Contribution of NKX2-3 Polymorphisms to Inflammatory Bowel Diseases: A Meta-Analysis of 35358 subjects

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Polymorphisms in NKX2-3 gene have been inconsistently associated with Crohn’s disease (CD) and ulcerative colitis (UC). To generate large-scale evidence on whether NKX2-3 polymorphisms are associated with CD or UC susceptibility, we have conducted a meta-analysis of 17 studies involving 17329 patients and 18029 controls. A significantly increased CD or UC risk was observed in persons carrying a G allele at rs10883365 polymorphism (A/G) compared with those with an A allele. (OR 1.226, 95%CI: 1.177–1.277 and OR 1.274, 95%CI: 1.175–1.382 respectively). In the subgroup analysis, a significantly increased CD risk was found in both Europeans and Asians. For rs11190140 polymorphism (C/T) and CD risk, the risk estimate for the allele contrast was OR 1.201 (1.136–1.269). This meta-analysis provided a robust result that persons with a G or T allele may have a moderately increased risk of CD, and suggested that rs10883365 polymorphism was also a candidate gene polymorphism for UC susceptibility.

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders characterized by chronic relapsing inflammation of the gastrointestinal tract that affect 0.1% of Western populations, comprising two major forms, Crohn’s disease (CD) and ulcerative colitis (UC). In Crohn’s disease, the inflammation is often transmural, whereas in ulcerative colitis, the inflammation is typically confined to the mucosa. Additionally, Crohn’s disease can be associated with intestinal granulomas, strictures, and fistulas, but these are not typical findings in ulcerative colitis. Although our understanding of disease pathogenesis remains incomplete, accumulating evidence suggests that IBD is a complex, multifactorial disease partly determined by a genetic predisposition. Strong familial aggregation, twin studies, and established genetic associations indicate that there is a genetic component to the disease susceptibility in IBD. Recently, sequence variations associated with IBD have been reported for several genes, including NOD2, IL23R, IRGM, ATG16L1, PTPN2, and NK2 transcription factor related and locus 3 (NKX2-3).

NKX2-3, located on 10q24, is a member of a family of genes that encode transcription factors containing homeodomains and, therefore, is implicated in basic developmental functions. During development, NKX2-3 is expressed in midgut and hindgut mesoderm and spleen, as well as in pharyngeal endoderm. The association between the NKX2-3 polymorphism and susceptibility of IBD was first reported in Caucasian patients. After the first report of the association, several studies confirmed the association of tag-SNPs (rs10883365 and rs1190140) in the NKX2-3 gene with CD and UC in Caucasian or Asian populations. However, several studies could not replicate the genetic association between IBD and NKX2-3 polymorphisms.

Thus, a quantitative synthesis may help to provide clearer evidence on the association of such genetic polymorphisms with IBD. In the present study, we conducted a meta-analysis of all eligible studies to quantitatively assess the associations between three common polymorphisms (rs10883365 and rs1190140) in the NKX2-3 gene and IBD susceptibility.

