REVIEW

Association between the c.415C > T, c.52G > A, and 36_37insGGAGTC polymorphisms of *NUDT 15* and thiopurine-induced leukopenia, thiopurine intolerance, and severe hair loss: an updated meta-analysis

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Purpose: As a common immunosuppressive and anticancer drug, thiopurine has achieved remarkable clinical success. However, higher inter-individual dose variability and unpredictable toxicity still challenge its use in clinical practices. Some studies indicate that *NUDT 15* polymorphisms are associated with this variation, but specific correlation remains controversial. This meta-analysis assessed the association between three polymorphisms of *NUDT 15* and thiopurine-induced toxicities.

Methods: Three databases were electronically searched: PubMed, Embase, and Web of Science. Only case–control studies and cohort studies were eligible. The overall pooled ORs and corresponding 95% CIs were used to represent the results.

Findings: We included 16 studies that focus on *NUDT 15* c.415C > T, c.52G > A, and 36_37insGGAGTC polymorphisms in patients treated with thiopurine. Significant associations between *NUDT 15* c.415C > T polymorphism and leukopenia were found in all genetic models (TC/TT vs CC, OR: 7.64, 95% CI: (6.19, 9.44), *P*<0.00001; TT vs CC/TC, OR: 29.66, 95% CI: (12.31, 71.46), *P*<0.00001; TT vs CC, OR: 45.60, 95% CI: (18.84, 110.37), *P*<0.00001; TC vs CC, OR: 6.41, 95% CI: (5.19, 7.94), *P*<0.00001; TT vs TC, OR: 6.38, 95% CI: (2.59, 15.72), *P*<0.00001), early/late leukopenia (in recessive and co-dominant model), leukopenia (grade 3–4), and severe hair loss in all genetic models. Besides, c.52G > A and 36_37insGGAGTC polymorphisms were also significantly associated with leukopenia. No significant association between *NUDT 15* c.415C > T polymorphism and early/late leukopenia in the Chinese population was determined in the co-dominant model (TC vs CC).

Implications: *NUDT 15* c.415C > T polymorphism could increase the risk of leukopenia, early/late leukopenia, leukopenia (grade 3–4), and severe hair loss. Meanwhile, c.52G > A and c.36_37insGGAGTC mutations also probably increase the risk of leukopenia. Preemptive tests for *NUDT 15* polymorphisms are highly recommended to individualize the treatment of thiopurine for a better outcome with less toxicity.

Keywords: NUDT 15, polymorphism, leukopenia, thiopurine, intolerance, meta-analysis

Introduction

As indispensable immunosuppressive and anticancer agents, thiopurines (azathioprine and 6-mercaptopurine), are widely used for maintenance therapy of child acute lymphoblastic leukemia (ALL), organ transplantation, autoimmune diseases,

including rheumatoid arthritis (RA) and inflammatory bowel disease (IBD).[1,2] However, due to highly variable individual response, thiopurines can cause severe toxicities, mainly leukopenia, resulting in therapy disruption, thiopurine dose reduction, even increasing the risk of relapse, and life-threatening infection.[3–5]

Thiopurines are metabolized into their active metabolites, 6-thioguanine nucleotides (6-TGNs), by a series of enzymes. 6-TGNs consist of 6-thio(d)-GMP, 6-thio(d)-GDP, 6-thio(d)-GTP, and 6-thio(d)-GTPs are incorporated into DNA and RNA, causing inhibition of nucleotide and protein synthesis, and an over accumulation of them can result in toxicity typified by leukopenia.[6]

Thiopurine methyltransferase (*TPMT*) is an imperative metabolic enzyme of 6-TGNs. Inherited deficiency of *TPMT* with a decreased enzymatic activity can lead to an increased level of 6-TGNs, thus causing hematological toxicity.[7] The association between thiopurine-induced leukopenia and *TPMT* variants has been assured, and, consequently, preemptive *TPMT* testing is recommended to individualize thiopurines dose to reduce the risk of adverse effects by the US Food and Drug Administration without compromising overall therapeutic efficacy.[8–10] However, a large proportion of patients with normal *TPMT* activity still experience severe leukopenia. Intriguingly, despite the fact that the frequency of *TPMT* variants in Asians is lower than in European descent (~3% vs ~10%),[11,12] thiopurine-induced leukopenia, and thiopurines intolerance occur more in Asians, which indicates that additional factors might contribute to the variability among different races.[13,14]

Recently, Moriyama, T[15] reported that a novel indicator, *NUDT 15*, could convert the thiopurine active metabolites 6-thio-GTP and 6-thio-dGTP into 6-thio-GMP and 6-thio-dGMP and that the variants of *NUDT 15* had lower enzyme activity. Thus, *NUDT 15* deficiency directly results in excessive levels of thiopurine active metabolites 6-thio-GTP and 6-thio-dGTP, and increased host toxicity.

And a series of studies found that *NUDT 15* polymorphism was possibly associated with thiopurine-induced leukopenia and thiopurine intolerance and severe hair loss.[16,17] Heretofore, both two published systematic reviews/meta-analyses[18,19] (Table 1) revealed that the *NUDT 15* c.415C > T mutation could increase the risk of thiopurine-induced leukopenia and thiopurine intolerance. However, studies included in the two systematic reviews and meta-analyses did not provide sufficient data to deeply delve into the effects of *NUDT 15* c.415C > T polymorphism on other thiopurine-related toxicities such as early/late leukopenia, leukopenia (Grade 3–4), and severe hair loss. Whereas, within the past two years, nearly 10 related studies were newly published and need to be included and reanalyzed to observe whether the results change. In addition, the updated data about whether early leukopenia (<8 weeks), late leukopenia (>8 weeks), leukopenia (grade 3–4), and severe hair loss could be caused by *NUDT 15* c.415C > T polymorphism, necessitates to be synthesized to provide a convincing evidence. Besides, several recent studies also explored the effect of two other *NUDT 15* polymorphisms (c.52G > A and c.36_37insGGAGTC) on leukopenia. In light of this information, we performed a meta-analysis to assess the possible association between the three *NUDT 15* polymorphisms and thiopurine-induced toxicities.

Materials and methods
Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement. We searched relevant literature published before 3 June 2018 from three databases: PubMed, Embase, and Web of Science, for cohort studies and case–control studies exploring the association between *NUDT 15* polymorphism and thiopurine-induced leukopenia and thiopurine intolerance. We also manually searched references of relevant studies and reviews to identify other additional articles which were not retrieved by the initial

Table 1 Characteristic of published systematic reviews/meta-analyses

Author (year)	Polymorphism	Patients	Outcomes	Search strategy
Yin DD (2017)[19]	*NUDT15* c.415C > T	ALL + IBD	Thiopurine-induced leukopenia	PubMed + Google Scholar + China National Knowledge Infrastructure (before 27 July 2016)
Zhang AL (2017)[18]	*NUDT15* c.415C > T	ALL + IBD + AIH	Thiopurine-induced leukopenia + thiopurine intolerance	PubMed + Embase + Web of Knowledge (before 10 July 2016)

Abbreviations: A, adults; P, pediatric; ALL, acute lymphoblastic leukemia; IBD, inflammatory bowel disease; AIH, autoimmune hepatitis.

search. Only English language articles were searched and only human studies were included. The following subject terms and keywords were used to search those databases: (*NUDT 15* protein) odds ratio (OR) (*NUDT 15* gene) OR (*NUDT 15*) OR (*NUDT 15* variant) OR (nudix hydrolase 15) OR (nucleoside diphosphate-linked moiety X-type motif 15) OR (MTH2 protein).

Study selection

Two reviewers (RLW and BGL) independently read the article titles and abstracts for relevant papers according to the inclusion and exclusion criteria. If there was any disagreement, a third independent reviewer (JPL) would be consulted. Inclusion criteria: 1) patients were treated with Mercaptopurine (MP/6-MP) or Azathioprine (AZA); 2) studies provided the patients' genotypes for any one of the newly found *NUDT 15* polymorphisms; 3) studies investigated the association between *NUDT 15* polymorphism and thiopurine-related toxicities; and 4) case–control studies or cohort studies. Exclusion criteria: 1) case reports, reviews, meeting abstracts, short communication, comments, and studies with inadequate *NUDT 15* gene frequency data; 2) full text could not be retrieved for further assessment; and 3) studies with complete duplicated data. If there was incomplete overlapping data in one author's several papers, we would select the article with the updated data or combine those papers to provide more detailed data.

