09 (0.93, 1.27) |
| Majumdar et al.   | 99         | 220            | 69          | 252                     | 0.0%  | 2.17 (1.48, 3.18) |
| **Subtotal (95% CI)** | **1,026** | 3,640          |             |                         |       | **1.09 (0.95, 1.26)** |
| Total events      | 429        | 1,429          |             |                         |       |                 |
| Heterogeneity: $\chi^2=0.00, df=1 (P=0.95); I^2=0\%$ Test for overall effect: $Z=1.20 (P=0.23)$ |

| **Mixed**         |            |                |             |                         |
| Bai et al.        | 6          | 52             | 49          | 290                     | 5.5%  | 0.64 (0.26, 1.58) |
| Clavel et al.     | 5          | 54             | 24          | 210                     | 4.6%  | 0.79 (0.29, 2.18) |
| Yamaguchi et al.  | 77         | 266            | 44          | 266                     | 13.3% | 2.06 (1.35, 3.12) |
| **Subtotal (95% CI)** | **372**  | **766**        |             |                         |       | **1.11 (0.48, 2.55)** |
| Total events      | 88         | 117            |             |                         |       |                 |
| Heterogeneity: $\chi^2=0.38, df=2 (P=0.80); I^2=72\%$ Test for overall effect: $Z=0.24 (P=0.81)$ |

| **Total (95% CI)** | **2,440** | **7,124**      | **100\%**   | **1.05 (0.82, 1.34)** |
| Total events      | 610        | 1,815          |             |                         |
| Heterogeneity: $\chi^2=0.07, df=8 (P=0.999); I^2=61\%$ Test for overall effect: $Z=0.37 (P=0.71)$ Test for subgroup differences: $\chi^2=0.72, df=2 (P=0.70); I^2=0\%$ |

**Figure 4** Meta-analysis of the association between CYP1A1 T3801C gene polymorphism and AML risk under three models: (A) recessive, (B) dominant, and (C) allele contrast. **Abbreviations:** AML, acute myeloid leukemia; CI, confidence interval; M–H, Mantel–Haenszel type; OR, odds ratio; SE, standard error.
CYP1A1 C4887A was associated with AML risk in Caucasians

In the meta-analysis of the single study that involved 193 cases and 273 controls (all of whom were Caucasians), when using the fixed effects model there was a significant association between the C4887A SNP and the risk of AML under the dominant model \( (P=0.005, \text{OR} = 2.16, 95\% \text{ CI} = 1.27–3.69) \) and the allele-contrast model \( (P=0.004, \text{OR} = 2.08, 95\% \text{ CI} = 1.26–3.44) \). However, this relationship needs to be confirmed in further studies.

CYP1A1 A2455G was associated with CML risk in Caucasians

In the meta-analysis of the three studies that involved 272 patients and 402 controls and investigated the effect of the A2455G polymorphism on the risk of CML, the forest plot revealed no heterogeneity under the recessive model \( (I^2 = 43\%, \text{P} = 0.17) \), and so the fixed effects model was applied. There was a high degree of heterogeneity under the dominant model \( (I^2 = 81\%, \text{P} = 0.006) \) and the allele-contrast model \( (I^2 = 80\%, \text{P} = 0.006) \), and so a sensitivity analysis was conducted. However, removing any particular study from the analysis did not reduce the degree of heterogeneity, and so the random effects model was used for these two contrast models. An association was found between the A2455G SNP and the risk of CML under the recessive model \( (P=0.001, \text{OR} = 9.91, 95\% \text{ CI} = 2.43–40.36) \) and the allele-contrast model \( (P=0.04, \text{OR} = 2.56, 95\% \text{ CI} = 1.05–6.23) \).

In subgroup analysis according to race, the risk of leukemia was increased in Caucasians under the recessive model \( (P=0.004, \text{OR} = 19.61, 95\% \text{ CI} = 2.62–146.76) \), dominant model \( (P=0.0010, \text{OR} = 3.93, 95\% \text{ CI} = 1.74–8.87) \), and allele-contrast model \( (P<0.00001, \text{OR} = 3.92, 95\% \text{ CI} = 2.61–5.90) \) (Figure 5).

