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ORIGINAL ARTICLE

Associations between UGT1A1*6 or UGT1A1*6/*28 polymorphisms and irinotecan-induced neutropenia in Asian cancer patients

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Abstract
Purpose Neutropenia is a life-threatening side effect of irinotecan, and uridine diphosphate glucuronosyltransferases (UGTs) gene polymorphisms are considered to be one of the predictive markers of irinotecan-related toxicities. Many studies have demonstrated that patients bearing UGT1A1*28 have a higher risk of severe neutropenia on toxicity of irinotecan. However, UGT1A1 (TA7/TA7) was very rare in Asian populations. Some researches reported that UGT1A1*28 and/or UGT1A1*6 could predict irinotecan-induced toxicities in Asian populations, but controversial conclusions still remained. This study aims to investigate the association between UGT1A1 gene polymorphisms *6, *6/*28 and irinotecan-related neutropenia in Asian cancer patients receiving irinotecan regimen chemotherapy.
Experimental design Meta-analyses were done to assess the relationship between UGT1A1*6 or UGT1A1*6/*28 and irinotecan-induced neutropenia.
Results The risk of neutropenia was significantly higher among patients with a UGT1A1*6 genotype than among those carrying the UGT1A1*1 allele(s) [odds ratio (OR) 3.276; 95 % confidence interval (CI) 1.887–5.688; $P = 0.000$ (*6/*6 vs. *1/*6 or *1/*1)], [OR 1.542; 95 % CI 1.180–2.041; $P = 0.001$ (*6/*6 or *1/*6 vs. *1/*1)]. Also, the risk was significantly higher among patients with a UGT1A1*6/*28 than among those carrying the UGT1A1*1 allele(s) [OR 3.275; 95 % CI 2.152–4.983; $P = 0.000$ (*6/*6 or *28/*28 or *6/*28 vs. *1/*6 or *1/*28 or *1/*1)].
Conclusions In conclusion, the UGT1A1*6 and UGT1A1*6/*28 genotypes were associated with an increased risk of irinotecan-induced neutropenia in Asian cancer patients.

Keywords UGT1A1*6 · UGT1A1*6/*28 · Neutropenia · Irinotecan · Asian cancer population

Fei-fei Han and Chang-long Guo have contributed equally to this work.

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Introduction

Camptothecin is a topoisomerase I inhibitor that causes cancer cell death by forming cleavable complexes with cell DNA, resulting in DNA strand breaks. Irinotecan hydrochloride (CPT-11, CAMPTOSAR) is a prodrug derivative of camptothecin, an alkaloid obtained from plants such as the Camptotheca acuminata tree. Irinotecan is a valuable drug in the treatment for several types of solid tumor,

especially colon, small cell lung [1–3], and gynecological cancers [4, 5]. First-line treatment with irinotecan plus fluorouracil and leucovorin had led to improved survival in patients with advanced colon cancer [6]. However, irinotecan has significant side effects, including neutropenia and delayed-type diarrhea. The risk of life-threatening neutropenia of irinotecan has been consistently associated with genetic variations in UGT1A1 [7, 8]. Irinotecan requires metabolic activation by carboxylesterase 2 to form the active metabolite SN-38, which is further cleared via formation of SN-38 glucuronide (SN-38G) by UGT1A1 isoforms in human liver [9]. Meta-analyses have shown that individuals with reduced UGT1A1 activity, as detected by the presence of the UGT1A1*28 allele, have increased risk of the two major adverse effects of irinotecan: neutropenia and diarrhea.

The US Food and Drug Administration (FDA) has informed that individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of irinotecan treatment. FDA amended the label of irinotecan in November 2004 and approved the diagnostic UGT1A1 test (Invader UGT1A1 Molecular Assay: Third Wave Technologies Inc., Madison, WI, USA) in August 2005 [10]. The frequency of UGT1A1*28 was higher in whites than in Asians (40–50 vs. 15–20 % for heterozygosity; about 10 vs. 4–6 % for homozygosity) [9, 11–15]. In contrast, the polymorphism of UGT1A1*6 characterized by a single-nucleotide substitution in exon 1 of UGT1A1 (211 G > A; GG, GA, and AA genotypes; G71R) and related with reduced SN-38 glucuronidation activity [16, 17] occurred at a higher frequency in Asians [18, 19]. Studies reported that the polymorphism of UGT1A1*6 was associated with irinotecan-induced neutropenia in Asians [16, 20].

