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Association of *Fucosyltransferase 2* Gene Variant with Inflammatory Bowel Diseases: A Meta-Analysis

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Background: Ulcerative colitis (UC) and Crohn's disease (CD) are the 2 main type of inflammatory bowel diseases (IBDs). Several studies have been conducted to investigate the association of *fucosyltransferase 2* gene (*rs601338*) variant with UC and CD, but the results were inconsistent. Here, we performed a meta-analysis to clarify this issue based on a relatively larger sample size.





Material/Methods: A systematic literature search was conducted in PubMed, Embase, CNKI, and Chinese Wangfang databases up to 31 May 2018. Meta results were synthesized by using crude odds ratio with 95% confidence interval. Heterogeneity, sensitivity analysis, subgroup analysis, and publication bias were assessed using STATA 11.0 software.

Results: A total of 8 relevant studies including 3874 IBDs patients (1872 UC cases, 2002 CD cases) and 5445 controls were included for meta-analysis. We found a significant association between *rs601338* A allele and risk of IBDs in the Chinese population (OR=2.35, 95%CI=1.66~3.34, $P=0.001$), but not in whites. Stratified by disease type, we found a significant association between *rs601338* polymorphism with CD and UC in the Chinese population, but not in the white population. In addition, funnel plot and Egger's linear regression test suggests no publication bias in all genetic models.

Conclusions: *Fucosyltransferase 2* gene (*rs601338*) polymorphism is associated with susceptibility to IBD, UC, and CD in the Chinese population, but these results might not be generalizable to other ethnic populations. Further well-designed studies are needed to confirm these findings.

MeSH Keywords: Colitis, Ulcerative • Crohn Disease • Fucosyltransferases • Meta-Analysis • Polymorphism, Genetic

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Background

Inflammatory bowel diseases (IBDs) are a group of chronic and nonspecific inflammatory diseases that mainly comprise ulcerative colitis (UC) and Crohn's disease (CD). Clinical features in both disorders include diarrhea, abdominal pain, weight loss, and increased risk of developing colorectal cancer [1]. The precise etiology of IBDs is not yet fully understood, but numerous studies have suggested that multiple factors, including heredity, environment, infection, and immunity, which interact each other, are involved in the development and exacerbation of the diseases [2]. With the wide application of genome-wide association studies (GWASs) and candidate gene association studies, many susceptibility *loci* for the predisposition of CD have been identified in the populations of northern European origin, such as *NOD2*, *ATG16L1*, and *IRGM* [3–8]. More than 30 single-nucleotide polymorphisms are definitively known to be associated with CD, although these *loci* account for only a minority of the genetic variance to CD in this population [9].

In humans, *Fucosyltransferase (FUT) 2* gene is located in the q13 region of chromosome 19 and encodes a specific fucosyltransferase enzyme. FUT2 enzyme can catalyze transfer of the sugar fucose to acceptor substrates and plays a vital role in the synthesis of histo-blood group antigens (HBGA), including ABH and Lewis (a) antigens [10]. In the past decade, an increasing number of studies has been conducted to explore the association between *FUT2* (*rs601338*) gene polymorphism and susceptibility to IBDs in different populations [11–18]. However, the role of genetic variations on *FUT2* gene (*rs601338*) in the progression of UC and CD remained unclear. These inconsistent results indicate the need for further analysis of the effect of *rs601338* polymorphism on UC and CD risks.

To date, no meta-analysis has been conducted to determine the correlation of *FUT2* gene (*rs601338*) polymorphism with UC and CD risk. Thus, the aim of this study was to clarify the relationship between *FUT2* (*rs601338*) gene variant with UC and CD risk by performing a meta-analysis.

Material and Methods

Identification of eligible studies

A comprehensive literature search was performed in the following databases: PubMed, EMBASE, CNKI, and Chinese Wangfang, up to 31 May 2018. The search terms and keywords were: “polymorphisms or variants”, “fucosyltransferase 2 or FUT2”, and “ulcerative colitis or Crohn's disease or inflammatory bowel disease”. The research subjects were limited to humans, and the language was limited to English or Chinese. References from retrieved papers were also examined for additional studies.

Inclusion criteria

Studies were included in the meta-analysis if they met the following criteria: (1) study on the genetic relationship of *fucosyltransferase 2* gene (*rs601338*) with ulcerative colitis or Crohn's disease or inflammatory bowel disease; (2) case-control study design; (3) genotype distributions were available for both cases and controls to calculate an OR and its 95%CI. Exclusion criteria were as follows: (1) abstract, case report, editorial comment, and review; (2) repeated publication; (3) studies with insufficient genotypic data; (4) studies performed on animal models.

