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REVIEW ARTICLE

Association of *NUDT15* c.415C>T allele and thiopurine-induced leukocytopenia in Asians: a systematic review and meta-analysis

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Abstract
Background Thiopurines, commonly used to treat autoimmune conditions and cancer, can be limited by life-threatening leucopenia. However, whether *NUDT15* (nucleoside diphosphate-linked moiety X-type motif 15) is associated with thiopurine-induced leucopenia in Asians is controversial.
Methods Relevant studies in English that were published until July 10, 2016 were identified through PubMed, EMbase, and other web knowledge databases. Study quality was assessed according to the Newcastle-Ottawa Scale (NOS) criteria. Summary risk ratio (RR) and 95% confidence intervals (CI) were estimated based on a fixed-effects model or a random-effects model, depending on the absence or presence of significant heterogeneity.
Results Seven studies of 1138 patients met our inclusion criteria. Random-effects model meta-analysis provided evidence that T carriers of *NUDT15* c.415C>T were significantly correlated with high incidences of thiopurine-induced leukocytopenia [CT + TT vs. CC: RR = 3.79, 95%CI (2.64 ~ 5.44), $P < 0.00001$]. This correlation was especially strong in TT patients, where it was found to be significantly increased by 6.54-fold compared with CC patients [TT vs. CC: RR = 6.54, 95%CI (3.34 ~ 12.82), $P < 0.00001$]. We also found that the *NUDT15* c.415C>T variant was common in Asians and Hispanics, but rare in Europeans and Africans; the frequency of the *NUDT15* c.415C>T distribution varied substantially by race/ethnicity.
Conclusion The results of this meta-analysis confirm that *NUDT15* c.415C>T may be an important predictor of thiopurine-induced leukocytopenia in Asians. Genotype targeting of *NUDT15* c.415C>T before initiating thiopurine treatment may be useful to limit leukocytopenia.

Keywords Asians · Leukocytopenia · *NUDT15* c.415C>T · Thiopurines

Introduction

Thiopurines (mercaptopurine, thioguanine, and azathioprine) remain one of the most important and extensively prescribed drugs for cancer and autoimmune disease. Myelosuppression is the most common adverse reaction of thiopurines, and includes macrocytosis, leucopenia megaloblastic anemia, thrombocytopenia, and pancytopenia [1]. Azathioprine (AZA) is rapidly metabolized following oral administration to form 6-mercaptopurine, (6-MP) which in turn crosses cell membranes and is converted intracellularly into a number of thiopurine analogues, including 6-thioguanine nucleotides (6-TGNs). There are three major competing routes for 6-MP. One important route is catalyzed by the enzyme thiopurine methyltransferase (TPMT). Most researchers have speculated that the cytotoxicity caused by thiopurines is due to DNA damage produced by the concentrations of 6-TGNs, and the wide interpatient variation in 6-TGN concentration is largely accounted for by variation in TPMT activity [2]. Thiopurine methyltransferase (TPMT) catabolizes an important thiopurine metabolic pathway and its genetic polymorphism affects thiopurine-induced toxicity [2–5]. A total of 31 *TPMT* allele genetic polymorphisms have been identified which are, or may be associated with, decreased or absent TPMT enzyme activity [6]. *TPMT*2*, **3A*, **3B*, **3C*, and **8* take up

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approximately 95% of all *TPMT* variants known to result in TPMT deficiency [7]. The predominant *TPMT* variant in Asian populations is **3C*, with an allele frequency of 2.3% [8, 9]. However, thiopurine-induced leukocytopenia is common in Asian populations [10–12]. Therefore, we believe that thiopurine-induced leucopenia can be affected by multiple factors. Some factors, such as *TPMT* and other genes might play a role in the development of the leucopenia caused by thiopurines.