Although many studies had been conducted to investigate the associations between UGT1A1*6 or UGT1A1*28/*6 polymorphisms and irinotecan-induced neutropenia, the conclusions were still controversial [21–36]. Our study was conducted to elucidate whether UGT1A1*6 and UGT1A1*6/*28 polymorphisms could predict irinotecan-induced neutropenia in Asian cancer patients on a large scale.

Materials and methods

Bioinformatics analysis of ugt1A1 G71R protein

The characteristics of wild-type ugt1A1 and the G71R mutation were calculated by CLC Protein Workbench software: hydrophobicity, protein charge, antigenicity, and secondary structure of wild-type and mutated ugt1A1.

Search strategy and selection criteria

Two investigators (Fei-fei Han and Chang-long Guo) independently searched PubMed and Embase (from 1980 until July 16, 2013) database using the terms “irinotecan” and “UGT1A1” and “neutropenia”. Furthermore, we reviewed citations in the retrieved articles to search for additional relevant studies. Articles included in meta-analysis were in English, with human subjects, published in the primary literature and with no obvious overlap of subjects with other studies. The retrieved literatures were then read in their entirety to assess their appropriateness for the inclusion in this meta-analysis. Conference abstracts, case reports, editorials, review articles, and letters were excluded. A priori we defined strict criteria for the inclusion of studies. Studies were included if (a) they could be defined as clinical trials, (b) the exposure of interest was the UGT1A1*6 or *6/*28 genotype, (c) the outcome of interest was irinotecan-induced neutropenia (grade III–IV/IV), and (d) the numbers of patients with and without neutropenia were provided. We excluded studies that were not published in English, studies that included <20 patients, and studies that included children patients.

Data extraction

The following information was abstracted from included publications: study design, year, race, irinotecan dose, number of patients with neutropenia (grade III–IV/IV) in each genotype group (UG T1A1*1/*1, UGT1A1*1/*6, and UGT1A 1*6/*6), (UGT1A1*6/*6, UGT1A1*28/*28, UGT 1A1*6/*28, UGT1A1*1/*1, UGT1A1*1/*6, and UGT1A1*1/*28), mutation detection method, and potential confounders.

Statistical analysis

Statistical analyses were performed using Review Manager (Review Manager 5.0 software) and Stata/MP 11.0. Cochran’s w^2 test and the inconsistency index (I^2) were used to evaluate heterogeneity across the included studies. P values of <0.1 for the w^2 test indicated a lack of heterogeneity, and the fixed-effects model was then used to calculate the summary odds ratio (OR). Otherwise, a random-effects model was applied. OR and their corresponding 95 % confidence intervals (CI) were estimated. Z test was performed to determine the statistical significance of pooled OR and was considered significant when $P < 0.05$. We also conducted sensitive analyses, where each study was excluded one at a time to determine the magnitude of influence on the overall summary estimate. We assessed potential publication bias by using a funnel plot and Egger’s test [37].