Quality score assessment

The Newcastle-Ottawa scale was used to evaluate the quality of studies. The scale consists of 3 aspects: selection, comparability, and exposure, with a maximum score of 9 [19]. Any disagreements were adjudicated by a third reviewer. A total score of ≤ 3 , 4–6, ≥ 7 was considered to indicate low-, medium-, and high-quality studies, respectively.

Data extraction

Two investigators independently and carefully extracted available data from each eligible study. The following details were extracted from all eligible studies: (1) first author's name, (2) year of study publication, (3) origin of participants, (4) race of included subjects, (5) source of control population, (6) sample size of cases and controls, and (7) results of the Hardy-Weinberg equilibrium (HWE) test for the controls. Discrepancies were resolved by discussion within our research team.

Statistical analysis

The effect sizes were calculated using odds ratios (ORs) and 95% confidence interval (95%CI) to evaluate the association between the *fucosyltransferase 2* gene (*rs601338*) polymorphism and inflammatory bowel disease, ulcerative colitis, and Crohn's disease risk. Pooled ORs were calculated by using 4 genetic models: allelic model (A vs. G), dominant model (AA+AG vs. GG), recessive model (AA vs. AG+GG), and homozygous model (AA vs. GG).

Heterogeneity among the eligible studies was analyzed by the chi-square test based on the Q statistic, with significant heterogeneity considered to be present at P value < 0.10 [20]. The I^2 statistic test was used to quantify the heterogeneity across individual studies ($P < 0.10$ and $I^2 > 50\%$ suggested heterogeneity). The fixed-effects model on the Mantel-Haenszel method was used to estimate the pooled OR if $I^2 < 50\%$; otherwise, the random-effects model on the DerSimonian and Laird method was used. Heterogeneity was also quantified by the I^2 test, the values of I^2 in 0–25%, 26–50%, and 50–100% were considered as lower, moderate, and high heterogeneity, respectively.

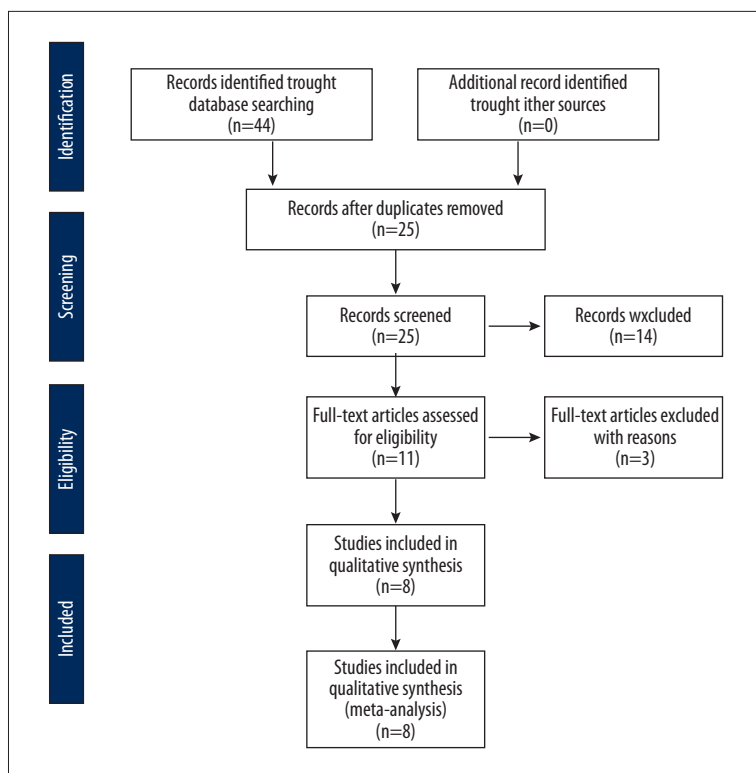


Figure 1. Selection of studies on the association between *FUT2* (*rs601338*) polymorphism and IBDs.

We evaluated the potential publication bias by using the Begg’s funnel plot and the Egger’s linear regression tests [21,22], which measures funnel plot asymmetry on the natural logarithm scale of the effect size. One-way sensitivity analysis was used to assess which study has a significant impact on the stability of results.