Data extraction and quality assessment

The following data were extracted from included studies by two independent investigators (RLW and BGL): first author's name, year of publication, study design, sample size, disease type, ethnicity, age, gender, medication, 6-MP/AZA initial daily dosage, *NUDT 15* gene sites, genotype, Hardy–Weinberg equilibrium (HWE) value for each *NUDT 15* polymorphism, thiopurine-induced toxicities, defined grade of leukopenia, and thiopurine tolerated dose. If some specific data were not provided, correspondence authors of papers were contacted by e-mail. The two investigators also applied Newcastle–Ottawa Quality Assessment Scale (NOS) to assess the quality of included studies. A third independent investigator (JPL) was consulted to resolve any discrepancies.

Statistical analysis

We used the Review Manager (Revman) 5.3 version to perform the meta-analysis. We used the overall pooled OR with a corresponding 95% confidence interval (95%CI) to assess each included study. Cochran's Q statistic and I^2 tests were used to assess the heterogeneity among these included studies. A $P>0.05$ for the Q test or the I^2 test value $<50\%$ indicates that there was no significant heterogeneity in these studies and a fixed-effects model was used. Otherwise, a random-effects model would be used. And meanwhile, we would explore the reasons for heterogeneity by sensitivity analysis and by performing a subgroup analysis. A Z test was used to evaluate the association between the *NUDT 15* polymorphisms and its clinical outcomes by calculating the significance of the pooled ORs and a $P<0.05$ level represented to be statistically significant.

Results
Selection and characteristics of the eligible studies

Study selection process is depicted in Figure 1. In total, 198 records were initially identified from the three databases. Titles and abstracts of 97 records were screened carefully after overlapping records were removed and 50 records were evaluated to be irrelevant and were excluded. The full-texts of the remaining 47 studies were retrieved and reviewed. Among them, 31 studies were excluded: 7 reviews or meta-analysis; 5 case reports; 2 short communications; 1 comment; 4 studies with continuous variables data, which could not be transformed into dichotomous variables; 5 studies with overlapping data; and 7 articles without available full-texts. Finally, 16 studies met the inclusion criteria, including 5 pediatric studies,[15,16,20–23] 9 adult studies,[24-33] and 2 both pediatric and adult studies.[17,34]

A total of 4458 subjects were included in the 16 studies, of which, 11 studies[16,17,21,22,24–27,31,32,34] only examined *NUDT 15* c.415C > T polymorphism, one study[23] examined both *NUDT 15* c.415C > T and c.52G > A gene, three studies[28–30] examined three *NUDT 15* polymorphisms: c.415C > T, c.52G > A, and c.36_37insGGAGTC and one study[15] examined all the found *NUDT 15* polymorphisms: c.415C > T, c.52G > A, c.36_37insGGAGTC, and c.416 G > A. For the ethnicity, population in most of studies were Asians: Japanese in six studies,[21,23,25,26,29,32] Korean in three studies,[17,24,34] Chinese in three studies,[22,27,30] Indian in one study,[31] and mixed population in three studies.[15,16,28] With regard to disease type, there were five studies[15,16,21–23] of ALL, eight studies[17,24–30] of IBD or CD, one study[32] of
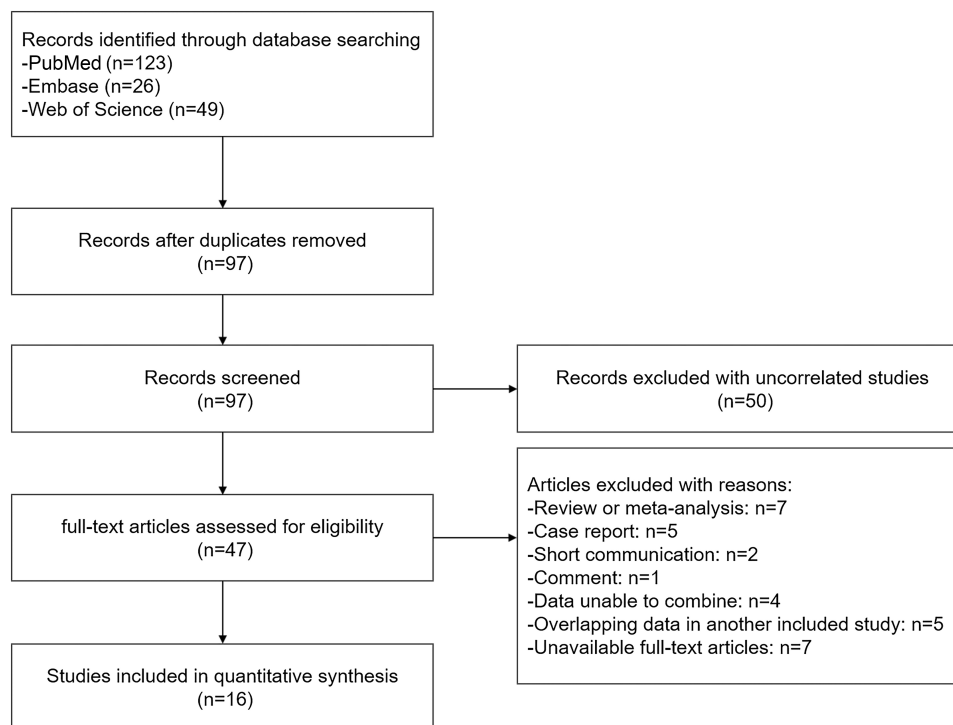
Figure 1 Flow diagram of study.

RA and two studies[31,34] of mixed diseases. The characteristics of studies included in the meta-analysis are provided in Table 2.

Quality of studies

The result of quality assessment for all the 16 cohort studies is shown in Table 3 with a total score ranging from 7 to 9 based on the NOS criteria (cohort study), which indicated a relatively high quality. Most of the studies represented well in selection and comparability but not in outcome due to lack of long-term follow-up.

Outcome of all the included studies

The association between *NUDT 15* c.415C > T polymorphism and thiopurine-induced toxicities was investigated in the 16 studies. The effects of *NUDT 15* c.52G > A and c.36_37insGGAGTC polymorphisms on the thiopurine-induced leukopenia were also separately researched in three,[20,29,30] and three[28–30] studies. Detailed data are shown in Table 4.

Association between NUDT 15 c.415C > T polymorphism and thiopurine-induced toxicities

A statistically significant association between the *NUDT 15* c.415C > T polymorphism and leukopenia was found in all genetic models (TC/TT vs CC, OR: 7.64, 95% CI: 6.19–9.44, $P<0.00001$; TT vs CC/TC, OR: 29.66, 95% CI: 12.31–71.46, $P<0.00001$; TT vs CC, OR: 45.60, 95% CI: 18.84–110.37, $P<0.00001$; TC vs CC, OR: 6.41, 95% CI: 5.19–7.94, $P<0.00001$; TT vs TC, OR: 6.38, 95% CI: 2.59–15.72, $P<0.00001$; (Figure 2 and Table 4).

Seven studies, which provided data on early leukopenia (<8 weeks) and late leukopenia (≥8 weeks), showed that *NUDT 15* c.415C > T polymorphism is significantly associated with early leukopenia and late leukopenia in the recessive model (TT vs CC/TC, OR: 49.42, 95% CI: 16.53–147.76, $P<0.00001$; OR: 0.02, 95% CI: 0.01–0.06, $P<0.00001$), co-dominant model (TT vs CC, OR: 99.30, 95% CI: 29.83–330.56, $P<0.00001$; OR: 0.01, 95% CI: 0.00–0.03, $P<0.00001$) and the model (TT vs TC, OR: 23.73, 95% CI: 7.77–72.46, $P<0.00001$; OR: 0.04, 95% CI: 0.01–0.13, $P<0.00001$). A subgroup analysis (Figure 3) was conducted to check the influences of ethnicity on the association between c.415C > T and the early leukopenia and late leukopenia without significant heterogeneity. The results showed a significant effect not only in the Japanese race in the dominant model (TC/TT vs CC, OR: 6.86, 95% CI: 2.32–20.26, $P=0.0005$; OR: 0.15, 95% CI: 0.05–0.43, $P=0.0005$) and co-dominant model (TC vs CC, OR: 3.96, 95% CI: 1.36–11.51, $P=0.01$; OR: 0.25, 95% CI: 0.09–0.73, $P=0.01$), but