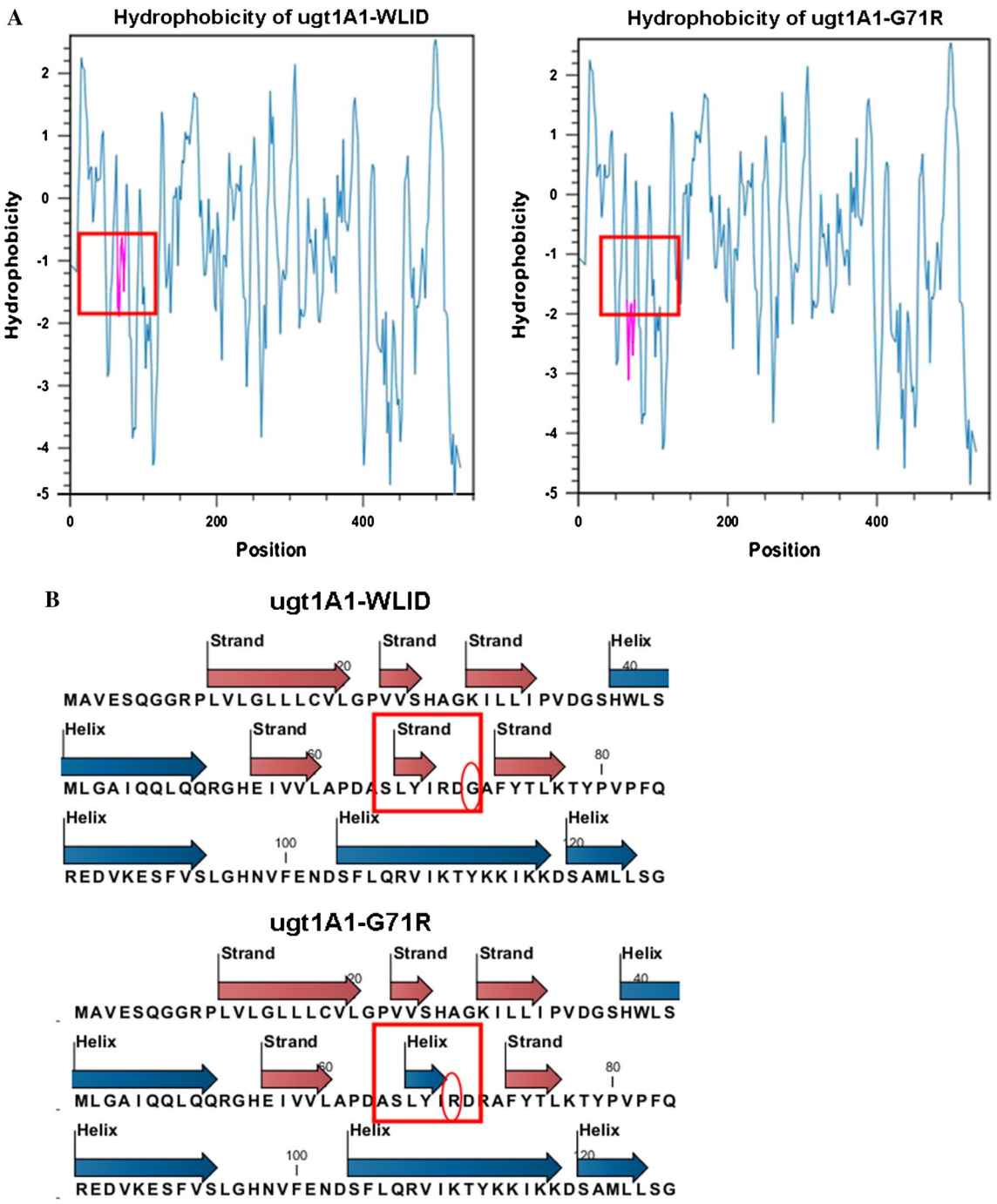

Fig. 1 Characteristics of wild and mutated UGT1A1 protein. **a** The hydrophobicity analysis of wild and mutated UGT1A1 protein. The *red box* indicates the hydrophobicity alteration of Gly to Arg at 71 site, **b** the second structure of wild and mutated UGT1A1 protein the *red box* indicates the changed second structure, and the *red ellipse* indicates the position of G71R

Results

Characteristics of ugt1A1 G71R protein

To assess the influence of G71R mutation to naive protein characteristics, CLC Protein Workbench software was used to test the alteration and the results turned (Fig. 1a, b): site 71 glycine is neutral amino acid and arginine is alkaline amino acid, the mutation of glycine 71 to arginine did not alter the protein charge and antigenicity of ugt1A1 greatly; however, the hydrophobicity seemed be different in ugt1A1 G71R (Fig. 1a). And the protein secondary structure

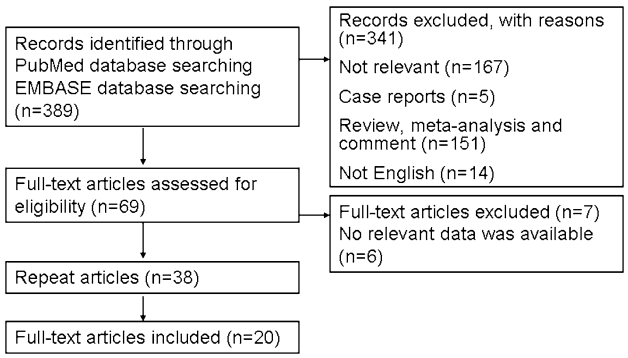

Fig. 2 Flow diagram for study selection in meta-analysis

prediction showed that the amino acid change also changed the seventh second structure of this protein, from alpha-strand to beta-helix (Fig. 1b).