Recently, a number of studies suggested that *NUDT15* c.415C>T was a novel predictor of thiopurine-induced leukocytopenia in Asians [13–15]. However, these studies have two major limitations: the sample size of the observational studies was relatively small and the statistical power was very insufficient. Furthermore, no meta-analysis has estimated the relationship between *NUDT15* c.415C>T and thiopurine-induced leukocytopenia in Asians. Therefore, it is necessary to perform a quantitative synthesis of the existing genetic association studies, despite their inconsistent results and inadequate power. The purpose of this paper is to systematically accumulate and quantitatively analyze the data regarding the genetic association between *NUDT15* c.415C>T and thiopurine-induced leukocytopenia.

Methods

Data sources and search strategy

We performed a computerized literature search of PubMed, EMbase, and Web of Knowledge databases (we search for articles published up until 10 July 2016) by using the Boolean combinations of the key terms "*NUDT15* OR MTH2" AND "polymorphisms OR polymorphism OR SNP" AND 'leukocytopenia OR myelosuppression" AND "Azathioprine OR 6-MP OR thiopurine OR thionucleosides." The Medical Subject Headings (MeSH) or keywords were used when the searching database had this option available. The language of the published papers was restricted in English, and only human studies were included. The bibliographies of the included articles were examined to identify additional studies.

Study selection

Two authors (Ailing Zhang and Jing Yang) independently selected the studies and retrieved data by using a standardized form. All disagreements were resolved by group consensus. For inclusion, the criteria were as follows: (1) patients were treated with thiopurines and then the association between *NUDT15* c.415C>T and thiopurine-induced leukocytopenia was investigated; (2) patients were genotyped for *NUDT15* c.415C>T; (3) leukopenia was graded by common toxicity criteria as follows: grade 2, 2000 ~ 3000 mm^{-3}; grade 3, 1000 ~ 2000 mm^{-3}; and grade 4, <1000 mm^{-3} [16]. Studies were excluded from the primary analysis if any of the following were met: (1) the patient populations were selected on the basis of their reported leukocytopenia or *NUDT15* c.415C>T genotype status; (2) letters, case reports, review articles, studies with insufficient information and duplicate studies were excluded.

For the systematic review of the frequencies of the genotype and allele of *NUDT15* c.415C>T, all articles had to meet our inclusion and exclusion criteria. Inclusion criteria: (1) included a cohort study or case-control study; (2) the article explicitly listed the genotype and allele frequencies of *NUDT15* c.415C>T. Exclusion criteria: (1) reviews, meta-analysis, letters or case reports; (2) literature without information on *NUDT15* c.415C>T frequencies; (3) the retrieval returned duplicate publications.

Data extraction and quality assessment

The following information was extracted from each included study: the first author's last name, year of publication, geographic origin, study design, age and gender of patients, thiopurine regimens, disease type, leukocyte classification criteria, patient demographics, the method of SNP detection, and the main results of *NUDT15* c.415C>T among patients. The methodological quality of the included studies were evaluated separately by two authors (Jingli Lu and Hua Wang) using the Newcastle-Ottawa quality assessment scale (NOS) criteria [17]. When the results were different, consensus was reached. The NOS criteria were based on three aspects: (1) subject selection: 0 ~ 4; (2) comparability of study groups: 0 ~ 2; (3) clinical outcome: 0 ~ 3. Total NOS scores ranged from 0 to 9 with a score ≥6 indicating good quality.

Statistical analysis

Rigorous statistical analysis was performed using the Review Manager (Revman) program version 5.2 (Cochrane Collaboration, Oxford, UK) in the meta-analysis and the STATA statistical software (Version 12.0, Stata Corporation, College Station, TX, USA) for sensitivity analyses and Egger's linear regression test. The risk ratio (RR) with a corresponding 95% confidence interval (95%CI) was calculated to evaluate the association between the *NUDT15* c.415C>T polymorphism and thiopurine-induced leukocytopenia. The Z test was used to estimate the statistical significance of pooled RRs. Between-study heterogeneity was assessed by Cochran's Q statistic and I^2 test [18]. If the Q test exhibited a $P > 0.05$ or the I^2 test was <50%, indicating that these studies were homogeneous, the fixed-effects model was used; otherwise, the random-effect model was used. We also made use of sensitivity analyses to explore sources of heterogeneity. $P < 0.05$

represented statistically significant heterogeneity. Funnel plots and Egger's linear regression test was used to investigate the potential publication bias [19]. Pooled data were performed to analyze the genotype and allele frequencies of *NUDT15* c.415C>T.