All statistical analyses were performed using STATA version 11.0 software (STATA Corporation, College Station, TX). A 2-sided *P* value of less than 0.05 was considered statistically significant.

Results

Characteristics of eligible studies

As Figure 1 shows, the selection process of the studies involved in this meta-analysis was performed according to PRISMA flow diagram. We found 44 potentially relevant papers from databases (16 in PubMed, 17 in Embase, 8 in CNKI, and 3 in Chinese Wangfang). Among these, 19 duplicates were removed, and another 14 studies were removed due to irrelevant topics, reviews, and not about IBDs or *fucosyltransferase 2* gene. The remaining 11 studies underwent full publication review, during which 3 studies were excluded due to insufficient data for calculating OR and 95%CI. Finally, a total of 8 studies were included in this meta-analysis. The basic characteristics of these studies are shown in Table 1.

FUT 2 gene (*rs601338*) variant with IBDs

The details of the association between *FUT 2* gene (*rs601338*) variant and risk of IBDs are shown in Table 2. The heterogeneity analysis of *rs601338* polymorphism showed significant heterogeneity in A vs. G ($I^2=79.6\%$, $P<0.001$), AA+AG vs. GG ($I^2=82.5\%$, $P<0.001$), AA vs. GG ($I^2=60.4\%$, $P=0.014$) genetic models in the all populations, so the random-effects model was used in these comparisons. Overall, significant associations between *FUT 2* gene (*rs601338*) polymorphism and risk for IBDs were found in the allelic model (A vs. G: OR=1.42, 95%CI=1.05~1.91, $P=0.022$) and recessive model (AA vs. AG+GG: OR=1.29, 95%CI=1.10~1.52, $P=0.002$) in all populations (Figure 2). No significant associations were found in dominant and homozygous models in any populations.

Further subgroup analysis was carried out by grouping the data based on the population (7 studies in Chinese and 3 studies in whites). The results showed significant associations between *FUT2* gene (*rs601338*) polymorphism and risk for IBDs in allelic model (A vs. G: OR=2.35, 95%CI=1.66~3.34, $P<0.001$) and dominant model (AA+AG vs. GG: OR=2.53, 95%CI=1.76~3.63, $P<0.001$), but not in recessive and homozygous models in Chinese populations. We did not find any significant association between *FUT2* gene (*rs601338*) polymorphism and risk for IBD in all genetic models in whites.

Table 1. Basic characteristics of the eligibility studies included in this meta-analysis.

First author [ref]	Publication year	Region	Population	Sample size			Genotyping method	NOS Score	HWE
				UC cases	CD cases	Controls			
McGovern [11]	2010	USA	Caucasian	0	896	3204	PCR	7	Y
Aheman [12]	2012	China	Chinese	102	0	310	PCR	7	Y
Parmar [13]	2012	Finland	Caucasian	496	280	2738	PCR	8	Y
Hu [14]	2014	China	Chinese	0	273	479	PCR	7	Y
Xu [15]	2014	China	Chinese	233	0	292	PCR	8	Y
Lan [16]	2015	China	Chinese	160	0	187	Direct sequence	7	Y
Hu [17]	2016	China	Chinese	485	0	580	PCR	8	Y
Wu [18]	2017	China	Chinese	396	275	502	PCR	8	Y

UC – ulcerative colitis; CD – Crohn’s disease; PCR – polymerase chain reaction; HWE – Hardy-Weinberg disequilibrium; NOS – Newcastle-Ottawa scale; USA –United States of America; Y – indicate genotype distribution in control conform to HWE.

Table 2. Meta-analysis of the association of fucosyltransferase 2 (rs601338) polymorphism with inflammatory bowel disease.