Table 2 Characteristics of included studies in the meta-analysis

Study	Disease	Age (years)	Sample size	Ethnicity	NUDT 15 sites	Medication	Daily initial dose[a]	Outcome of study	HWE
Yang JJ (2015)[16]	ALL(P)	—	1028	Europeans/Africans/Hispanics/East Asians/Others	c.415C > T	6-MP	75 mg/m²	Thiopurine intolerance	×
Tanaka Y (2015, 2017)[20,23]	ALL(P)	1–17	95	Japanese	c.415C > T c.52G > A	6-MP	40 mg/m²	Myelotoxicity and thio-purine intolerance	× ×
Liang DC (2015)[22]	ALL(P)	0.1–18	310	Chinese (Taiwan)	c.415C > T	6-MP	40 mg/m²	Thiopurine intolerance	√
Moriyama T (2016)[15]	ALL(P)	—	270	Guatemala/Singapore/Japan	c.415C > T c.36_37insGGAGTC c.52G > A c.416 G > A	6-MP	(SO75)/50(SR/IR) 75 (HR)/50 mg/m²	Thiopurine intolerance	√ √ √ √
Suzuki H (2016)[21]	ALL(P)	5.1 (1.6–15.8)	51	Japanese	c.415C > T	6-MP	40 mg/m²	Myelotoxicity and thio-purine intolerance	√
Yang SK (2014)[17]	CD(A + P)	13–64	978	Korean	c.415C > T	AZA	25–50 mg	Myelotoxicity and thio-purine intolerance	√
Kakuta Y(2015)[26]	IBD(A)	35.3±12.2	135	Japanese	c.415C > T	AZA/6-MP	0.5–1.0 mg/kg	Myelotoxicity and thio-purine intolerance	×
Asada A (2016)[25]	IBD(A)	44.1±0.89	161	Japanese	c.415C > T	AZA/6-MP	0.5–1.0 mg/kg	Myelotoxicity and thio-purine intolerance	√
Chao K / Zhu X (2017/2016)[30,33]	IBD(A)/CD(A)	28 (4–68)/—	732/253	Chinese	c.415C > T c.36_37insGGAGTC/— c.52G > A/—	AZA/6-MP	—	Myelotoxicity	√ √/— √/—
Sato T (2017)[29]	IBD(A)	40.3 (18–74)	149	Japanese	c.415C > T c.36_37insGGAGTC c.52G > A	AZA/6-MP	25–50 mg	Myelotoxicity and thio-purine intolerance	× √ √
Lee JH (2017)[24]	CD(A)	33.6±8.8	165	Korean	c.415C > T	AZA/6-MP	0.5–1.0 mg/kg	Myelotoxicity	×
Sutiman N (2018)[28]	IBD(A)	—	129	Chinese/Malay/Indian/Others	c.415C > T c.36_37insGGAGTC c.52G > A	AZA/6-MP	0.5–1.0 mg/kg	Myelotoxicity	√ √ √

(Continued)

Table 2 (Continued).

Study	Disease	Age (years)	Sample size	Ethnicity	NUDT 15 sites	Medication	Daily initial dose[a]	Outcome of study	HWE
Wang HH(2018)[27]	IBD(A)	33.18±11.50	80	Chinese	c.415C > T	AZA	0.5–1.5 mg/kg	Myelotoxicity	√
Kim SY (2017)[34]	MG/CIDP/ NMO/ Vasculitis/ others(P + A)	15–84	84	Korean	c.415C > T	AZA	50 mg	Myelotoxicity and thio- purine intolerance	×
Tsuchiya A (2017)[32]	RA(A)	66±9.1	22	Japanese	c.415C > T	AZA	–	Myelotoxicity and thio- purine intolerance	√
Shah SA (2017)[31]	IBD/AIH(A)	59.5±11.6	69	Indian	c.415C > T	AZA/6-MP	50 mg	Myelotoxicity and thio- purine intolerance	√

Notes: —, not mentioned; √/×, genotype distribution were/were not consistent with Hardy–Weinberg equilibrium; [a]Thiopurine dose is 6-MP-based for ALL and AZA-based for other diseases.
Abbreviations: P, pediatric; A, adult; ALL, acute lymphoblastic leukemia; IBD, inflammatory bowel disease; CD, Crohn's disease; AZA, azathioprine; 6-MP, 6-mercaptopurine; MG, myasthenia gravis; CIDP, chronic inflammatory demyelinating polyneuropathy; NMO, neuromyelitis optica; RA, rheumatoid arthritis; AIH, autoimmune hepatitis; SR, standard risk; IR, intermediate risk; HR, high risk.

Table 3 The quality of studies included in meta-analysis with the method of NOS

Study	Selection				Comparability	Outcome			Score (total)
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	
Yang JJ (2015)[16]	☆	☆	☆	☆	☆☆	☆	—	—	7☆
Tanaka Y (2015, 2017)[20,23]	☆	☆	☆	☆	☆☆	☆	☆	—	8☆
Liang DC (2015)[22]	☆	☆	☆	☆	☆☆	☆	☆	☆	9☆
Moriyama T (2016)[15]	☆	☆	☆	☆	☆☆	☆	—	—	7☆
Suzuki H (2016)[21]	☆	☆	☆	☆	☆☆	☆	—	—	7☆
Yang SK (2014)[17]	☆	☆	☆	☆	☆☆	☆	☆	☆	9☆
Kakuta Y (2015)[26]	☆	☆	☆	☆	☆☆	☆	☆	☆	9☆
Asada A (2016)[25]	☆	☆	☆	☆	☆☆	☆	—	—	7☆
Chao K (2017)[30] / Zhu X (2016)[33]	☆	☆	☆	☆	☆☆	☆	—	—	7☆
Sato T (2017)[29]	☆	☆	☆	☆	☆☆	☆	☆	—	8☆
Lee JH (2017)[24]	☆	☆	☆	☆	☆☆	☆	—	—	7☆
Sutiman N (2018)[28]	☆	☆	☆	☆	☆☆	☆	—	—	7☆
Wang HH (2018)[27]	☆	☆	☆	☆	☆☆	☆	—	—	7☆
Kim SY (2017)[34]	☆	☆	☆	☆	☆☆	☆	—	—	8☆
Tsuchiya A (2017)[32]	☆	☆	☆	☆	☆☆	☆	—	—	7☆
Shah SA (2017)[31]	☆	☆	☆	☆	☆☆	☆	—	—	7☆

Notes: —, the question has no score. One score was represented by one star. Q1: The exposed cohort was truly or somewhat representative? Q2: The non-exposed cohort was drawn from the same community as the exposed cohort? Q3: Exposure was ascertained by secure record or structured interview? Q4: Outcome of interest was not present at the start of study? Q5: On the basis of the design or analysis, cohorts had comparability? (controls for the most important factor? Controls for any additional factor?) Q6: Outcome was independent blind assessment or record linkage? Q7: Follow-up was long enough for outcomes to occur? Q8: Follow-up of cohorts was adequate? A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability.
Abbreviations: NOS, Newcastle–Ottawa Quality Assessment Scale; Q, question.

Table 4 Pooled odds ratios of the association between *NUDT 15* polymorphism and thiopurine-induced toxicities

Genotype comparison models	Toxicity	No. of studies	Subjects	P-value	Pooled OR (95% CI)	Heterogeneity test I^2 (%)	P-value	Effect model
NUDT 15 c.415C > T								
TC + TT vs CC	Leukopenia	10	2697	<0.00001	7.64 (6.19, 9.44)	38	0.1	Fixed
	Early leukopenia	7	719	<0.0001	9.26 (3.35, 25.58)	74	0.0008	Random
	Subgroup							
	Japanese	3	138	0.0005	6.86 (2.32, 20.26)	13	0.32	—
	Korean	3	404	<0.00001	20.48 (9.77, 42.91)	0	0.84	—
	Chinese	1	177	0.009	2.28 (1.23, 4.22)	—	—	—
	Late leukopenia	7	719	<0.0001	0.11 (0.04, 0.30)	74	0.0008	Random
	Subgroup							
	Japanese	3	138	0.0005	0.15 (0.05, 0.43)	13	0.32	—
	Korean	3	404	<0.00001	0.05 (0.02, 0.10)	0	0.84	—
	Chinese	1	177	0.009	0.44 (0.24, 0.81)	—	—	—
	Leukopenia (G3–G4)	5	612	<0.00001	4.17 (2.44, 7.11)	33	0.2	Fixed
	Severe hair loss	7	1016	<0.00001	43.45 (14.51, 130.10)	0	0.97	Fixed
TT vs CC + TC	Leukopenia	10	2697	<0.00001	29.66 (12.31, 71.46)	0	0.95	Fixed
	Early leukopenia	7	719	<0.00001	49.42 (16.53, 147.76)	0	0.97	Fixed
	Late leukopenia	7	719	<0.00001	0.02 (0.01, 0.06)	0	0.97	Fixed
	Leukopenia (G3–G4)	5	612	<0.00001	43.97 (8.44, 229.00)	49	0.1	Random
	Excluded one study with CD	4	266	<0.00001	20.25 (6.83, 60.04)	0	0.44	Fixed
	Severe hair loss	7	1016	<0.00001	417.50 (109.76, 1588.04)	0	0.58	Fixed
TT vs CC	Leukopenia	10	2191	<0.00001	45.60 (18.84, 110.37)	0	0.89	Fixed
	Early leukopenia	7	441	<0.00001	99.30 (29.83, 330.56)	0	0.84	Fixed
	Late leukopenia	7	441	<0.00001	0.01 (0.00, 0.03)	0	0.84	Fixed
	Leukopenia (G3–G4)	5	370	<0.00001	60.98 (21.10, 176.20)	39	0.16	Fixed
	Severe hair loss	7	831	<0.00001	656.15 (150.21, 2866.13)	0	0.73	Fixed
TC vs CC	Leukopenia	11	2717	<0.00001	6.41 (5.19, 7.94)	37	0.11	Fixed
	Early leukopenia	7	670	0.001	5.15 (1.92, 13.81)	69	0.004	Random
	Subgroup							
	Japanese	3	125	0.01	3.96 (1.36, 11.51)	0	0.41	—