Results

Study characteristics and selection

Our primary searches by search terms independently yielded 32 articles. Among these articles, two publications were excluded as they were duplicates and 12 articles were deemed not relevant after reading the abstract. Then, we reviewed the full texts of the remaining 18 articles. Letters or case reports (n = 2), not reporting an association between *NUDT15* and leukopenia (n = 3), insufficient information (n = 4), Japanese language (n = 1), and overlapping with another included study (n = 1) were excluded after reading the full text. Finally, seven remaining studies were included in the meta-analysis (Fig. 1) [13, 20–25]. Our study included a total of 1138 patients with Crohn's disease, ALL or IBD. Among them, 311 patients carried the *NUDT15* 415T allele. The sample size of each trial ranged from 69 to 346 (Table 1). One study was a case-control study and six articles were cohort studies. Their scores ranged from 6 to 9.

Association between *NUDT15* c.415C>T and thiopurine-induced leukocytopenia

For the *NUDT15* c.415C>T polymorphism, quantitative synthesis from seven studies showed significant differences in the comparisons of CT + TT vs. CC [RR = 3.79, 95%CI (2.64 ~ 5.44), P < 0.00001, Fig. 2a], CT vs. CC [RR = 3.41, 95%CI (2.44 ~ 4.77), P < 0.00001, Fig. 2b], TT vs. CC [RR = 6.54, 95%CI (3.34 ~ 12.82), P < 0.00001, Fig. 2c]. However, no significant difference was found when comparing TT vs. CT [RR = 1.80, 95%CI (0.93 ~ 3.51), P = 0.08, Fig. 2d]. The funnel plots and Egger's test demonstrated no evidence of publication bias for CC vs. CT + TT (P = 0.118) (Fig. 3). The result of sensitivity analysis, which omitted individual studies to assess their influence on the pooled estimates, indicated that no single study could influence the pooled RRs (Fig. 4).

The genotype and allele frequencies of *NUDT15* c.415C>T in Asians

We assessed the literature to determine frequencies of *NUDT15* c.415C>T and identified 11 studies [13–15, 20, 22–27]. The following information was extracted, including the first author's last name, year of publication, geographic origin, disease type, the number of patients, genotype and allele data. Details on demographic and other data are summarized in Table 2. All the studies clearly report the ethnic origin of patients, and most of patients were East Asians. Only one study included Hispanics and Europeans. Pooling the same ethnic populations of the *NUDT15* c.415C>T genotype, the genotype frequencies of *NUDT15* c.415C>T (CC, CT and TT) in Asians were 75.84%, 21.76%, and 2.39%, respectively. The genotype frequencies were 92.34%, 7.21%, and 0.45% in Hispanics; 99.51%, 0.49%, and 0% in Europeans; and 100%, 0, 0% in Africans. The respective allele frequencies of *NUDT15* c.415C>T (C and T) in Asians were 86.72% and 13.28%, respectively; 95.95% and 4.05% in Hispanics; 99.76% and 0.24% in Europeans; and 100% and 0% in Africans.