Groups	Statistical model	Allele/genotype	Method	I ² (%)	P ^a	OR (95% CI)	P ^b	Begg’s (P-value)	Egger’s (P-value)
Overall	Allelic	A vs. G	Random	79.6	<0.001	1.42 (1.05~1.91)	0.022	0.592	0.137
	Recessive	AA vs. AG+GG	Fixed	24.6	0.217	1.29 (1.10~1.52)	0.002	0.858	0.849
	Dominant	AA+AG vs. GG	Random	82.5	<0.001	1.46 (1.00~2.13)	0.053	1.000	0.092
	Homozygous	AA vs. GG	Random	60.4	0.014	1.30 (0.86~1.97)	0.211	0.536	0.664
Chinese	Allelic	A vs. G	Fixed	0.0	0.450	2.35 (1.66~3.34)	<0.001	0.221	0.505
	Recessive	AA vs. AG+GG	Fixed	0.0	0.999	1.34 (0.62~2.90)	0.462	0.086	0.345
	Dominant	AA+AG vs. GG	Fixed	0.0	0.472	2.53 (1.76~3.63)	<0.001	0.027	0.140
	Homozygous	AA vs. GG	Fixed	0.0	0.998	1.68 (0.77~3.63)	0.190	1.000	0.347
Caucasian	Allelic	A vs. G	Random	90.4	<0.001	1.05 (0.96~1.15)	0.665	1.000	0.707
	Recessive	AA vs. AG+GG	Random	83.1	0.003	1.29 (0.84~1.98)	0.248	1.000	0.758
	Dominant	AA+AG vs. GG	Random	84.5	0.002	1.00 (0.70~1.39)	0.936	0.296	0.564
	Homozygous	AA vs. GG	Random	88.1	<0.001	1.23 (0.70~2.15)	0.473	1.000	0.633

R – odds ratio; CI – confidence interval; P^a – P value for between-study heterogeneity; P^b – P value for test of the association.

FUT2 gene (rs601338) variant with UC

The details of the association between *FUT2* gene (rs601338) variant and risk of UC are shown in Table 3. Overall, no significant association was found in any genetic models in any populations. However, when stratified by population, significant associations were found in the allelic model (A vs. G; OR=2.18, 95%CI=1.48~3.23, P<0.001) and dominant model (AA+AG vs. GG; OR=2.38, 95%CI=1.57~3.62, P<0.001), but not in recessive or homozygous models in Chinese populations (Figure 3).

Because there was only 1 study in a white population, it was excluded from subgroup analysis.

FUT2 gene (rs601338) variant with CD

The detailed results of the association between *FUT2* gene (rs601338) variant and risk of CD are shown in Table 3. Overall, a significant association was found in the recessive model (AA vs. AG+GG; OR=1.55, 95%CI=1.25~1.93, P<0.001), but not in allelic, dominant, and homozygous models. Subgroup analysis