Identification of studies, data extraction, and assessment of study quality

Of the 389 possibly relevant reports identified, 18 studies matched the eligibility criteria. The results of the stages of identifying relevant studies (with reasons for study exclusion) are depicted in Fig. 2. The major reason for exclusion was missing data required to estimate the OR (including the standard error) for the OR between UGT1A1 genotypes. Characteristics of the studies included in meta-analyses are shown in Table 1. Data comparison of OR between *6/*6 and *1/*6 plus *1/*1 genotype patients were available in 8 of the included studies for the analysis [24–27, 30–33]. For the comparison of OR between *6/*6 plus *1/*6 and *1/*1 genotype groups, nine studies had relevant data [23–28, 30, 31, 34]. For the comparison of OR between *6/*28 groups, nine studies had data [23, 30, 31, 38–42]. All studies included in the meta-analyses were generally of comparable methodological quality. Table 2 shows the quality assessment results.

Association between UGT1A1*6 and irinotecan-induced neutropenia

Analysis of pooled data from all samples indicated that UGT1A1*6 allele was significantly associated with irinotecan-induced neutropenia in Asian cancer patients. In the homozygous model, the OR was 3.276 [95 % CI 1.887–5.688; $P = 0.000$ (*6/*6 vs. *1/*6 or *1/*1)] (Fig. 3a). For UGT1A1*1/*6 or *6/*6 versus UGT1A1*1/*1, the OR was 1.542 [95 % CI 1.180–2.041; $P = 0.001$ (*6/*6 or *1/*6 vs. *1/*1)] (Fig. 3b). The heterogeneity across all studies was not statistically significant for any model. I^2 values were 3.83 % ($P = 0.799$) and 30.6 % ($P = 0.173$), respectively, for homozygous and heterozygous models (Table 2). No publication bias was detected by either the funnel plot (Fig. 3a, b) or Egger's tests ($P > 0.05$, each comparison) (Figure S). However, the sensitivity analysis conducted by removed and cumulative statistics have showed that combined ORs of UGT1A1*6 polymorphism was influenced by individual study under *6/*6 and *1/*6 plus *1/*1 genotype comparison.

Association between UGT1A1*6/*28 and irinotecan-induced neutropenia

The results showed that UGT1A1*6/*28 allele was associated with irinotecan-induced neutropenia in Asian cancer patients. In the homozygous model, the OR was 3.275 [95 % CI 2.152–4.983; $P = 0.000$ (*6/*6 or *28/*28 or *6/*28 vs. *1/*6 or *1/*28 or *1/*1)] (Fig. 3c). The heterogeneity across all study was not statistically significant. I^2 value was 10.3 % ($P = 0.65$) (Table 2). No publication bias was detected by either the funnel plot (Fig. 3c) or Egger's tests ($P > 0.05$, each comparison) (Figure S).

Discussion

UGT1A1*6 polymorphism is characterized by a single amino acid substitution (G71R). Based on the bioinformatic analysis, the alteration of Gly to Arg at this site changed the hydrophobicity and second structure of this protein and these might be the decreased efficiency of SN-38 glucuronidation activity. Also, the protein expression levels were found to vary among the UGT1A1s, from a low of approximately 40 %. Some researches suggested that G71R could be critical in combination with other polymorphisms in the UGT1A1 gene [17].

Personal treatment has been a popular field in recent years, and consequently, the molecules involved in the targeting and metabolism of drugs were highlighted in many studies to predict the efficacy and toxicity of treatment. The role of UGT1A1*28 polymorphism in the development of irinotecan-induced neutropenia had been documented in many studies from western countries, the US FDA claimed in 2005 that UGT1A1*28 testing should be included in the label of irinotecan as a risk factor for severe toxicity. However, many studies of Asian cancer patients showed that UGT1A1*28 was not significantly associated with irinotecan-induced neutropenia [25, 27, 28] and this might be because of the lower allelic frequency of UGT1A1*28 than whites and individuals of African descent. In Asian population, UGT1A1*6 is an important mutation variant. Some researches pointed out the importance of UGT1A1*6 in combination with UGT1A1*28 for predicting irinotecan-related neutropenia [25, 39, 43, 44].