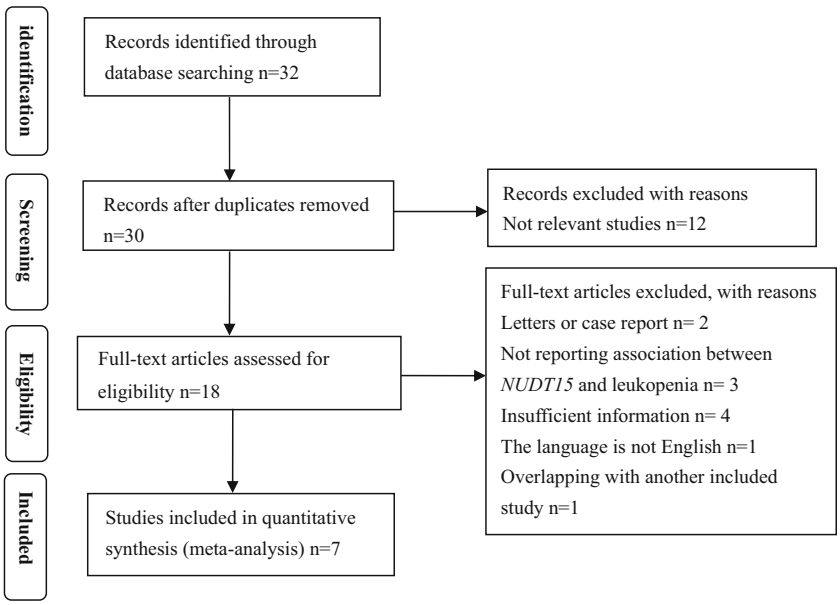


Fig. 1 A flow diagram for study identification, inclusion, and exclusion

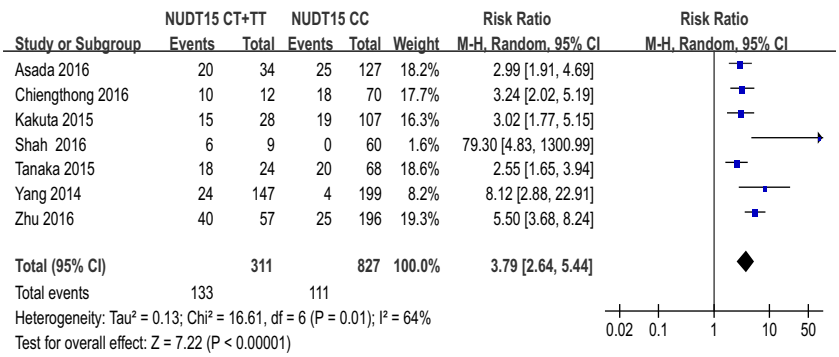
Table 1 Demographic and clinical characteristics of studies included in the meta-analysis

Study(year)	Location	Study design	Patients, *n* (male%)	Age, mean (SD)	Disease type	Thiopurine regimens	Leukopenia classification criteria	*NUDT15* SNP	Method of *NUDT15* SNP analysis	NOS
Asada et al. [13]	Japanese	Case-control Study	161(97)	44.1 ± 0.89	IBD	AZA/6-MP	Grade 2 2000 ~ 3000/ul, grade 3 1000 ~ 2000/ul, grade 4 < 1000/ul	rs116855232	PCR	9
Chiengthong et al. [20]	Thai	Cohort Study	82(33)	8(1 ~ 20)	ALL	6-MP	ANC <500	rs116855232	Pyrosequencing	6
Kakuta et al. [21]	Japanese	Cohort Study	135(98)	35.3 ± 12.2	IBD	AZA/6-MP	Grade 2 2000 ~ 3000/ul,grade 3 1000 ~ 2000/ul, grade 4 < 1000/ul	rs116855232	Real-time PCR	9
Tanaka et al. [22]	Japanese	Cohort Study	92(47)	5 (1–17)	ALL	6-MP	Leukocyte < $2.0*10^9$ was defined as grade 3	rs116855232	Real-time PCR	9
Yang et al. [23]	Korean	Cohort Study	346(NA*)	NA*	CD	AZA	Grade 3 1000 ~ 2000/ul, grade 4 < 1000/ul	rs116855232	TaqMan SNP-Immunochip	7
Zhu et al. [24]	Chinese	Cohort Study	253(185)	NA*	IBD	AZA	Leukocyte <$3.5*10^9$/L, Neutrophils <$1.5*10^9$/L	rs116855232	PCR-RFLP	6
Shah et al. [25]	Indian	Cohort Study	69(37)	59.5 ± 11.6	UC, CD, and AIH	AZA/6-MP	Grade 2 2000 ~ 3000/ul, grade 3 1000 ~ 2000/ul, grade 4 < 1000/ul,	rs116855232	ARMS-PCR-RFLP	9