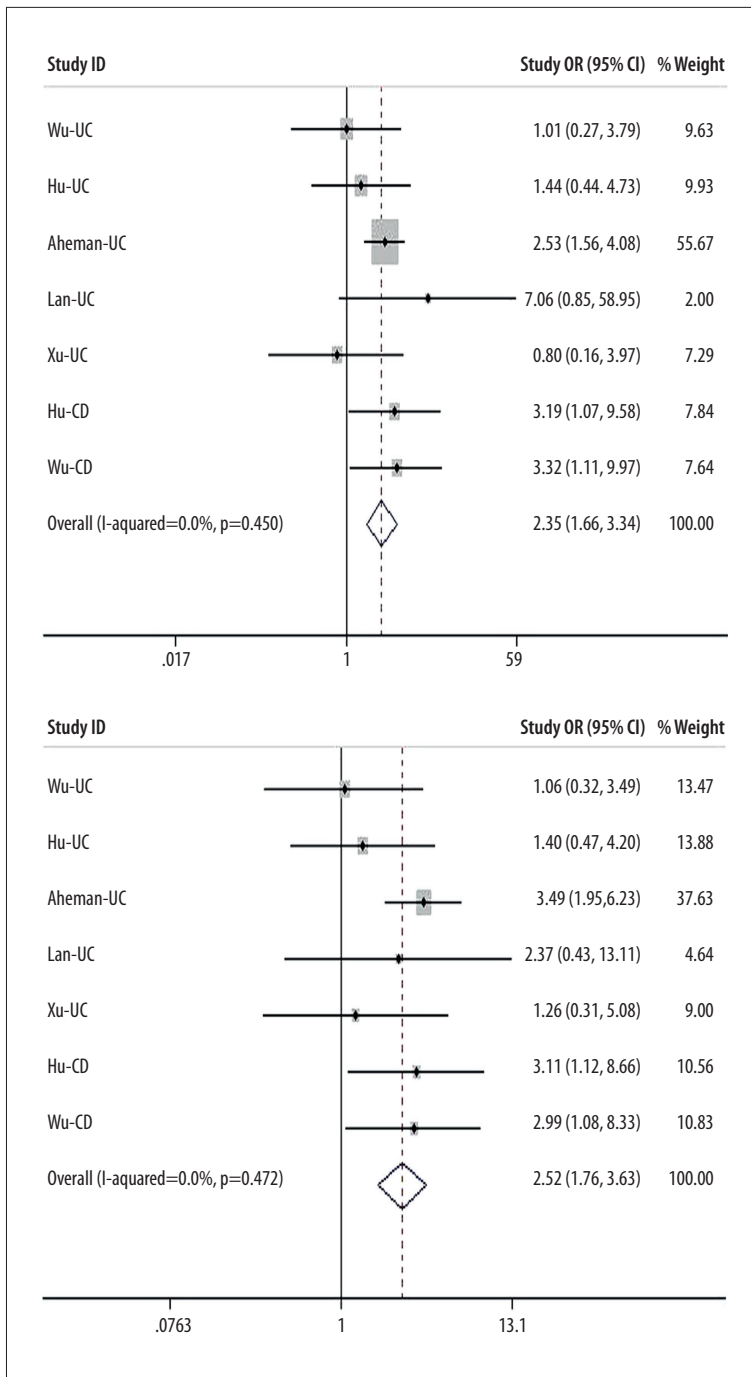


Figure 2. Forest plot for pooled ORs for the associations between allelic (A vs. G) and dominant (AA+AG vs. GG) models of *rs601338* and IBDs risk in the Chinese population.

showed that fucosyltransferase 2 gene (*rs601338*) variant was associated with CD risk in the allelic model (A vs. G: OR=3.26, 95%CI=1.50~7.08, $P=0.003$) and dominant model (AA+AG vs. GG: OR=3.05, 95%CI=1.48~6.29, $P=0.003$), but not in recessive and homozygous models in Chinese populations. We did not find any significant association between *FUT2* gene (*rs601338*) polymorphism and risk for CD in all genetic models in whites.

Sensitive analysis and publication bias

Sensitive analysis was conducted to determine if our results were substantially affected by any individual study. Our results suggested that the pooled effects were not significantly influenced by the omission of any individual study. Begg’s and Egger’s tests were performed in all comparisons except for comparisons of *FUT2* gene (*rs601338*) polymorphism and risk for CD in all genetic models in Chinese and white populations because only 2