Results

Characteristics of the included studies. The combined search yielded 75 references, of which 31 were duplicate studies, 9 were reviews, 4 were about cell studies, 8 were only with abstracts, 7 reported other mutations, 1 reported other disease. Finally, a total of 15 articles were finally included. Among them, one publication contained data on two different subpopulations, one included Welcome Trust Case Control Consortium (WTCCC) samples and replication Crohn’s disease (RCD) samples, and we treated them independently. In total, 17 studies comprising 17329 cases and 18029 controls were included in the present meta-analysis.
| Author, Year of publication | Ethnicity | NKX2-3 variant | Phenotype Studied | Number | Males (%) | Age or Age at diagnosis | Number | Males (%) | Age | Matching |
|-----------------------------|----------|----------------|-------------------|--------|-----------|-------------------------|--------|-----------|-----|----------|
| Tanaka, 2009                | Asians   | rs10883365     | CD and UC separately | 174    | 65.5      | CD: 16–61               | 394    | 48.0      | 19–76 | nr       |
| Meggyesi, 2010              | Europeans| rs10883365     | CD and UC separately | 810    | 53.6      | CD: 37.1 ± 12.6 and 26.5 ± 10.6 at diagnosis | 469    | 53.5      | 40.5 ± 11.5 | Age and sex |
| Meggyesi, 2010              | Europeans| rs10883365     | CD and UC separately | 428    | 47.2      | UC: 43.7 ± 15.0 and 31.3 ± 13.4 at diagnosis | 2017   | nr        | nr    | nr       |
| Fisher, 2008                | Europeans| rs10883365     | UC separately       | 1841   | nr        | nr                      | 1841   | nr        | nr    | nr       |
| Franke, 2008                | Europeans| rs10883365     | CD and UC separately | 1850   | 32.0      | CD: mean 38 and 31.3 at diagnosis | 253    | nr        | nr    | nr       |
| Parkes, 2007                | Europeans| rs10883365     | CD                 | 1182   | 40.3      | CD: mean 43.9 and 25.5 at diagnosis | 2024   | nr        | nr    | nr       |
| Parkes, 2007                | Europeans| rs10883365     | CD                 | 1748   | 39.2      | CD: mean 45.7 and 26.1 at diagnosis | 5740   | nr        | nr    | nr       |
| Yu, 2009                    | Europeans| rs10883365     | CD                 | 75     | nr        | nr                      | 255    | nr        | nr    | nr       |
| Yamazaki, 2009              | Asians   | rs10883365     | CD                 | 484    | 72.8      | CD: 22.4 (7–55) at diagnosis | 470    | 50.2      | 38.7 (21–77) | Age and sex |
| Pang, 2010                  | Asians   | rs10883365     | CD                 | 66     | 48.5      | CD: mean 36.26 ± 11.82 | 243    | nr        | nr    | nr       |
| Arai, 2011                  | Asians   | rs10883365     | CD and UC separately | 344    | nr        | nr                      | 253    | nr        | nr    | nr       |
| Weersma, 2009               | Europeans| rs10883365     | CD and UC separately | 1656   | nr        | nr                      | 1086   | nr        | nr    | nr       |
| van der Heide, 2010         | Europeans| rs10883365     | CD                 | 310    | 34.5      | CD: 26.6 (7.5–73.9) at diagnosis | 976    | nr        | nr    | nr       |
| Latano, 2011                | Europeans| rs11190140     | CD                 | 1070   | 56%       | nr                      | 783    | nr        | nr    | nr       |
| Laukens, 2010               | Europeans| rs11190140     | CD                 | 1051   | nr        | nr                      | 676    | nr        | nr    | nr       |
| Peter, 2011                 | Europeans| rs11190140     | CD                 | 369    | nr        | nr                      | 503    | nr        | nr    | nr       |
| Waterman, 2011              | Europeans| rs11190140     | CD                 | 1144   | 53%       | CD: 16(2–62) at diagnosis | 1057   | 36%       | nr    | nr       |

NKX2-3: NK2 transcription factor related and locus 3; CD: Crohn’s disease, UC: ulcerative colitis, nr: not report.
The 17 separate studies consisted of 13 European and 4 Asian. The distribution of genotypes in the control groups of all studies was in agreement with HWE except for 1 study19. Summaries of all included studies were summarized in Table 1, and the flow chart of study selection process was shown in Figure 1.

**Quantitative synthesis. Crohn’s disease.** The summary of meta-analysis for the NKX2-3 polymorphisms with CD is shown in Table 2, Figure 2A and Supplementary Figure S1. Regarding rs10883365 polymorphism, the results of combined analyses comprising 8699 cases and 13540 controls revealed a significantly increased risk of CD in all genetic models. In addition, the OR was 1.481 (1.351–1.623) in carriers of two risk G alleles compared with non-risk allele carriers (GG vs AA), which was higher than the risk of one G allele carriers (GA vs AA, OR = 1.141 (1.055–1.234), suggesting a dose–response with increasing number of the variant allele. In the subgroup analysis, significantly increased risks were found both among European and Asian population. No between-study heterogeneity was observed in all genetic models of rs11190140 variant and CD risk.

**Ulcerative colitis.** Seven studies with 4996 UC patients and 5479 controls for rs10883365 polymorphism were investigated. Meta-analysis findings of associations between rs10883365 in NKX2-3 gene and the risk of UC were shown in Table 3 and Figure 2B. Significantly increased UC risk was observed in all comparisons (G vs A: OR = 1.274 (1.175–1.382), GG vs AA: OR = 1.672 (1.474–1.896), GA vs AA = 1.207 (1.084–1.343), dominant model: OR = 1.342 (1.213–1.485), and recessive model: OR = 1.470 (1.325–1.630)). (Fig. 2B) When stratified by ethnicity, significant association was found both in European and Asian subgroups except for one genetic model in Asian (GA vs AA: OR = 1.260 (0.971–1.634)). No heterogeneity was detected in major genetic models.