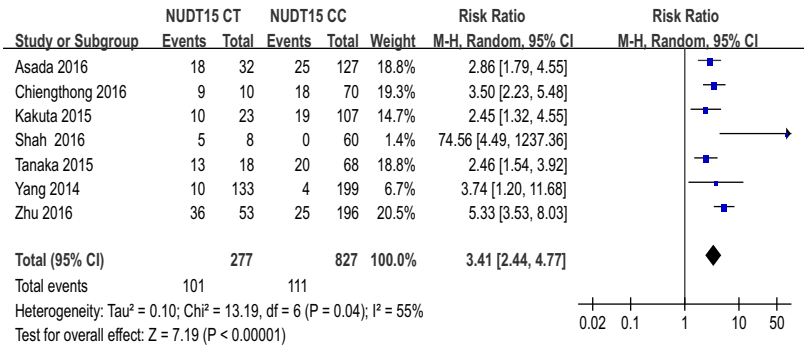
For Asada et al. [13], the number of patients was described 264 in this research, but only 161 patients were taking thiopurines, 103 subjects were healthy control, and then the number of patients were 161. Leukopenia was graded by common toxicity criteria as follows: grade 2, 2000 ~ 3000 mm^{-3}; grade 3, 1000 ~ 2000 mm^{-3}; and grade 4, <1000 mm^{-3}

IBD inflammatory bowel disease, *ALL* acute lymphoblastic leukemia, *CD* Crohn's disease, *UC* ulcerative colitis, *AIH* atutoimmune liver diseases, *NA* the results could not be found in these articles, *PCR* polymerase chain reaction, *PCR-RFLP* polymerase chain reaction-restriction fragment length polymorphism, *ARMS-PCR-RFLP* amplification refractory mutation system-polymerase chain reaction-restriction fragment length polymorphism, *AZA* azathioprine, *6-MP* 6-mercaptopurine