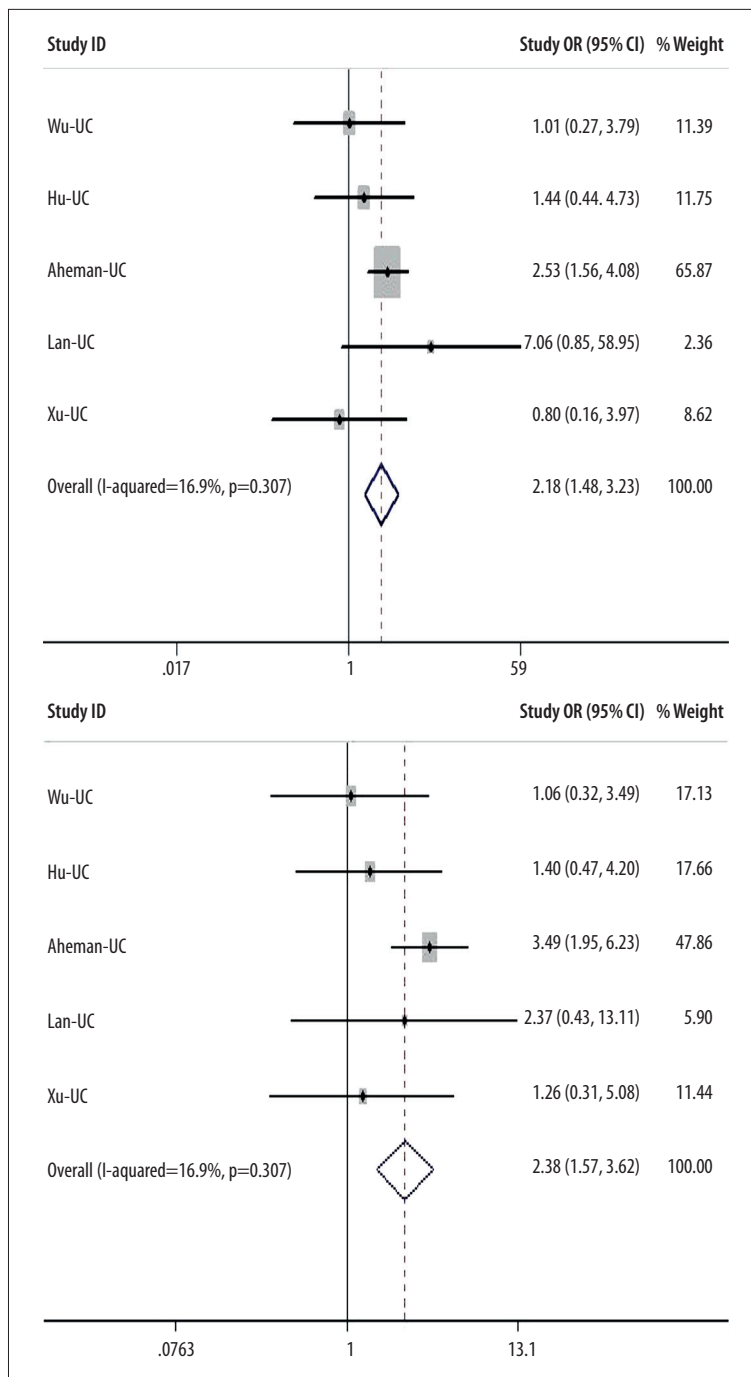


Figure 3. Forest plot for pooled ORs for the associations between allelic (A vs. G) and dominant (AA+AG vs. GG) models of *rs601338* and UC risk in the Chinese population.

studies were included in these comparisons. Begg's funnel plots showed the shape was symmetrical, and Egger's linear regression analysis indicated no publication bias (Tables 2, 3 and Figure 4).

Discussion

The associations between *FUT2* genes and susceptibility to IBDs in different populations have been widely reported.

However, the outcomes of these studies vary from study to study. Hu et al. found that mutant A allele and AG genotype of *FUT2* gene (*rs601338*) were significantly increased in CD patients in Chinese populations [14], but they failed to find any association between *rs601338* of *FUT2* and UC severity [17]. Aheman et al. [12] observed that *rs601338* was statistically correlated with UC risk in Chinese populations, and AA homozygous frequencies of *rs601338* were lower in the UC groups than in the controls (12.2% vs. 15.2%). Parmar et al. [13]

Table 3. Meta-analysis of the association of fucosyltransferase 2 (rs601338) polymorphism with ulcerative colitis and Crohn's disease.

Groups	Statistical model	Allele/genotype	Method	I ² (%)	P ^a	OR (95% CI)	P ^b	Begg's (P-value)	Egger's (P-value)
UC									
Overall	Allelic	A vs. G	Random	82.2	0.001	1.37 (0.68~2.75)	0.378	1.000	0.414
	Recessive	AA vs. AG+GG	Fixed	0.0	0.951	1.00 (0.78~1.30)	0.984	0.734	0.242
	Dominant	AA+AG vs. GG	Random	86.4	<0.001	1.44 (0.61~3.45)	0.407	1.000	0.397
	Homozygous	AA vs. GG	Fixed	0.0	0.562	0.94 (0.71~1.23)	0.645	0.734	0.363
Chinese	Allelic	A vs. G	Fixed	16.9	0.307	2.18 (1.48~3.23)	<0.001	0.296	0.110
	Recessive	AA vs. AG+GG	Fixed	0.0	0.999	1.27(0.55~2.94)	0.572	1.000	0.428
	Dominant	AA+AG vs. GG	Fixed	22.3	0.273	2.38 (1.57~3.62)	<0.001	0.296	0.037
	Homozygous	AA vs. GG	Fixed	0.0	0.951	1.65 (0.72~3.82)	0.240	1.000	0.055
CD									
Overall	Allelic	A vs. G	Random	84.0	<0.001	1.47(0.96~2.26)	0.078	0.734	0.447
	Recessive	AA vs. AG+GG	Fixed	49.1	0.117	1.55 (1.25~1.93)	<0.001	0.734	0.980
	Dominant	AA+AG vs. GG	Random	81.3	0.001	1.49 (0.89~2.50)	0.130	1.000	0.308
	Homozygous	AA vs. GG	Random	68.5	0.023	1.50 (0.79~2.85)	0.216	0.734	0.952
Chinese	Allelic	A vs. G	Fixed	0.0	0.960	3.26 (1.50~7.08)	0.003	–	–
	Recessive	AA vs. AG+GG	Fixed	0.0	0.984	1.79 (0.25~12.74)	0.561	–	–
	Dominant	AA+AG vs. GG	Fixed	0.0	0.957	3.05 (1.48~6.29)	0.003	–	–
	Homozygous	AA vs. GG	Fixed	0.0	0.984	1.83 (0.26~13.04)	0.546	–	–
Caucasian	Allelic	A vs. G	Random	91.9	<0.001	1.17 (0.76~1.81)	0.477	–	–
	Recessive	AA vs. AG+GG	Random	83.0	0.015	1.49 (0.86~2.59)	0.158	–	–
	Dominant	AA+AG vs. GG	Random	88.4	0.003	1.09 (0.65~1.84)	0.749	–	–
	Homozygous	AA vs. GG	Random	89.4	0.002	1.47 (0.68~3.19)	0.332	–	–