Discussion

This study identified 26 articles describing research into the associations between the CYP1A1 T3801C, CYP1A1 A2455G, and CYP1A1 C4887A polymorphisms and the risks of ALL, AML, and CML. The conclusions drawn using the data obtained in these studies were not consistent. This situation prompted the use of meta-analysis in this study – which is a common method applied in systematic reviews – to integrate these contradictions, and to obtain more accurate results. All of the finally included studies were of high quality and had a rigorous scientific design, accurate data, and clear results. The main conclusion is that the presence of the CYP1A1 T3801C polymorphism increased the risks of AML among Asians, while the CYP1A1 A2455G polymorphism increased the risks of ALL among Caucasians.

Few studies have investigated the CYP1A1 polymorphism as a possible risk factor for CML.\(^2\) The present meta-analysis found an association between the A2455G SNP and the risk of CML among Caucasians. However, this result was based on a relatively small number of cases where the statistical power was weak, and so, this conclusion should be treated with caution. The accumulation of disadvantageous environmental factors might be required to develop chronic disease, and so, investigating environment – genetic interactions – would be meaningful for this kind of chronic disease. Although, in this study, we endeavored to extract relevant information regarding smoking and alcohol consumption from the primary literature, insufficient data were obtained. Further investigations concerning the interactions between smoking, alcohol consumption, and gene variations with CML are required.

This meta-analysis included studying the associations between three SNPs (T3801C, A2455G, and C4887A) and the risk of AML. The results showed that the CYP1A1 T3801C polymorphism might not be significantly correlated with the risk of AML. Possible racial variations in presentation, treatment patterns, and survival with respect to AML might exist,\(^23\) which made subgroup analysis according to race necessary. We found a significant increased risk among Asians under the dominant model, but not under the recessive or allele-contrast model. Compared with the meta-analysis of Zhuo et al\(^24\) who also researched the association between T3801C and the risk of AML, the dominant model for Asians utilized a fixed effects in the present meta-analysis, which makes our conclusions more convincing. For A2455G, the subgroup analyses found no association among either Asians or Caucasians with the risk of AML. The meta-analysis of Zhuo et al\(^25\) also investigated the association between A2455G and the risk of AML, but our conclusions are more convincing due to the inclusion of a larger number of articles. In addition, we believe that the article of Zhuo et al contained some data errors.\(^25\) The research data of Majumdar et al\(^21\) defined the allele *2B as an m1 (T3801C) and m2 (A2455G) combined locus, and so the data for *2B cannot represent the data for A2455G. Moreover, the raw data for A2455G genotypes in controls did not conform with HWE, and so our meta-analysis excluded that group of data. Zhuo et al also included the combined mutation data, which undermines the credibility of their meta-analysis.\(^25\) Our meta-analysis included only one study of the C4887A SNP and revealed an association between this SNP and the risk of AML under the dominant and allele-contrast models. However, the sample was too small to reliably characterize the intrinsic
CYP1A1 Polymorphisms and Leukemia