**Sensitivity analyses and cumulative meta-analysis.** Sensitivity analysis showed no single study qualitatively changed the pooled ORs. (see Supplementary Fig. S2 and S3) Moreover, there was a study which deviated from HWE, when excluded, the estimated

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**Figure 1 | Study selection procedures for a meta-analysis of NKX2-3 polymorphisms and risk of CD or UC. NKX2-3: NK2 transcription factor related and locus 3; CD: Crohn’s disease; UC: ulcerative colitis.**
and C. Do rU Cr i s k. indicate any evidence of obvious asymmetry for rs10883365 variant polymorphism in CD. (see Supplementary Fig. S6) As shown in publication bias was detected for T vs C contrast of rs11190140 5 1.56, p 0.04, p = 0.966 and t = 1.56, p = 0.181 in CD and UC, respectively). Similarly, no publication bias was detected for T vs C contrast of rs11190140 polymorphism in CD. (see Supplementary Fig. S6) As shown in Supplementary Figure S5, the shapes of the funnel plots did not indicate any evidence of obvious asymmetry for rs10883365 variant and CD or UC risk.

**Discussion**

Presently the mechanisms of the etiology and progression of IBD are far from clear. Several genes have been identified to be associated with IBD risk, including NOD2, NKKX2-3 and IL-23. Recently, accumulating meta-analysis has been performed to investigate the association of genetic variants with susceptibility to CD or UC. Polymorphisms in several genes, including ATG16L1 T300A34, TGF-α G308A35, MIF G173C36, OCTN1 C1672T37, CD14 C260T38 and MDR1 C3435T39, were identified as risk factors of CD or UC. Patients with mutant allele of NOD1 rs695857140 and PPARγ Pro12Ala41 might have a decreased susceptibility to IBD. Additionally, some genetic variants were not association with CD or UC risk, such as MDR1 C12367T42 and IL10 G1082A43 and IL18 A607C44. Therefore, we saw the need to perform pooled analyses with larger sample size by summarizing previous case–control or cohort studies in order to better understand the association between the NKKX2-3 variants and IBD risk.

NKKX2-3, located on chromosome 10q24, is predominantly expressed in mesoderm of midgut and hindgut during embryonic mouse development45. Postnatally, NKKX3-expression continues in gut mesenchyme and in spleen. In addition, mice lacking Nkkx3-exhibit severe defects in gut development; primarily in the epithelium of the small intestine46. The perturbations of the gut tissue architecture lead to early postnatal death presumably due to digestive malfunctions. Moreover, analysis of Nkkx2-3-deficient mice has revealed a critical role for Nkkx2-3 in spleen development and in establishing the correct environment for normal B cell development and T cell dependent immune response40,46. Recently, associations between the two common polymorphisms (rs10883365 and rs11190140) in NKKX2-3 gene and susceptibility of CD or UC have been reported in several studies.