R – odds ratio; CI – confidence interval. P^a – P value for between-study heterogeneity; P^b – P value for test of the association between rs601338 polymorphism with ulcerative colitis and Crohn's disease.

showed that the A allele of rs601338 was associated with UC and UC+CD, indicating that FUT2 secretor status may play a role in IBD in the Finnish population. Wu et al. [18] showed that mutant A allele and genotype of FUT2 rs601338 were significantly increased in CD patients from southeast China. However, there were no statistically significant differences in allele and genotype frequencies of FUT2 gene in UC patients compared to controls.

The inconsistency among different studies seems to be mainly due to the relatively small sample size of most studies and the different populations studied, and there was inadequate statistical power to detect a slight association between FUT2 genes and susceptibility to IBDs. Other possible explanations

include diverse study designs and methods, differences in race and geography, and publication bias. Meta-analysis is an effective statistical method that pools the results of independent studies to get comprehensive results. It has been widely used in evaluating the relationship between candidate genes and complex diseases with genetic predisposition.

This systematic review and meta-analysis was performed to determine the association between rs601338 polymorphism and susceptibility to IBDs. The results demonstrated that rs601338 polymorphism was associated with IBD in allelic and dominant genetic models in Chinese, but not in whites, in all genetic models. After being stratified by disease type, similar results were also presented in CD. In UC, this association was