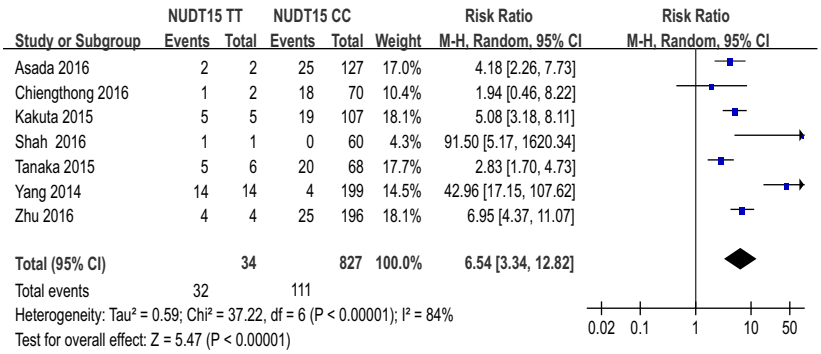
(a) *NUDT15* CT+TT *vs* CC



(b) *NUDT15* CT *vs* CC



(c) *NUDT15* TT *vs* CC



(d) *NUDT15* TT *vs* CT

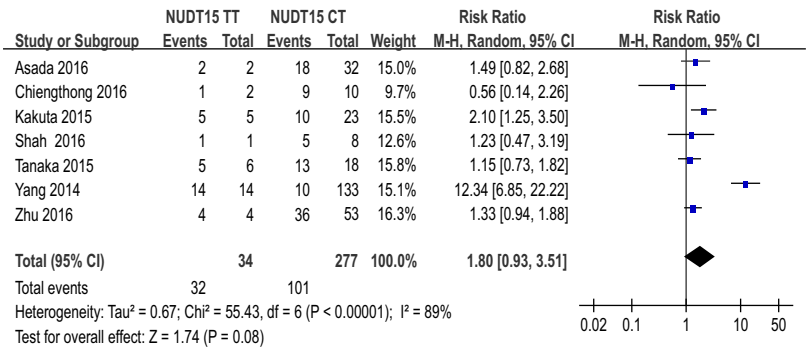


Fig. 2 The forest plots for the association of *NUDT15* c.415C>T variants with AZA-induced leukocytopenia. **a** *NUDT15* CT + TT vs CC. **b** *NUDT15* CT vs CC. **c** *NUDT15* TT vs CC. **d** *NUDT15* TT vs CT

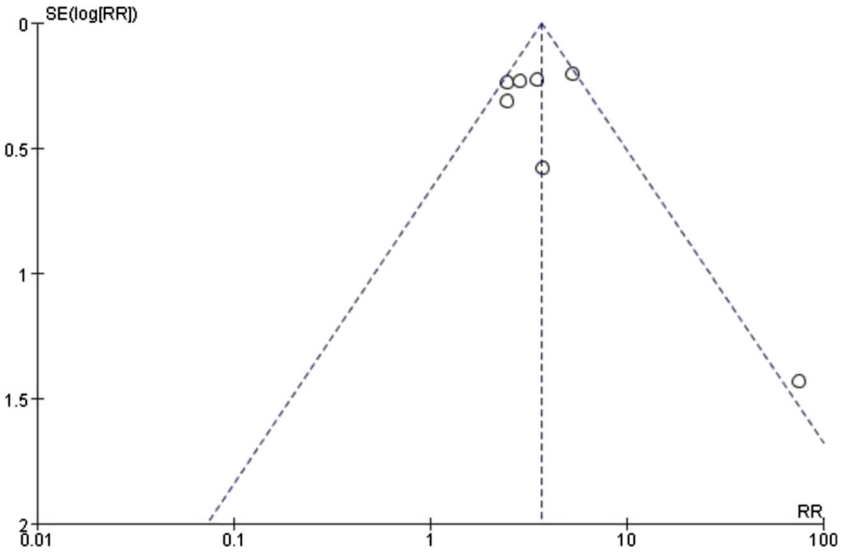


Fig. 3 Funnel plots for the assessment of publication bias of studies included in this meta-analysis

Discussion

The current meta-analysis demonstrated that the *NUDT15* c.415C>T allele is strongly associated with an increased risk of developing leucopenia in patients who are given thiopurines. It also revealed that the risk of developing leucopenia among thiopurine users with *NUDT15* c.415C>T is significantly increased by 3.79-fold compared to patients without the gene. The analysis of genotype and allele frequencies of *NUDT15* c.415C>T showed that the *NUDT15* c.415C>T variant was most common in Asians and Hispanics, and rare in Europeans and Africans. The genotype and allele distribution of *NUDT15* c.415C>T varied substantially by race/ethnicity. The higher prevalence of the *NUDT15* variant in East Asians may contribute to over-representation of thiopurine intolerance in this population. However, more studies, including those with a greater number of Europeans and Africans, are needed to evaluate the frequencies of *NUDT15* c.415C>T.