| Study or subgroup | ALL Events | Control Events | Weight M-H, fixed, 95% CI OR M-H, fixed, 95% CI |
|------------------|------------|---------------|-----------------------------------------------|
| Caucasian        |            |               |                                               |
| Gallegos-Arreola et al \(^{50}\) | 22          | 136           | 136 17.6% 3.09 (1.32, 7.21)                   |
| Selvin \(^{51}\) | 5           | 175           | 175 10.2% 1.26 (0.33, 4.76)                   |
| Swinney et al \(^{52}\) | 13         | 71            | 204 18.9% 2.47 (1.13, 5.38)                   |
| Yamagushi et al \(^{51}\) | 3          | 99            | 99 7.8% 1.00 (0.20, 5.06)                     |
| Subtotal (95% CI) | 481       | 614           | 614 54.3% 2.23 (1.36, 3.68)                   |
| Total events     | 43         | 32            |                                               |
| Heterogeneity: \(\chi^2=2.28, df=3\) (P=0.52); I\(^2=0\%\) |
| Test for overall effect: \(Z=3.16\) (P=0.002) |
| Asian             |            |               |                                               |
| Gao et al \(^{54}\) | 10         | 78            | 112 20.7% 1.35 (0.54, 3.35)                   |
| Joseph et al \(^{55}\) | 10        | 118           | 118 7.2% 3.55 (0.95, 13.24)                   |
| Lee et al \(^{56}\) | 6          | 105           | 159 17.7% 1.01 (0.35, 2.93)                   |
| Subtotal (95% CI) | 301       | 389           | 389 45.7% 1.57 (0.87, 2.83)                   |
| Total events     | 26         | 23            |                                               |
| Heterogeneity: \(\chi^2=2.24, df=2\) (P=0.33); I\(^2=11\%\) |
| Test for overall effect: \(Z=1.48\) (P=0.14) |
| Mixed             |            |               |                                               |
| Razmkhah et al \(^{53}\) | 0          | 85            | 94 Not estimable                              |
| Subtotal (95% CI) | 85         | 94            | Not estimable                                 |
| Total events     | 0          | 0             |                                               |
| Heterogeneity: not applicable |
| Test for overall effect: not applicable |
| Total (95% CI)    | 867        | 1,097         | 1,097 100% 1.93 (1.32, 2.82)                 |
| Total events     | 69         | 55            |                                               |
| Heterogeneity: \(\chi^2=5.42, df=6\) (P=0.49); I\(^2=0\%\) |
| Test for overall effect: \(Z=3.39\) (P=0.0007) |
| Test for subgroup differences: \(\chi^2=0.81, df=1\) (P=0.37); I\(^2=0\%\) |

Figure 5 (Continued)
Figure 5 (Continued)
### CYP1A1 Polymorphisms and Leukemia

**Figure 5** Meta-analysis of the association between CYP1A1 A2455G gene polymorphism and CML risk under three models: (A) recessive, (B) dominant, and (C) allele contrast.

**Abbreviations:** ALL, acute lymphoblastic leukemia; CI, confidence interval; M–H, Mantel–Haenszel type; OR, odds ratio; SE, standard error; CML, chronic myeloid leukemia.

| Study or subgroup | ALL Events | Total | Control Events | Total | Weight | OR M–H, fixed, 95% CI | OR M–H, fixed, 95% CI |
|------------------|-----------|-------|----------------|-------|--------|----------------------|----------------------|
| **Caucasian**    |           |       |                |       |        |                      |                      |
| Gallegos-Arreola et al<sup>27</sup> | 109 | 272 | 75 | 272 | 14.8% | 1.76 (1.23, 2.52) |                      |
| Selvin<sup>28</sup> | 49 | 350 | 52 | 350 | 14.7% | 0.93 (0.61, 1.42) |                      |
| Swinney et al<sup>12</sup> | 51 | 142 | 125 | 408 | 13.6% | 1.27 (0.85, 1.90) |                      |
| Yamaguchi et al<sup>13</sup> | 42 | 198 | 35 | 198 | 9.1% | 1.25 (0.76, 2.07) |                      |
| **Subtotal (95% CI)** | 962 |       | 1,228 | 52.3% | 1.31 (1.07, 1.61) |                      |
| **Total events** | 251 |       | 287 |                |        |                      |                      |
| Heterogeneity: $\chi^2=5.09, df=3 (P=0.17); I^2=41\%$ |       |       |                |        |        |                      |                      |
| Test for overall effect: $Z=2.58$ (P=0.010) |       |       |                |        |        |                      |                      |
| **Asian**        |           |       |                |       |        |                      |                      |
| Gao et al<sup>29</sup> | 64 | 156 | 81 | 224 | 12.9% | 1.23 (0.81, 1.87) |                      |
| Joseph et al<sup>30</sup> | 54 | 236 | 56 | 236 | 14.2% | 0.95 (0.62, 1.46) |                      |
| Lee et al<sup>31</sup> | 51 | 210 | 83 | 318 | 16.5% | 0.91 (0.61, 1.36) |                      |
| **Subtotal (95% CI)** | 602 |       | 778 | 43.7% | 1.02 (0.80, 1.29) |                      |
| **Total events** | 169 |       | 220 |                |        |                      |                      |
| Heterogeneity: $\chi^2=1.17, df=2 (P=0.56); I^2=0\%$ |       |       |                |        |        |                      |                      |
| Test for overall effect: $Z=0.14$ (P=0.89) |       |       |                |        |        |                      |                      |
| **Mixed**        |           |       |                |       |        |                      |                      |
| Razmkhah et al<sup>32</sup> | 13 | 170 | 14 | 188 | 4.0% | 1.03 (0.47, 2.26) |                      |
| **Subtotal (95% CI)** | 170 |       | 188 | 4.0% | 1.03 (0.47, 2.26) |                      |
| **Total events** | 13 |       | 14 |                |        |                      |                      |
| Heterogeneity: not applicable |       |       |                |        |        |                      |                      |
| Test for overall effect: $Z=0.07$ (P=0.94) |       |       |                |        |        |                      |                      |