Table 1 Characteristics and methodological quality of trails included in the meta-analysis

	Study design	No. of patients	Age (median or mean)	Mutation detection methods	Type of tumors	Chemotherapy regimens	Irinotecan doses (mg/m^2)/ schedule	Grade criteria	Race
Han [32]	Prospective	81	Unknown	Sequencing	Non-small cell lung cancer	Irinotecan and cisplatin	80 mg/m^2 (days 1 and 8, every 3 weeks)	NCI	Korea
Minami [39]	Prospective	117	Unknown	Sequencing	Unknown	Irinotecan alone Irinotecan and cisplatin	100 mg/m^2 weekly 150 mg/m^2 biweekly	NCI	Japanese
Sai [40]	Retrospective	75	50.7 (34–75)	Sequencing	Lung, stomach, colon, breast cancers	Irinotecan alone Irinotecan and other anticancer drugs	60 (weekly or biweekly) or 100 (biweekly) or 150 (biweekly) mg/m^2	NCI	Japanese
Yamamoto [36]	Prospective	39	76	Sequencing	mNSCLC	CPT-11	60–100 mg/m^2	NCI	Japanese
Han [45]	Prospective	107	58 (29–76)	Sequencing	Non-small cell lung cancer	Irinotecan	80 or 65 mg/m^2 (days 1 and 8, every 3 weeks)	NCI	Korea
Seo [22]	Prospective	74	54	PCR–RFLP	Gastric cancer	FOLFOX or FOLFIRI	150 mg/m^2	NCI–CTC	Korea
Takano [42]	Prospective	30	58 (37–75)	Invader assay	Gynecologic cancers	Irinotecan and cisplatin	60 mg/m^2 (days 1, 8, and 15, every 4 weeks)	NCI	Japanese
Onoue [25]	Prospective	133	Unknown	Sequencing	Lung, gastric, colorectal, and other cancers	Irinotecan alone Irinotecan and platinum Irinotecan and other anticancer drugs	60–100 mg/m^2	CTC	Japanese
Park [28]	Prospective	44	54 (17–66)	Sequencing	Gastric cancer	Irinotecan and S1 and oxaliplatin	150 mg/m^2 (day 1, every 3 weeks)	NCI–CTC	Korea
Nakamura [34]	Prospective	78	Unknown	Sequencing	Non-small cell lung cancer	Irinotecan and platinum Irinotecan and Gemcitabine	50 (days 1, 8, and 15, every 4 weeks) or 100 (days 1 and 8, every 3 weeks) mg/m^2	NCI	Japanese
Okuyama [26]	Prospective	52	64 (35–79)	PCR-restriction fragment length polymorphism method	Colorectal cancer	Irinotecan and 5-FU	150 mg/m^2 (day 1, every 2 weeks)	NCI	Japanese
Satoh [41]	Prospective	82	21–88	Invader assay	Gastrointestinal cancer	Irinotecan	150 mg/m^2 (biweekly)	NCI	Japanese
Sunakawa [29]	Retrospective	42	60 (39–72)	Polymerase chain reaction-restriction fragment length polymorphism	Colorectal cancer	FOLFIRI	180 mg/m^2	NCI	Japanese
Jo [21]	Prospective	40	51	Sequencing	Gastric cancer	Irinotecan	350 mg/m^2	NCI	Korea
Choi [38]	Prospective	30	55 (25–67)	Sequencing	Colorectal cancer	CPY-11 and S1	225 mg/m^2 (day 1, every 3 weeks)	NCI	Korea
Wang [27]	Prospective	130	Unknown	Sequencing	Colorectal cancer	FOLFIRI IFL	180 mg/m^2 (day 1, biweekly) 125 mg/m^2 (day 1,8, 15, and 22, every 6 weeks)	NCI	Chinese
Gao [30]	Prospective	276	55 (21–79)	Sequencing	Colorectal cancer	FOLFIRI XELIRI	180 mg/m^2	NCI	Chinese