(Continued)

Table 4 (Continued).

Genotype comparison models	Toxicity	No. of studies	Subjects	P-value	Pooled OR (95% CI)	Heterogeneity test		Effect model
						I^2 (%)	P-value	
	Korean	3	379	<0.00001	13.57 (6.34, 29.05)	0	0.84	—
	Chinese	1	166	0.11	1.70 (0.89, 3.22)	—	—	—
	Late leukopenia	7	670	0.001	0.19 (0.07, 0.52)	69	0.004	Random
	Subgroup							
	Japanese	3	125	0.01	0.25 (0.09, 0.73)	0	0.41	—
	Korean	3	379	<0.00001	0.07 (0.03, 0.16)	0	0.84	—
	Chinese	1	166	0.11	0.59 (0.31, 1.12)	—	—	—
	Leukopenia (G3–G4)	5	578	0.01	2.38 (1.22, 4.64)	0	0.48	Fixed
	Severe hair loss	3	396	0.0002	26.18 (4.73, 144.95)	0	0.91	Fixed
TT vs TC	Leukopenia	10	566	<0.0001	6.38 (2.59, 15.72)	0	0.89	Fixed
	Early leukopenia	7	327	<0.00001	23.73 (7.77, 72.46)	0	0.98	Fixed
	Late leukopenia	7	327	<0.00001	0.04 (0.01, 0.13)	0	0.98	Fixed
	Leukopenia (G3–G4)	5	276	<0.0001	28.77 (10.89, 76.03)	46	0.12	Random
	Severe hair loss	7	215	<0.00001	66.29 (17.46, 251.74)	3	0.41	Fixed
c.52G > A								
GA vs GG	Leukopenia	3	975	0.003	3.52 (1.52, 8.17)	0	0.77	Fixed
c.36_37insGGAGTC								
-/ins vs -/-	Leukopenia	3	1010	<0.00001	3.84 (2.50, 5.91)	0	0.85	Fixed

Notes: Statistically significant values (*P*<0.05). Entries in italics represent heterogeneity analysis.
Abbreviations: CD, Crohn disease; CI, confidence interval; OR, odds ratio.

Study or subgroup	TC+TT Events	Total	CC Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Ayumi Asada 2016	20	34	25	127	7.4%	5.83 [2.59, 13.12]
Ji Hyeon Lee 2017	20	34	18	131	5.2%	8.97 [3.85, 20.88]
Kang Chao 2017	87	175	90	557	37.0%	5.13 [3.53, 7.44]
Natalia Sutiman 2018	7	18	3	111	0.9%	22.91 [5.17, 101.44]
Suk-Kyun Yang 2014	147	190	199	788	29.9%	10.12 [6.95, 14.74]
Sun-Young Kim 2017	8	13	12	71	2.4%	7.87 [2.19, 28.24]
Swarup A. V. Shah 2017	6	9	0	60	0.1%	224.71 [10.41, 4848.71]
Toshiyuki Sato 2017	30	40	29	109	6.7%	8.28 [3.60, 19.02]
Y Kakuta 2015	15	28	19	107	6.3%	5.34 [2.19, 13.05]
Yoichi Tanaka 2015	19	25	19	70	4.1%	8.50 [2.95, 24.49]
Total (95% CI)		566		2131	100.0%	7.64 [6.19, 9.44]
Total events	359		414			

Heterogeneity: Chi^2=14.55, df=9 (P=0.10); I^2=38%
Test for overall effect: Z=18.93 (P<0.00001)

Favours [CT+TT]   Favours [CC]

Study or subgroup	TT Events	Total	CC Events	Total	Weight	Odds ratio M-H, random, 95% CI
Ayumi Asada 2016	2	2	25	127	8.3%	20.10 [0.94, 431.73]
Ji Hyeon Lee 2017	6	6	18	131	9.2%	79.76 [4.31, 1476.01]
Kang Chao 2017	11	11	90	557	9.7%	118.81 [6.94, 2034.28]
Natalia Sutiman 2018	2	2	3	111	7.5%	155.00 [6.21, 3869.77]
Suk-Kyun Yang 2014	14	14	199	788	9.8%	85.69 [5.09, 1443.05]
Sun-Young Kim 2017	5	5	12	71	8.9%	52.36 [2.72, 1009.02]
Swarup A. V. Shah 2017	1	1	0	60	4.3%	363.00 [5.22, 25232.81]
Toshiyuki Sato 2017	6	7	29	109	16.8%	16.55 [1.91, 143.41]
Y Kakuta 2015	5	5	19	107	9.1%	49.92 [2.65, 940.84]
Yoichi Tanaka 2015	6	7	19	70	16.4%	16.11 [1.82, 142.69]
Total (95% CI)		60		2131	100.0%	45.60 [18.84, 110.37]
Total events	58		414			

Heterogeneity: Tau^2=0.00; Chi^2=4.25, df=9 (P=0.89); I^2=0%
Test for overall effect: Z=8.47 (P<0.00001)

Favours [TT]   Favours [CC]

Study or subgroup	TC Events	Total	CC Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Ayumi Asada 2016	18	32	25	127	7.2%	5.25 [2.30, 11.96]
Hong-Hui Wang 2018	8	16	11	64	3.6%	4.82 [1.49, 15.61]
Ji Hyeon Lee 2017	14	28	18	131	5.2%	6.28 [2.57, 15.32]
Kang Chao 2017	76	164	90	557	35.9%	4.48 [3.06, 6.56]
Natalia Sutiman 2018	5	16	3	111	0.8%	16.36 [3.44, 77.87]
Suk-Kyun Yang 2014	133	176	199	788	29.0%	9.15 [6.26, 13.38]
Sun-Young Kim 2017	3	8	12	71	2.5%	2.95 [0.62, 14.04]
Swarup A. V. Shah 2017	5	8	0	60	0.1%	190.14 [8.66, 4174.94]
Toshiyuki Sato 2017	24	33	29	109	6.0%	7.36 [3.06, 17.66]
Y Kakuta 2015	10	23	19	107	6.2%	3.56 [1.36, 9.32]
Yoichi Tanaka 2015	13	18	19	70	3.5%	6.98 [2.19, 22.22]
Total (95% CI)		522		2195	100.0%	6.41 [5.19, 7.94]
Total events	309		425			