### Table 2 | Pooled analysis for the associations between the polymorphism of NKX2-3 and the risk of Crohn’s disease

| Variant | Comparison | Variables | No. of studies | Case | Control | OR (95% CI) | P-value | Model | P-value | Test of heterogeneity |
|---------|------------|-----------|----------------|------|---------|-------------|---------|-------|---------|----------------------|
| rs10883365 G vs A | Overall | | 12 | 8699 | 13540 | 1.226 (1.177–1.277) | <0.001 | F | 0.0 | 0.968 |
| & All in HWE | 9 | 4883 | 9661 | 1.215 (1.154–1.280) | <0.001 | F | 0.0 | 0.913 |
| & European | 8 | 761 | 12367 | 1.226 (1.174–1.280) | <0.001 | F | 0.0 | 0.944 |
| & Asian | 4 | 1068 | 1173 | 1.223 (1.082–1.382) | 0.001 | F | 0.0 | 0.613 |
| GG vs AA | Overall | | 10 | 6733 | 11478 | 1.481 (1.351–1.623) | <0.001 | F | 0.0 | 0.936 |
| & All in HWE | 9 | 4883 | 9661 | 1.476 (1.328–1.639) | <0.001 | F | 0.0 | 0.893 |
| & European | 6 | 5665 | 10305 | 1.481 (1.342–1.635) | <0.001 | F | 0.0 | 0.905 |
| & Asian | 4 | 1068 | 1173 | 1.477 (1.148–1.901) | 0.002 | F | 0.0 | 0.566 |
| GA vs AA | Overall | | 10 | 6733 | 11478 | 1.414 (1.055–2.34) | 0.001 | F | 0.0 | 0.836 |
| & All in HWE | 9 | 4883 | 9661 | 1.159 (0.599–2.68) | 0.001 | F | 0.0 | 0.807 |
| & European | 6 | 5665 | 10305 | 1.116 (0.242–1.215) | 0.012 | F | 0.0 | 0.796 |
| & Asian | 4 | 1068 | 1173 | 1.280 (0.555–1.533) | 0.012 | F | 0.0 | 0.807 |
| GG + GA vs AA | Overall | | 10 | 6733 | 11478 | 1.241 (1.153–1.336) | <0.001 | F | 0.0 | 0.887 |
| & All in HWE | 9 | 4883 | 9661 | 1.254 (1.152–1.365) | <0.001 | F | 0.0 | 0.846 |
| & European | 6 | 5665 | 10305 | 1.328 (1.106–1.595) | 0.002 | F | 0.0 | 0.814 |
| & Asian | 4 | 1068 | 1173 | 1.362 (1.263–1.468) | 0.001 | F | 0.0 | 0.960 |
| GG vs GA + GA | Overall | | 10 | 6733 | 11478 | 1.345 (1.235–1.465) | <0.001 | F | 0.0 | 0.948 |
| & All in HWE | 9 | 4883 | 9661 | 1.345 (1.235–1.465) | <0.001 | F | 0.0 | 0.927 |
| & European | 6 | 5665 | 10305 | 1.373 (1.268–1.486) | <0.001 | F | 0.0 | 0.927 |
| & Asian | 4 | 1068 | 1173 | 1.297 (1.024–1.598) | 0.030 | F | 0.0 | 0.710 |
| rs11190140 T vs C | Over(Europeans) | | 5 | 5484 | 4836 | 1.201 (1.136–1.269) | <0.001 | F | 0.0 | 0.773 |
| & All in HWE | 2 | 2121 | 1426 | 1.190 (1.080–1.311) | <0.001 | F | 0.0 | 0.544 |
| TT vs CC | Over(Europeans) | | 3 | 3971 | 3276 | 1.485 (1.297–1.700) | <0.001 | F | 0.0 | 0.631 |
| & All in HWE | 2 | 2121 | 1426 | 1.412 (1.162–1.716) | 0.001 | F | 0.0 | 0.516 |
| TC vs CC | Over(Europeans) | | 3 | 3971 | 3276 | 1.535 (1.259–1.898) | <0.001 | F | 0.0 | 0.478 |
| & All in HWE | 2 | 2121 | 1426 | 1.427 (1.032–1.458) | 0.020 | F | 0.0 | 0.430 |
| TT + TC vs CC | Over(Europeans) | | 3 | 3971 | 3276 | 1.253 (1.122–1.398) | <0.001 | F | 0.0 | 0.867 |
| & All in HWE | 2 | 2121 | 1426 | 1.289 (1.095–1.516) | 0.002 | F | 0.0 | 0.785 |
| TT vs TC + CC | Over(Europeans) | | 3 | 3971 | 3276 | 1.344 (1.204–1.501) | <0.001 | F | 0.0 | 0.135 |
| & All in HWE | 2 | 2121 | 1426 | 1.239 (1.061–1.446) | 0.007 | F | 45.4 | 0.176 |

NKX2-3: NK2 transcription factor related and locus 3; R: Random-effects model; F: fixed-effects model; HWE: Hardy-Weinberg equilibrium; OR: odds ratio; CI: confidence interval.
Table 1: OR estimates with the corresponding 95% CI for the association between rs10883365 polymorphism in NKX2-3 gene and CD or UC risk.

(a): rs10883365 polymorphism and CD risk (G vs. A), (b): rs10883365 polymorphism and UC risk (G vs. A). The sizes of the squares reflect the weighting of included studies. OR: odds ratio; CI: confidence interval.

### a. OR estimates for CD risk

| First author (year) | OR (95% CI) | Weight (%) |
|----------------------|-------------|------------|
| Asians               |             |            |
| Tanaka (2009)        | 1.08 (0.83, 1.41) | 2.56       |
| Yamazaki (2009)      | 1.29 (1.07, 1.54) | 4.94       |
| Pang (2010)          | 1.03 (0.64, 1.67) | 0.78       |
| Arai (2011)          | 1.29 (1.02, 1.63) | 2.90       |
| Subtotal (I-squared = 0.0%, p = 0.613) |             |            |
|                      | 1.22 (1.08, 1.38) | 11.18      |