Table 1 continued

	Study design	No. of patients	Age (median or mean)	Mutation detection methods	Type of tumors	Chemotherapy regimens	Irinotecan doses (mg/m^2)/ schedule	Grade criteria	Race
Gao [31]	Retrospective	133	Unknown	Sequencing	Gastric and esophageal cancer	Irinotecan and platinum Irinotecan and cetuximab FOLFIRI	130 mg/m^2 180 mg/m^2	NCI	Chinese
Zhou [23]	Prospective	94	Unknown	Sequencing	Gastrointestinal cancer	FOLFIRI	180 mg/m^2 (day 1, biweekly)	CTC	Chinese
Takahara [46]	Prospective	56	66 (36–85)	Sequencing	Pancreatic cancer	Irinotecan	100 mg/m^2 (days 1, 8, and 15 every 4 weeks)	NCI	Japanese

NCI National Cancer Institute common toxicity criteria; *CTC* common terminology criteria

Table 2 Summary of meta-analysis

Comparison of outcome	No. of trials	No. of participants	Statistical method	Effect size (95 % confidence intervals)	*P*	Test for heterogeneity		Begg's test	*t*	Egger's test
						I^2 (%)	*P*	*P*		*P*
*6/*6 versus *1/*6 or *1/*1 (recessive genetic model)	7	984	Fixed	3.276 (1.887, 5.688)	0.000	2.79	0.835	0.764	−0.94	0.393
*6/*6 or *1/*6 versus *1/*1 (dominant genetic model)	9	994	Fixed	1.542 (1.180, 2.041)	0.001	18.2	0.281	0.754	0.07	0.942
*6/*6 or *28/*28 or *6/*28 versus *1/*6 or *1/*28 or *1/*1 (recessive genetic model)	11	923	Fixed	3.275 (2.152, 4.983)	0.000	0	0.65	0.213	0.86	0.411