Heterogeneity: Chi^2=15.75, df=10 (P=0.11); I^2=37%
Test for overall effect: Z=17.12 (P<0.00001)
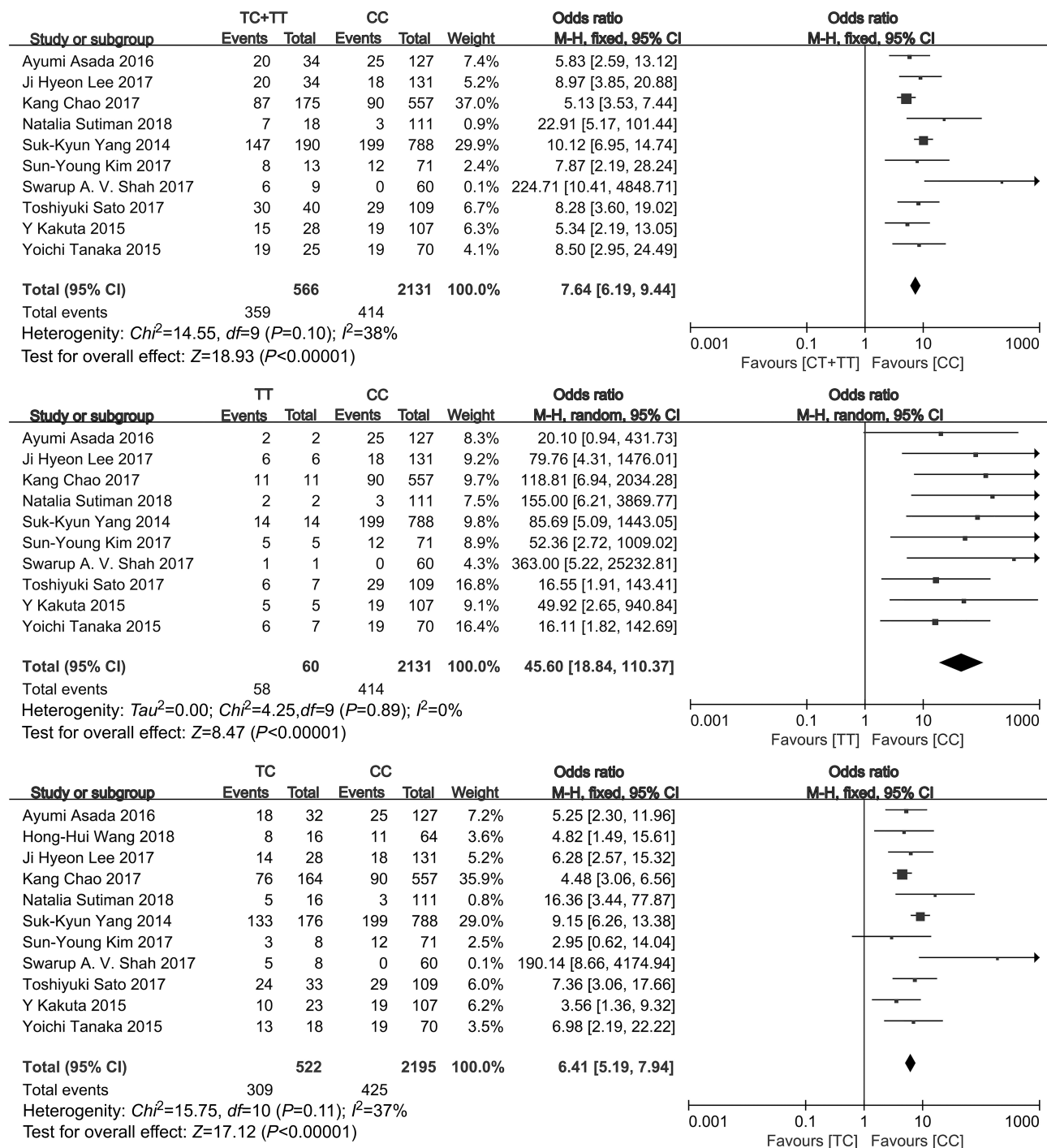
Favours [TC]   Favours [CC]

Figure 2 The forest plots for the meta-analysis of association between NUDT 15 c.415C > T polymorphism and risk of leukopenia in the dominant model and co-dominant model.

also in the Korean race in its dominant model (TC/TT vs CC, OR: 20.48, 95% CI: 9.77–42.91, P<0.00001; OR:0.05, 95% CI: 0.02–0.10, P<0.00001) and co-dominant model (TC vs CC, OR: 13.57, 95% CI: 6.34–29.05, P<0.00001; OR: 0.07, 95% CI: 0.03–0.16, P<0.00001). However, the significant effect was only in the Chinese in the dominant model (TC/TT vs CC, OR: 2.28, 95% CI: 1.23–4.22, P=0.009; OR:0.44, 95% CI: 0.24–0.81, P=0.009), but not in that co-dominant model (TC vs CC, OR: 1.70, 95% CI: 0.89–3.22, P=0.11; OR: 0.59, 95% CI: 0.31–1.12, P=0.11) (Table 4).

Five studies (612 subjects), which mentioned the leukopenia (grade 3–4), revealed significant effects in the
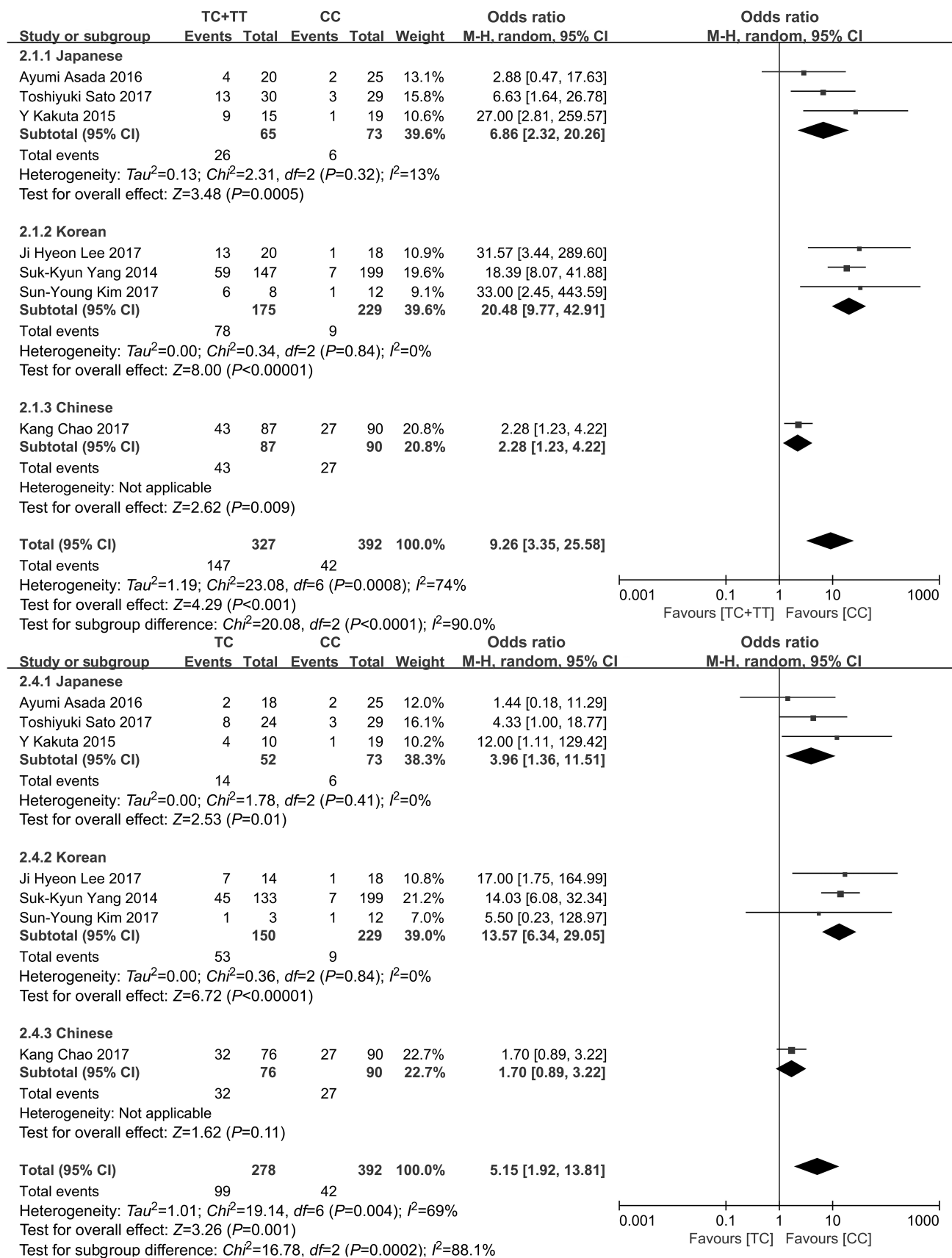
| | TC+TT | | CC | | | Odds ratio | Odds ratio |
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, random, 95% CI
2.1.1 Japanese							
Ayumi Asada 2016	4	20	2	25	13.1%	2.88 [0.47, 17.63]	
Toshiyuki Sato 2017	13	30	3	29	15.8%	6.63 [1.64, 26.78]	
Y Kakuta 2015	9	15	1	19	10.6%	27.00 [2.81, 259.57]	
Subtotal (95% CI)		65		73	39.6%	**6.86 [2.32, 20.26]**	
Total events	26		6				

Heterogeneity: Tau^2=0.13; Chi^2=2.31, df=2 (P=0.32); I^2=13%
Test for overall effect: Z=3.48 (P=0.0005)