As prodrugs, thiopurines are enzymatically converted into the active end-metabolite of thiopurines, 6-thioguanine nucleotides (6-TGNs), consisting of 6-thioguanine-monophosphate (6-TGMP), 6-thioguanine-diphosphate (6-TGDP) and 6-thioguanine-diphosphate-triphosphate (6-TGTP) [28]. 6-TGTP is further reduced to 6-deoxythioguanosine-triphosphate (6-TdGTP). Then, 6-TGTP and 6-TdGTP are incorporated into RNA or DNA to trigger futile mismatch repair and, eventually, apoptosis [29–31]. Thiopurines have a narrow therapeutic index owing to frequent toxicity. NUDT15 (nucleoside diphosphate-linked moiety X-type motif 15), also known as MTH2, is a 164-amino-acid protein which can convert 8-oxo-dGTP and 8-oxo-dGDP to 8-oxo-dGMP, thereby removing the oxidatively damaged guanine nucleotides from cells to

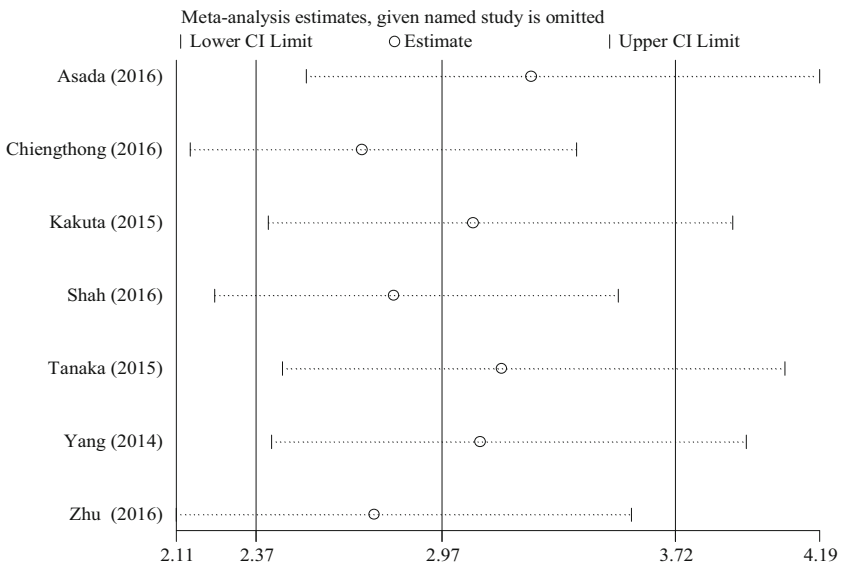


Fig. 4 Sensitivity analysis for the relationships of *NUDT15* c.415C>T variants with AZA-induced leukocytopenia

Table 2 The frequencies of genotype and allele of *NUDT15* c.415C>T in these literatures

Authors	Year	Location	Number	Genotype			Allele	
				CC	CT	TT	C	T
Yang et al. [27]	2015	Hispanics	222	205 (92.34%)	16 (7.21%)	1 (0.45%)	426 (95.95%)	18 (4.05%)
Yang et al. [27]	2015	European	205	204 (99.51%)	1 (0.49%)	0 (0%)	409 (99.76%)	1 (0.24%)
Yang et al. [27]	2015	Africans	93	93(100%)	0(0%)	0(0%)	186(100%)	0(0%)
Tanaka et al. [22]	2015	Japanese	92	68	18	6	154	30
Yang et al. [23]	2014	Korean	346	199	133	14	531	161
Lee et al. [14]	2016	Korean	81	75	3	3	153	9
Liang et al. [15]	2015	Chinese-Taiwanese	404	315	84	5	714	94
Yang et al. [27]	2015	Asian	61	50	10	1	110	12
Chiengthong et al. [20]	2016	Thai	82	70	10	2	150	14
Asada et al. [13]	2016	Japanese	264	213	48	3	474	54
Kakuta et al. [21]	2015	Japanese	135	107	23	5	237	33
Suzuki et al. [26]	2016	Japanese	51	41	10	0	92	10
Zhu et al. [24]	2016	Chinese	253	196	53	4	445	61
Shah et al. [25]	2016	Indian	69	60	8	1	128	10
Total *n* (%)	–	Asian	1838	1394(75.84%)	400(21.76%)	44(2.39%)	3188(86.72%)	488(13.28%)