**Total (95% CI)**

| Total events | 433 | 521 |
|--------------|-----|-----|
| Heterogeneity: $\chi^2=8.79, df=7 (P=0.27); I^2=20\%$ |       |       |
| Test for overall effect: $Z=2.02$ (P=0.04) |       |       |
| Test for subgroup differences: $\chi^2=2.56, df=2 (P=0.28); I^2=21.9\%$ |       |       |
link between the *CYP1A1* C4887A polymorphism and risk of AML. Further investigations are needed to confirm this conclusion.

Our meta-analysis also studied the associations between three SNPs (T3801C, A2455G, and C4887A) and the risk of ALL. The results showed that the *CYP1A1* T3801C polymorphism might have a strong correlation with an increased risk of ALL. However, in the subgroup analyses stratified by race, the data did not reveal such an association among either Asians or Caucasians when they were analyzed separately. Our analysis included more studies than that of Zhuo et al., which also researched the association between T3801C and the risk of ALL, and so our conclusions are more plausible. The results for the *CYP1A1* A2455G polymorphism indicated that this is significantly correlated with the risk of ALL among Caucasians. Again, our analysis included more studies than that of Zhuo et al., which also researched the association between A2455G and ALL. In addition, we believe that the article of Zhuo et al. contained some data errors. Krajinovic et al. found that *CYP1A1* *2B* represents both m1 (T3801C) and m2 (A2455G), and so, the data for *2B* cannot represent the data for A2455G alone. Moreover, Zhuo et al. included combined mutation data, which would produce incorrect results. More importantly, our study only extracted data for a single race from the study of Swinney et al. which makes our race subgroup analyses more credible. Only one study related to the *CYP1A1* C4887A polymorphism was included in our meta-analysis. The results showed that this polymorphism might not be correlated with the risk of ALL. Also, the subgroup analyses found no association among either Asians or Caucasians when they were analyzed separately. The sample was too small to reliably characterize the intrinsic link between the *CYP1A1* C4887A polymorphism and the risk of ALL, and so further studies are needed to clarify this.

There are two implications of this study that are particularly significant: 1) the *CYP1A1* A2455G polymorphism can be used as a screening index for the risk of ALL and CML, while the *CYP1A1* T3801C polymorphism can be used as a screening index for the risk of AML; and 2) genetic screening can be used to identify individuals with the susceptible genotype who could take early defense measures to reduce their risk of leukemia.

Three limitations of this meta-analysis should be considered when interpreting its findings. First, our findings only related to the relationships between specific genes and diseases, whereas leukemia is influenced by multiple factors, and so, future studies need to consider age, race, family history, and environmental and lifestyle factors when attempting to draw more accurate conclusions. Second, a relatively small number of eligible studies were included in this meta-analysis, which could limit the generalizability of the results. This also restricted the statistical power of the subgroup analyses. As is well known, the inclusion of studies with very small samples may lead to overestimations of the associations. Third, only published studies were included in the present meta-analysis. A certain degree of publication bias is always present due to the possibility of nonsignificant or negative findings not being published.

In conclusion, this meta-analysis suggests that Asians who carry the T3801C C allele might have an increased risk of AML, while Caucasians with the A2455G GG genotype might have an increased risk of ALL. In addition, we found an association between the *CYP1A1* A2455G polymorphism and risk of CML among Caucasians. Future large studies of these sites are recommended in order to confirm the findings of this study and also to eventually identify the underlying mechanisms.

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**Disclosure**

The authors report no conflicts of interest in this work.

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