2.1.2 Korean							
Ji Hyeon Lee 2017	13	20	1	18	10.9%	31.57 [3.44, 289.60]	
Suk-Kyun Yang 2014	59	147	7	199	19.6%	18.39 [8.07, 41.88]	
Sun-Young Kim 2017	6	8	1	12	9.1%	33.00 [2.45, 443.59]	
Subtotal (95% CI)		175		229	39.6%	**20.48 [9.77, 42.91]**	
Total events	78		9				

Heterogeneity: Tau^2=0.00; Chi^2=0.34, df=2 (P=0.84); I^2=0%
Test for overall effect: Z=8.00 (P<0.00001)

2.1.3 Chinese							
Kang Chao 2017	43	87	27	90	20.8%	2.28 [1.23, 4.22]	
Subtotal (95% CI)		87		90	20.8%	**2.28 [1.23, 4.22]**	
Total events	43		27				

Heterogeneity: Not applicable
Test for overall effect: Z=2.62 (P=0.009)

Total (95% CI)		327		392	100.0%	**9.26 [3.35, 25.58]**	
Total events	147		42				

Heterogeneity: Tau^2=1.19; Chi^2=23.08, df=6 (P=0.0008); I^2=74%
Test for overall effect: Z=4.29 (P<0.001)
Test for subgroup difference: Chi^2=20.08, df=2 (P<0.0001); I^2=90.0%

0.001   0.1   1   10   1000
Favours [TC+TT]   Favours [CC]

| | TC | | CC | | | Odds ratio | Odds ratio |
Study or subgroup	Events	Total	Events	Total	Weight	M-H, random, 95% CI	M-H, random, 95% CI
2.4.1 Japanese							
Ayumi Asada 2016	2	18	2	25	12.0%	1.44 [0.18, 11.29]	
Toshiyuki Sato 2017	8	24	3	29	16.1%	4.33 [1.00, 18.77]	
Y Kakuta 2015	4	10	1	19	10.2%	12.00 [1.11, 129.42]	
Subtotal (95% CI)		52		73	38.3%	**3.96 [1.36, 11.51]**	
Total events	14		6				

Heterogeneity: Tau^2=0.00; Chi^2=1.78, df=2 (P=0.41); I^2=0%
Test for overall effect: Z=2.53 (P=0.01)

2.4.2 Korean							
Ji Hyeon Lee 2017	7	14	1	18	10.8%	17.00 [1.75, 164.99]	
Suk-Kyun Yang 2014	45	133	7	199	21.2%	14.03 [6.08, 32.34]	
Sun-Young Kim 2017	1	3	1	12	7.0%	5.50 [0.23, 128.97]	
Subtotal (95% CI)		150		229	39.0%	**13.57 [6.34, 29.05]**	
Total events	53		9				

Heterogeneity: Tau^2=0.00; Chi^2=0.36, df=2 (P=0.84); I^2=0%
Test for overall effect: Z=6.72 (P<0.00001)

2.4.3 Chinese							
Kang Chao 2017	32	76	27	90	22.7%	1.70 [0.89, 3.22]	
Subtotal (95% CI)		76		90	22.7%	**1.70 [0.89, 3.22]**	
Total events	32		27				

Heterogeneity: Not applicable
Test for overall effect: Z=1.62 (P=0.11)

Total (95% CI)		278		392	100.0%	**5.15 [1.92, 13.81]**	
Total events	99		42				

Heterogeneity: Tau^2=1.01; Chi^2=19.14, df=6 (P=0.004); I^2=69%
Test for overall effect: Z=3.26 (P=0.001)
Test for subgroup difference: Chi^2=16.78, df=2 (P=0.0002); I^2=88.1%

0.001   0.1   1   10   1000
Favours [TC]   Favours [CC]

Figure 3 The forest plots for the meta-analysis of association between NUDT 15 c.415C > T polymorphism and risk of early leukopenia in the dominant model and co-dominant model.

dominant model (TC/TT vs CC, OR:4.17, 95% CI: 2.44–7.11, $P<0.00001$), co-dominant model (TT vs CC, OR: 60.98, 95% CI: 21.10–176.20, $P<0.00001$), co-dominant model (TC vs CC, OR: 2.38, 95% CI: 1.22–4.64, $P=0.01$), and the model (TT vs TC, OR: 28.77, 95% CI: 10.89–76.03, $P<0.0001$). A significant effect was also found in the recessive model (TT vs CC/TC, OR: 20.25, 95% CI: 6.83–60.04, $P<0.00001$) after excluding one study with CD (Table 4).

An obvious difference between *NUDT 15* c.415C > T polymorphism and tolerated thiopurine dose was observed in child ALL and IBD patients. (Figure 4).

A significant association between the *NUDT 15* c.415C > T polymorphism and severe hair loss was observed in all genetic models (TC/TT vs CC, OR: 43.45, 95% CI: 14.51–130.10, $P<0.00001$; TT vs CC/TC, OR: 417.50, 95% CI: 109.76–1588.04, $P<0.00001$; TT vs CC, OR: 656.15, 95% CI: 150.21–2866.13, $P<0.00001$; TC vs CC, OR: 26.18, 95% CI: 4.73–144.95, $P<0.00001$; TT vs TC, OR: 66.29, 95% CI: 17.46–251.74, $P<0.00001$) (Figure 5 and Table 4).

Association between NUDT 15 c.52G > A polymorphism and thiopurine-induced leukopenia

Three studies with 975 subjects presented a significant association between c.52G > A polymorphism and thiopurine-induced leukopenia in the co-dominant model (GA vs GG, OR: 3.52, 95% CI: 1.52–8.17, $P=0.003$) (Figure 6).

Association between NUDT 15 36_37insGGAGTC polymorphism and thiopurine-induced leukopenia

A significant association between 36_37insGGAGTC polymorphism and thiopurine-induced leukopenia was observed in the co-dominant model (-/ins vs -/-, OR: 3.84, 95% CI: 2.50–5.91, $P<0.00001$) (Figure 7).

Heterogeneity and sensitivity analysis

Some significant heterogeneity results between studies were identified when we conducted the meta-analysis. Thus, a random-effect model was performed and the root of heterogeneity was evaluated by subgroup analysis for ethnicity (Table 4). Heterogeneity might also be derived from different diseases, dosage criteria, sample size, or other factors. One study[17] with CD, different from other studies with IBD, was excluded and finally I^2 of the recessive model in leukopenia (grade 3–4) remarkably decreased to less than 50%.

Discussion

To the best of our knowledge, this meta-analysis provides a comprehensive assessment of the association between three *NUDT 15* polymorphisms and specific types of thiopurine-induced leukopenia, and thiopurine intolerance and severe hair loss. After conducting a systematic search across three databases, 16 articles were identified and were eligible for inclusion. The main findings were that *NUDT 15* c.415C > T mutation can significantly increase the risks of thiopurine-induced leukopenia, early
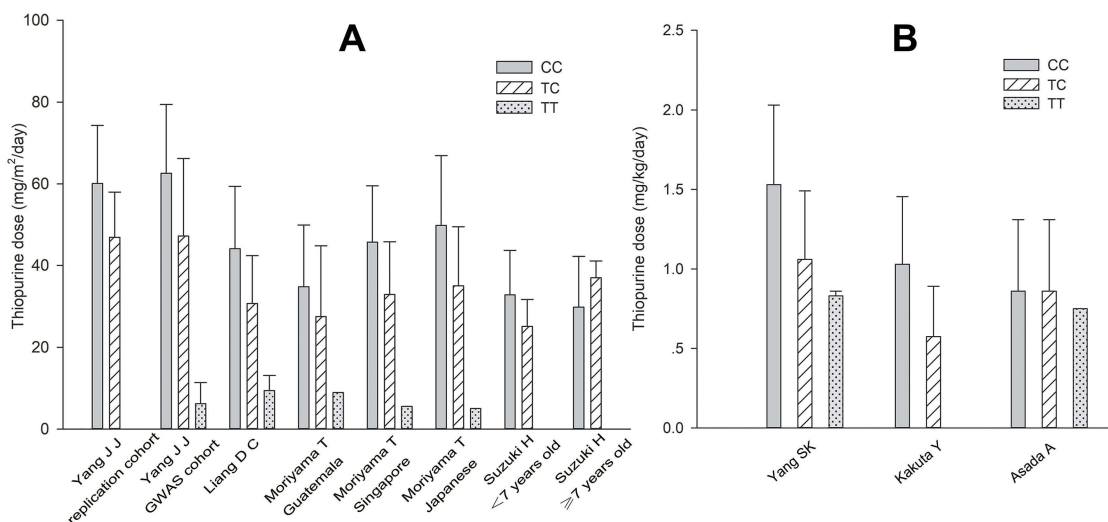