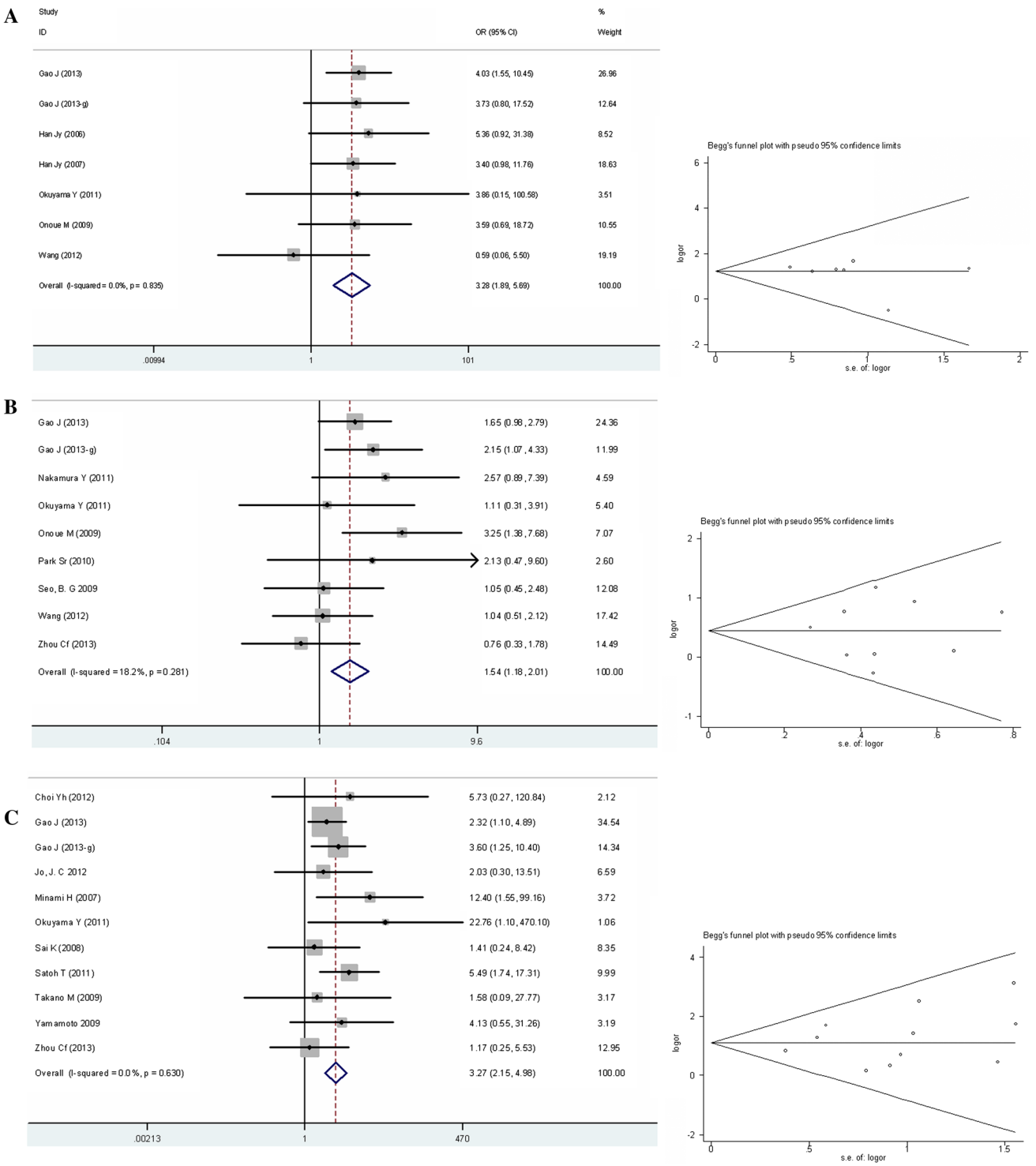

Fig. 3 Summary odds ratio (OR) of irinotecan-induced neutropenia and the Begg's funnel plot for the publication bias test for UGT1A1*6 or UGT1A1*6/*28. **a** *6/*6 versus *1/*6 or *1/*1, **b** *6/*6 or *1/*6 versus *1/*1, **c** *6/*6 or *28/*28 or *6/*28 versus *1/*6 or *1/*28 or *1/*1. A fixed-effects model was used for all analyses. *Squares* represent study-specific estimates (size of the square reflects the study-specific statistical weight); *horizontal lines* represent 95 % confidence intervals (CIs); *diamonds* represent summary estimates with corresponding 95 % CIs

A total of 20 publications were selected in this meta-analysis, and different data were extracted from publications for different analysis. In the UGT1A1*6 genotype analysis, significant effects were observed in both recessive genetic model (*6/*6 vs. *1/*6 and *1/*1) and dominant genetic model (*6/*6 and *1/*6 vs. *1/*1) on irinotecan-induced neutropenia in Asian. For the UGT1A1*6/*28 analysis, significant effects were observed in recessive genetic model (*6/*6, *28/*28, and *6/*28 vs. *1/*6, *1/*28 and *1/*1). Taken together, the above results provided strong evidence that the combination of UGT1A1*6 and *28 can be more clinically important than that of UGT1A1*28 in predicting the risk of irinotecan-related neutropenia in Asian.

There are limitations to this analysis. First, not all studies included adequate data for all comparison analyses. Further, there is inherent heterogeneity to all meta-analyses, and in the analyzed studies, different combinations of chemotherapy regimens were used and patients were of varied performance status. Second, there were differences in study design, doses, polymorphism detection methods, toxicity grade criteria, kinds of cancer, and pretreatment with other regimens. Especially, different combinations of chemotherapy regimens (different types and doses) could have impacted on treatment tolerability, these regimes, such as combination with 5-FU, S1, gemcitabine, with diverse doses will lead to neutropenia with different degrees, but most references involved in this study did not provide detailed data to analyze, and it should be emphasized in future researches. Especially, in most researches, grade 3 (1,000–500/mm^3) or 4 (<500/mm^3) neutropenia was used as the criteria. Grade 3 neutropenia is quite an acceptable toxicity from cytotoxic treatment. So, in the future studies UGT1A1*28 and UGT1A1*6, grade 4 neutropenia should be the criteria used, which is reasonable, as clinicians would wish to either reduce dose or consider colony-stimulating factors in this circumstance, but certainly not so with grade 3 neutropenia without fever or sepsis.

In summary, this meta-analysis provided evidence for the association between the UGT1A1*6 and UGT1A1*6/*28 polymorphism and an increased risk of irinotecan-induced neutropenia in Asian cancer patients. The combination of UGT1A1*6 and *28 might be a hypothetical biomarker for irinotecan in Asian. However, clinical validity is only the first step of several that determine whether a biomarker is applied into clinical. The clinical significance of this last finding requires replication and further research. More larger studies on patients of studies stratified for interactions between tumor stage, genotyping method, and clinical outcome should be conducted to confirm the predictive roles of UGT1A1*6/*28 for irinotecan-induced neutropenia.

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Conflict of interest All authors declare no conflicts of interest.

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