### Europeans

| First author (year) | OR (95% CI) | Weight (%) |
|----------------------|-------------|------------|
| Meggyesi (2010)     | 1.20 (0.97, 1.48) | 3.73       |
| Meggyesi (2010)     | 1.31 (1.03, 1.68) | 2.63       |
| Franke (2008)       | 1.21 (1.11, 1.33) | 19.59      |
| Parkes (2007)       | 1.22 (1.13, 1.31) | 29.10      |
| Parkes (2007)       | 1.18 (1.05, 1.32) | 13.85      |
| Yu (2009)           | 1.44 (1.00, 2.07) | 1.15       |
| Weersma (2009)      | 1.27 (1.14, 1.42) | 13.79      |
| van der Heide (2010)| 1.27 (1.06, 1.53) | 4.99       |
| Subtotal (I-squared = 0.0%, p = 0.944) |             |            |
|                      | 1.23 (1.17, 1.28) | 88.82      |

### Overall

| First author (year) | OR (95% CI) | Weight (%) |
|----------------------|-------------|------------|
|                      | 1.23 (1.18, 1.28) | 100.00     |

### b. OR estimates for UC risk

| First author (year) | OR (95% CI) | Weight (%) |
|----------------------|-------------|------------|
| Asians               |             |            |
| Tanaka (2009)        | 1.39 (1.12, 1.73) | 6.00       |
| Arai (2011)          | 1.54 (1.20, 1.99) | 4.18       |
| Subtotal (I-squared = 0.0%, p = 0.540) |             |            |
|                      | 1.45 (1.23, 1.71) | 10.18      |

### Europeans

| First author (year) | OR (95% CI) | Weight (%) |
|----------------------|-------------|------------|
| Meggyesi (2010)     | 1.25 (0.98, 1.58) | 5.26       |
| Meggyesi (2010)     | 1.54 (1.14, 2.07) | 2.97       |
| Fisher (2008)       | 1.19 (1.08, 1.31) | 31.70      |
| Franke (2008)       | 1.33 (1.19, 1.48) | 25.24      |
| Weersma (2009)      | 1.13 (1.01, 1.26) | 24.64      |
| Subtotal (I-squared = 41.1%, p = 0.147) |             |            |
|                      | 1.23 (1.16, 1.30) | 89.82      |

### Overall

| First author (year) | OR (95% CI) | Weight (%) |
|----------------------|-------------|------------|
|                      | 1.25 (1.18, 1.32) | 100.00     |

Figure 2: OR estimates with the corresponding 95% CI for the association between rs10883365 polymorphism in NKX2-3 gene and CD or UC risk. (a): rs10883365 polymorphism and CD risk (G vs. A), (b): rs10883365 polymorphism and UC risk (G vs. A). The sizes of the squares reflect the weighting of included studies. OR: odds ratio; CI: confidence interval.
Table 3 | Pooled analysis for the associations between the polymorphism of NKX2-3 and the risk of ulcerative colitis

| Variant     | Comparison | Variables | No. of studies | Sample Size | Test of association | Test of heterogeneity |
|-------------|------------|-----------|----------------|-------------|---------------------|-----------------------|
| rs10883365  | G vs A     | Overall   | 7              | 4996        | 5479                | 1.274 (1.175–1.382)   | <0.001 R 44.5 0.094 |
|             |            | All in HWE| 5              | 2818        | 2576                | 1.268 (1.174–1.369)   | <0.001 F 36.5 0.178 |
|             |            | Europeans | 5              | 4447        | 4842                | 1.225 (1.156–1.298)   | <0.001 F 41.1 0.147 |
|             |            | Asians    | 2              | 549         | 637                 | 1.452 (1.232–1.712)   | <0.001 F 0.0 0.176 |
| GG vs AA    |            | Overall   | 6              | 3921        | 4393                | 1.672 (1.474–1.896)   | <0.001 F 20.1 0.282 |
|             |            | All in HWE| 5              | 2818        | 2576                | 1.619 (1.387–1.889)   | <0.001 F 30.5 0.218 |
|             |            | Europeans | 4              | 3372        | 3756                | 1.609 (1.404–1.844)   | <0.001 F 26.0 0.255 |
|             |            | Asians    | 2              | 549         | 637                 | 2.078 (1.500–2.878)   | <0.001 F 0.0 0.654 |
| GA vs AA    |            | Overall   | 6              | 3921        | 4393                | 1.207 (1.084–1.343)   | <0.001 F 0.0 0.901 |
|             |            | All in HWE| 5              | 2818        | 2576                | 1.242 (1.090–1.416)   | <0.001 F 0.0 0.905 |
|             |            | Europeans | 4              | 3372        | 3756                | 1.196 (1.063–1.345)   | 0.003 F 0.0 0.814 |
|             |            | Asians    | 2              | 549         | 637                 | 1.260 (0.971–1.634)   | 0.082 F 0.0 0.466 |
| GG + GA vs AA|            | Overall  | 6              | 3921        | 4393                | 1.342 (1.213–1.485)   | <0.001 F 0.0 0.801 |
|             |            | All in HWE| 5              | 2818        | 2576                | 1.356 (1.199–1.533)   | <0.001 F 0.0 0.688 |
|             |            | Europeans | 4              | 3372        | 3756                | 1.317 (1.179–1.472)   | <0.001 F 0.0 0.767 |
|             |            | Asians    | 2              | 549         | 637                 | 1.467 (1.151–1.869)   | 0.002 F 0.0 0.454 |
| GG vs GA + GA|            | Overall  | 6              | 3921        | 4393                | 1.470 (1.325–1.630)   | <0.001 F 43.9 0.112 |
|             |            | All in HWE| 5              | 2818        | 2576                | 1.391 (1.223–1.581)   | <0.001 F 41.2 0.146 |
|             |            | Europeans | 4              | 3372        | 3756                | 1.455 (1.202–1.761)   | <0.001 R 53.9 0.089 |
|             |            | Asians    | 2              | 549         | 637                 | 1.534 (1.160–2.028)   | <0.001 F 0.0 0.894 |