Figure 4 Bar plot of NUDT 15 c.415C > T genotype and the average of 6-MP/AZA among child ALL patients with 6-MP (**A**), and IBD patient with AZA (**B**) in included studies. Each bar includes data with bar height and error bar separately indicating mean and standard deviation of tolerated thiopurine dose. <7 years, the younger age group (under 7 years old); ≥7 years, the older age group (above 7 years old or older).
Abbreviations: ALL, acute lymphoblastic leukemia; IBD, inflammatory bowel disease; 6-MP, 6-mercaptopurine; AZA, azathioprine.
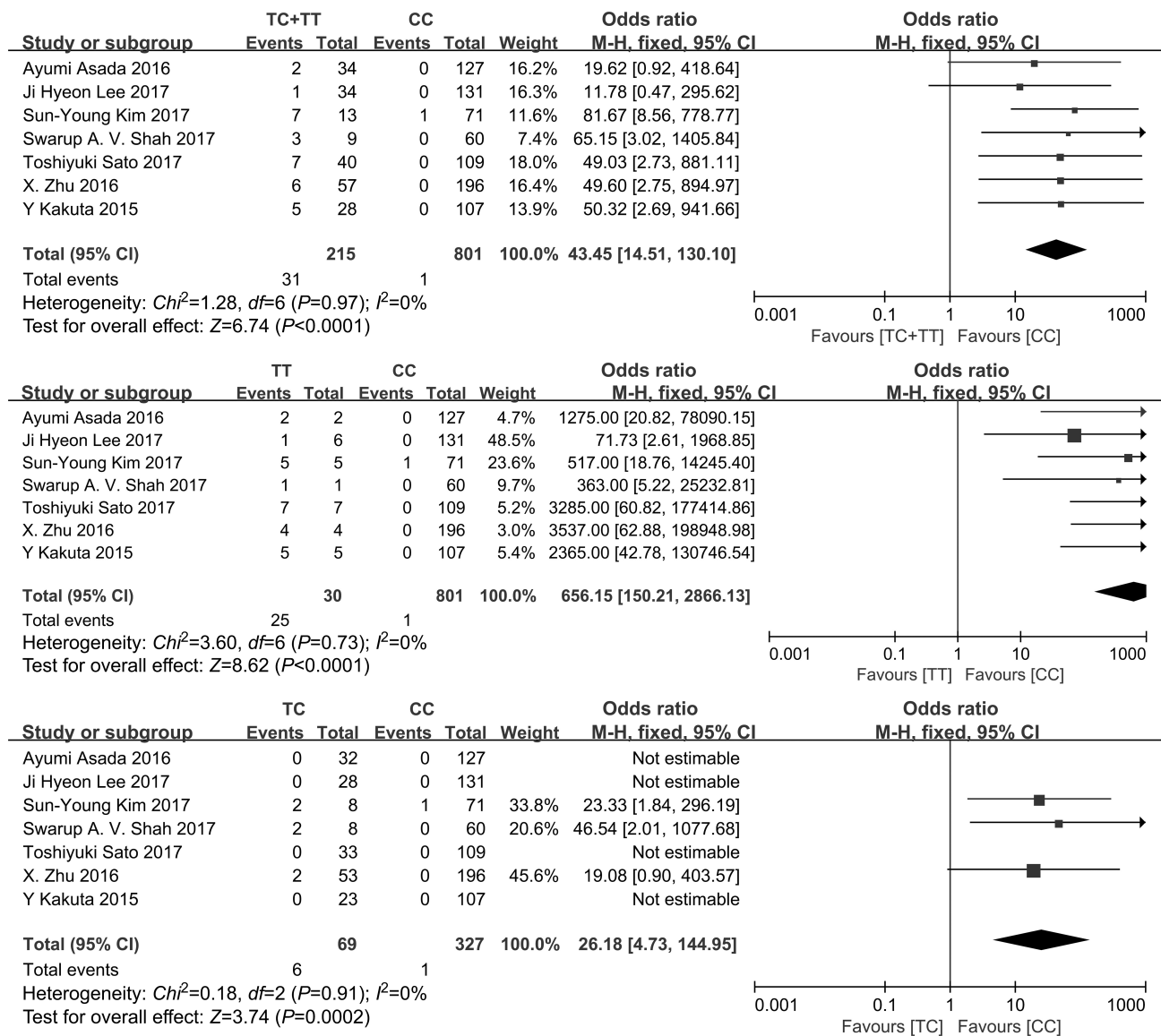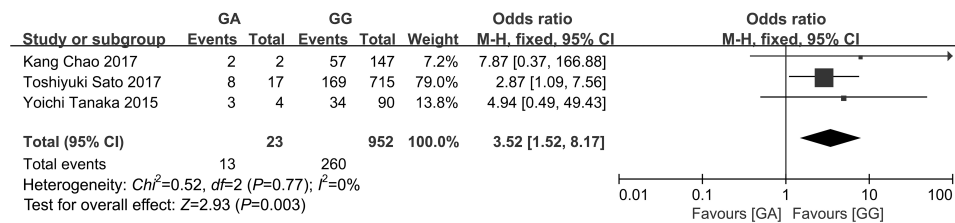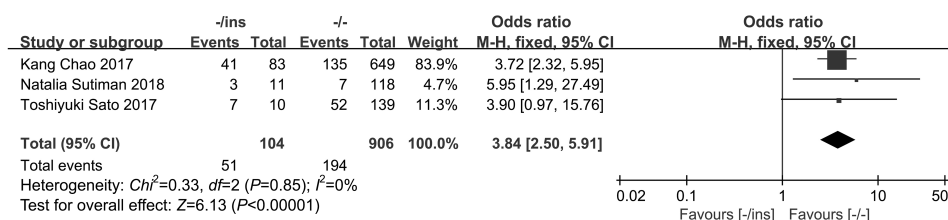
Study or subgroup	TC+TT Events	Total	CC Events	Total	Weight	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
Ayumi Asada 2016	2	34	0	127	16.2%	19.62 [0.92, 418.64]	
Ji Hyeon Lee 2017	1	34	0	131	16.3%	11.78 [0.47, 295.62]	
Sun-Young Kim 2017	7	13	1	71	11.6%	81.67 [8.56, 778.77]	
Swarup A. V. Shah 2017	3	9	0	60	7.4%	65.15 [3.02, 1405.84]	
Toshiyuki Sato 2017	7	40	0	109	18.0%	49.03 [2.73, 881.11]	
X. Zhu 2016	6	57	0	196	16.4%	49.60 [2.75, 894.97]	
Y Kakuta 2015	5	28	0	107	13.9%	50.32 [2.69, 941.66]	
Total (95% CI)		215		801	100.0%	43.45 [14.51, 130.10]	
Total events	31		1				

Heterogeneity: Chi^2=1.28, df=6 (P=0.97); I^2=0%
Test for overall effect: Z=6.74 (P<0.0001)

0.001   0.1   1   10   1000
Favours [TC+TT]   Favours [CC]

Study or subgroup	TT Events	Total	CC Events	Total	Weight	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
Ayumi Asada 2016	2	2	0	127	4.7%	1275.00 [20.82, 78090.15]	
Ji Hyeon Lee 2017	1	6	0	131	48.5%	71.73 [2.61, 1968.85]	
Sun-Young Kim 2017	5	5	1	71	23.6%	517.00 [18.76, 14245.40]	
Swarup A. V. Shah 2017	1	1	0	60	9.7%	363.00 [5.22, 25232.81]	
Toshiyuki Sato 2017	7	7	0	109	5.2%	3285.00 [60.82, 177414.86]	
X. Zhu 2016	4	4	0	196	3.0%	3537.00 [62.88, 198948.98]	
Y Kakuta 2015	5	5	0	107	5.4%	2365.00 [42.78, 130746.54]	
Total (95% CI)		30		801	100.0%	656.15 [150.21, 2866.13]	
Total events	25		1				

Heterogeneity: Chi^2=3.60, df=6 (P=0.73); I^2=0%
Test for overall effect: Z=8.62 (P<0.0001)

0.001   0.1   1   10   1000
Favours [TT]   Favours [CC]

Study or subgroup	TC Events	Total	CC Events	Total	Weight	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
Ayumi Asada 2016	0	32	0	127		Not estimable	
Ji Hyeon Lee 2017	0	28	0	131		Not estimable	
Sun-Young Kim 2017	2	8	1	71	33.8%	23.33 [1.84, 296.19]	
Swarup A. V. Shah 2017	2	8	0	60	20.6%	46.54 [2.01, 1077.68]	
Toshiyuki Sato 2017	0	33	0	109		Not estimable	
X. Zhu 2016	2	53	0	196	45.6%	19.08 [0.90, 403.57]	
Y Kakuta 2015	0	23	0	107		Not estimable	
Total (95% CI)		69		327	100.0%	26.18 [4.73, 144.95]	
Total events	6		1				

Heterogeneity: Chi^2=0.18, df=2 (P=0.91); I^2=0%
Test for overall effect: Z=3.74 (P=0.0002)

0.001   0.1   1   10   1000
Favours [TC]   Favours [CC]

Figure 5 The forest plots for the meta-analysis of association between NUDT 15 c.415C > T polymorphism and risk of severe hair loss in the dominant model and co-dominant model.