minimize DNA damage [32]. Studies from comprehensive in vitro and in vivo studies strongly indicate that NUDT15 can convert 6-TGTP to 6-TGMP and TdGTP to TdGMP and then prevent the incorporation of these thiopurine metabolites into DNA (DNA-TG) and negatively regulate thiopurine activation and, consequently, cytotoxicity [27].

NUDT15 c.415C>T is a missense variant in the *NUDT15* gene (rs116855232, encoding p.Arg139Cys) [27]. Yang et al. found that c.415C > T was significantly associated with AZA-induced leukopenia (OR = 35.6, $p = 4.88\text{^}10^{-94}$) among 978 individuals [23]. Meanwhile, our meta-analysis also found that patients carrying *CT* or *TT* for the *NUDT15* c.415C>T risk alleles experience especially excessive thiopurine toxicity compared to those with the CC genotype. However, Yang et al. reported that individuals homozygous for the risk allele encoding p.Arg139Cys were exquisitely sensitive to mercaptopurine and tolerated only 8% of the standard dose, while this *NUDT15* variant alone explained 22% of variance in thiopurine tolerance [27]. Based on these facts, *NUDT15* c.415C>T variants may be another important predictor for thiopurine-induced leucopenia.

The mechanism of *NUDT15 c.415C>T* gene mutation related thiopurine-induced early severe hair loss and leukopenia is controversial. So far, several researchers had proposed some ideas. For instance, a gene-dose effect for the risk allele. Jurkat cells transfected with the variant (CT or TT) showed increased AZA-induced toxicity and signs of apoptosis compared to cells transfected with wild type *NUDT15* (CC). These findings suggested that *NUDT15* is a pharmacogenetic determinant for thiopurine-induced leukopenia in diverse populations [23]. However, Asada et al. did not agree with this view. They suggested that if *NUDT15* c.415C>T induces loss-of-function, accumulation of oxidative stress and increased apoptosis in bone marrow progenitor cells might be a potential mechanism of *NUDT15* c.415C>T-related thiopurine-induced leucopenia [13]. Moriyama et al. found that *NUDT15* c.415C>T variants resulted in partial loss of nucleotide diphosphatase activity and excessive levels of toxic thiopurine active metabolites [33]. Further studies are ongoing in our group to elucidate how this gene is involved in the pathogenesis of thiopurine-induced leucopenia.

Our meta-analysis also has a number of potential limitations. For instance, due to the small number of studies, except for Asians, our study did not include all the data required to assess the relationship between *NUDT15* c.415C>T genetic polymorphisms and thiopurine-induced leucopenia. Although our search strategy is relatively comprehensive, it still cannot cover all relevant studies. Hence, it is possible that larger and better designed studies might have identified an impact on thiopurine-induced leucopenia. The monitoring of signs and symptoms in these patients is still needed.

This meta-analysis suggests that patients carrying the *NUDT15* T risk allele are at greater risk of thiopurine-induced leucopenia compared with the C homozygotes. Suzuki et al. [26] also found that *NUDT15* can predict the dose reduction of 6-MP for children with acute lymphoblastic leukemia. However, a larger study is required to clarify this observed dosing effect in variant carriers.

Conclusion

In conclusion, based on our meta-analysis, *NUDT15* c.415C>T gene polymorphisms may be an important predictor of thiopurine-induced leukocytopenia in Asians. Furthermore, the frequency of *TPMT* variants was rare, while thiopurine-induced leukocytopenia is common in Asians. Therefore, genotyping for *NUDT15* c.415C>T before initiating thiopurine treatment may be useful to avoid leukocytopenia.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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