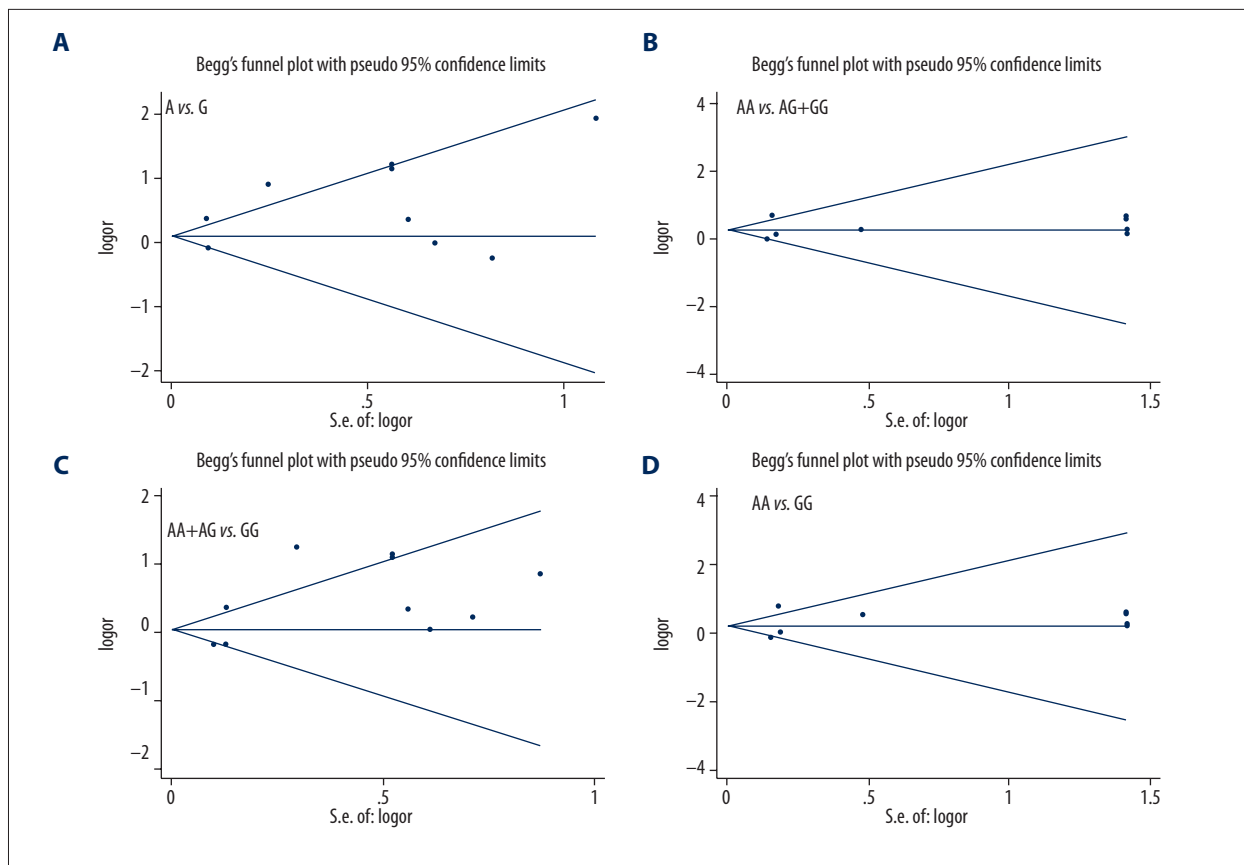


Figure 4. (A–D) Begg's funnel plot for association between *rs601338* polymorphism and IBDs under 4 genetic models.

only observed in the Chinese population. The different results presented in different populations illustrates that *FUT2* genes polymorphisms with IBDs susceptibility might be associated with race. Of note, the results of *rs601338* polymorphism with CD risk in whites in this meta-analysis were inconsistent with the findings of the previous GWAS replication study (*rs601338* not covered in this GWAS, but covered in the replication study), which used a confirmatory cohort of 1174 cases and 357 controls and demonstrated that *FUT2 rs601338* is associated with CD in whites [11]. The cause of this inconsistency may be population differences (genetic and/or microbial), but it is also not unlikely that our study lacked power to identify an association of *FUT2* with CD. A larger follow-up study of CD in the white population will help elucidate the true effect of *FUT2* variation in CD risk.

Although the etiology and pathology of IBDs are unknown, a previous study showed that imbalances in the species of bacteria that live in our guts may be linked to the development of diseases [23]. *FUT2* is the key enzyme determining the presentation of HBGA antigens in intestinal mucosal tissue [24]. HBGA, including ABH antigens and Lewis antigens, act not only as binding sites for intestinal microbes such as *Helicobacter pylori*, *Campylobacter jejuni*, norovirus, and rotavirus, but also are

a carbon source for microbes, including *Escherichia coli* [25–27]. The *FUT2* gene that codes for an alpha-(1,2)-fucosyltransferase is a Golgi stack membrane protein involved in creation of a precursor of the H antigen, which forms the basis of A and B antigen synthesis [28]. *FUT3* encodes alpha-(1,3/4)- fucosyltransferase, which is required to synthesize Lewis a antigens, and mostly utilizes the H antigen, determined by *FUT2*, as a substrate to synthesize Lewis b antigen [29]. The intestinal microbiota can be influenced by *FUT2* and *FUT3*, which control presentation of HBGA on the gastrointestinal mucosa and in bodily secretions [30]. *FUT2* gene polymorphisms influence presentation of HBGA antigens in the gastrointestinal mucosa and their secretion, and further affect the microbiota composition in the human intestine [31].

Although an advantage of this meta-analysis is pooling good-quality individual studies with relatively large sample sizes for a comprehensive result, but several limitations should be addressed when interpreting our results. Firstly, we included relevant articles published only in English and Chinese, so language bias may exist in this study. Secondly, most of the studies are conducted in Chinese populations, and there were few studies in the white subgroup analyses, which could have led to insufficient statistic power to detect weak relationships. Thirdly,

the onset of IBD is affected by risk factors such as age, sex, genetic variants, and exposure to environmental factors and their interactions. However, only gene polymorphisms were considered in this study. The effects of gene-gene and gene-environment interactions on the initiation and development of the disease need to be further studied.

Conclusions

Our meta-analysis provides statistical evidence that the *FUT2* gene (rs601338) polymorphism is associated with IBD, UC, and

CD in the Chinese population, but these results might not be generalizable to other ethnic populations. To provide better guidance for clinical practice, further well-designed studies are warranted to clarify the mechanism and increase comprehensive understanding of the role of the *FUT2* gene (rs601338) polymorphism in IBDs.

Conflicts of interest

None.

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