Study or subgroup	GA Events	Total	GG Events	Total	Weight	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
Kang Chao 2017	2	2	57	147	7.2%	7.87 [0.37, 166.88]	
Toshiyuki Sato 2017	8	17	169	715	79.0%	2.87 [1.09, 7.56]	
Yoichi Tanaka 2015	3	4	34	90	13.8%	4.94 [0.49, 49.43]	
Total (95% CI)		23		952	100.0%	3.52 [1.52, 8.17]	
Total events	13		260				

Heterogeneity: Chi^2=0.52, df=2 (P=0.77); I^2=0%
Test for overall effect: Z=2.93 (P=0.003)

0.01   0.1   1   10   100
Favours [GA]   Favours [GG]

Figure 6 The forest plots for the meta-analysis of association between *NUDT 15* c.52G > A polymorphism and risk of leukopenia in the co-dominant model.

leukopenia, leukopenia (grade 3–4), and severe hair loss and thiopurine intolerance. Besides, both c.52G > A and c.36_37insGGAGTC were significantly associated with the increased risk of leukopenia. However, the study number and sample size for the two newly found gene mutation sites were relatively small. Thus, further studies on c.52G > A and c.36_37insGGAGTC are needed to demonstrate the association convincingly.

Study or subgroup	-/ins Events	Total	-/- Events	Total	Weight	Odds ratio M-H, fixed, 95% CI	Odds ratio M-H, fixed, 95% CI
Kang Chao 2017	41	83	135	649	83.9%	3.72 [2.32, 5.95]	
Natalia Sutiman 2018	3	11	7	118	4.7%	5.95 [1.29, 27.49]	
Toshiyuki Sato 2017	7	10	52	139	11.3%	3.90 [0.97, 15.76]	
Total (95% CI)		104		906	100.0%	3.84 [2.50, 5.91]	
Total events	51		194				

Heterogeneity: Chi^2=0.33, df=2 (P=0.85); I^2=0%
Test for overall effect: Z=6.13 (P<0.00001)

0.02   0.1   1   10   50
Favours [-/ins]   Favours [-/-]

Figure 7 The forest plots for the meta-analysis of association between NUDT 15 c.36_37insGGAGTC polymorphism and risk of leukopenia in the co-dominant model.

No significant association between c.415C > T and early leukopenia and late leukopenia by subgroup analysis was found in only one Chinese study in the co-dominant model (TC vs CC) in our meta-analysis, which indicated that more studies about the effect of *NUDT 15* c.415C > T polymorphism on early/late leukopenia in Chinese patients were needed to verify this conclusion.

Both the two published systematic reviews/meta-analyses, Yin, D.D.[19] (2750 subjects) and Zhang, A.L.[18] (1138 subjects) revealed that *NUDT 15* c.415C > T mutation could increase the risk of leukopenia, which is in agreement with our findings (4458 subjects). Different from them, we also explore the effect of c.415C > T polymorphism on early/late leukopenia, leukopenia (grade 3–4), and severe hair loss, which could provide physicians with more helpful details such as when leukopenia occurs, how severe leukopenia is, and whether severe hair loss brings patients about anxiety and thiopurine discontinuation. Although, Yin, D.D.[19] probed into the impact of *NUDT 15* c.415C > T polymorphism on thiopurine intolerance, the results only presented that the c.415C > T is associated with thiopurine intolerance in dominant model (TT + TC vs CC) and did not provide further information in other models, from which more specific relative effects could not be read. Besides, it is not appropriate to combine the thiopurine tolerated dose of patients with TT genotype and patients with TC genotype. While we used a bar plot to represent a visualized relative effect for tolerated thiopurine dose among c.415C > T three genotypes both in child ALL and IBD patients instead of synthesizing the data into a meta-analysis, due to insufficient data and difficulty in dose unit mutual conversion between mg/kg and mg/m². And from the bar plot, we can observe that in child ALL patients, thiopurine tolerated dose of c.415C > T homozygous variants is lowest and followed by heterozygous variants and wild-type patients except in the older age group (above 7 years old or older) in Suzuki, H.'s study.[21] However, this study only included 51 patients, and we need more convincing studies to investigate whether c.415C > T

polymorphism has different effects on thiopurine tolerated dose between different age groups. Besides, due to the thiopurine dose for pediatric ALL patients being higher than those for IBD patients, the effect of the c.415C > T polymorphism on thiopurine tolerated dose in IBD patients was not the same obvious effect as the effect in child ALL patients.

Besides the thiopurine-induced specific types of leukopenia, thiopurine intolerance and severe hair loss, several studies also explored whether *NUDT 15* c.415C > T polymorphism can affect other aspects in thiopurine treatment, such as co-effect with *TPMT* mutation, therapy interrupted days, relapse, 5-year event-free survival, and 6-TGNs. Therefore, it can provide us additional information to optimize treatment protocols and improve the clinical outcomes. Yang, J.J.[16] revealed that patients with both TPMT and *NUDT 15* variants required greater dose reductions compared with heterozygous variants at only one of the two loci, indicating additive effects of the two genes on thiopurine intolerance. Yi, E.S.[35] indicated that patients with the *NUDT 15* c.415C > T mutation are likely to have longer therapy interrupted days (P<0.01). Both Tanaka, Y.[20] and Suzuki, H.[21] observed that there existed no significant association between *NUDT 15* c.415C > T polymorphism and increased risk of relapse. Similarly, Liang, D. C.[22] also found *NUDT 15* c.415C > T polymorphism was not significantly associated with 5-year event-free survival. Sutiman, N[28] did not discover significant differences between *NUDT 15* c.415C > T genotypes and 6-TGNs levels after adjustments for thiopurine doses. And Moriyama, T[36] further found the ratio of thio-d-GTP (TdGTP) to TGN (the percent of TGN converted to TdGTP) was significantly higher in *NUDT 15*-deficient patients (P=3.6×10^{-9}). So far, due to the limit number of studies, the data of those outcomes could not be synthesized to provide a more persuasive conclusion. Thus, further studies with a larger sample size, multiple centers, and rational designs should be conducted to better evaluate the impacts of the *NUDT 15* polymorphisms on those newly found outcomes.

Several limitations of our meta-analysis are as follows. Firstly, the diseases of included studies were not limited to a single one and different treatment protocols were applied to different diseases, which possibly influenced the accuracy of the thiopurine-induced toxicities combination. Secondly, studies included in this meta-analysis adopted different chemotherapy regiments of thiopurines even for the same disease, and various thiopurines doses, duration of thiopurines, and combined chemotherapy agents might influence the occurrence of thiopurine toxicities to some extent. Thirdly, different toxicity criteria in those studies would also weaken the reliability of the results in some extent. Therefore, further studies with a larger sample size, multiple centers, and rational designs should be conducted to better evaluate the association between the *NUDT 15* polymorphism and increased risk of thiopurine-induced toxicities for each single disease, especially in Asians.

Conclusion

In conclusion, this meta-analysis confirms that the *NUDT 15* c.415C > T polymorphism, especially in Asians, is significantly associated with thiopurine-induced leukopenia, early/ late leukopenia, leukopenia (grade 3–4), and severe hair loss. Meanwhile, c.52G > A and c.36_37insGGAGTC mutations also probably increase the risk of leukopenia. Thus, preemptive tests for the genotypes of *NUDT 15* polymorphisms are highly recommended to individualize the treatment of thiopurines for a better outcome with less toxicity. However, better-designed and larger trials and further investigations for each single disease conducted separately for pediatrics and adults are required to provide more detailed and applicable conclusions for a better thiopurine-based clinical therapeutic outcome.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this study type informed consent is not required.

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Disclosure

The authors declare no conflicts of interest in this work.

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