NKX2-3: NK2 transcription factor related and locus 3; R: Random-effects model, F: fixed-effects model, HWE: Hardy-Weinberg equilibrium; OR: odds ratio; CI: confidence interval.
OR was determined by the Z-test; a P-value of <0.05 was considered significant. The Hardy-Weinberg equilibrium (HWE) in the control group was assessed, and a P < 0.05 was considered as significant disequilibrium. For rs10883365 polymorphism, the pooled ORs were estimated for G versus A, GG versus AA, GA versus AA, dominant model (GG + GA versus AA), and recessive model (GG versus GA + AA). Because of only three studies available for the association between rs11190140 variant and UC risk, we have performed meta-analysis of correlation between rs11190140 polymorphism and CD risk. Subgroup analysis was performed according to ethnicity. Between-study heterogeneity was evaluated by using the Chi-square based Q test and I² test. Heterogeneity was considered significant for P < 0.10, and a random-effects model was used, otherwise, fixed-effects model was used. In addition, if heterogeneity was detected, Galbraith plots were used to visualize the impact of individual studies on the overall homogeneity, which spot the outliers as the possible major sources of heterogeneity. Moreover, a meta-regression was used to delineate the major sources of between-study heterogeneity.

Sensitivity analysis was carried out to evaluate the stability of the results after sequential removal of each study or by excluding those studies deviated from HWE. In addition, cumulative meta-analyses were carried out for each polymorphism through assortment of studies with publication time. Graphical evaluation of funnel plots and Egger’s linear regression test were performed to assess publication bias. If significant publication bias was detected, ORs and 95% CI would be adjusted by trim and fill methods. All statistical analyses were performed by STATA software, version 12 (StataCorp LP, College Station, Texas).

**Figure 3** | Cumulative meta-analysis on the association between rs10883365 polymorphism and CD or UC risk. (a): rs10883365 variant and CD risk (G vs. A); (b): rs10883365 variant and UC risk (G vs. A). Pooled OR estimates with the 95% CI as information accumulates at the end of each year (left column). CD: Crohn’s disease; UC: ulcerative colitis; OR: odds ratio; CI: confidence interval.

### Table 1

| Firstauthor | Year | OR (95%CI) |
|-------------|------|------------|
| Parkes      | 2007 | 1.22 (1.13, 1.31) |
| Parkes      | 2007 | 1.20 (1.13, 1.28) |
| Franke      | 2008 | 1.21 (1.15, 1.27) |
| Weersma     | 2009 | 1.22 (1.16, 1.28) |
| Yu          | 2009 | 1.22 (1.17, 1.28) |
| Yamazaki    | 2009 | 1.23 (1.17, 1.28) |
| Tanaka      | 2009 | 1.22 (1.17, 1.28) |
| Pang        | 2010 | 1.22 (1.17, 1.27) |
| Meggyesi    | 2010 | 1.22 (1.17, 1.27) |
| van der Heide | 2010 | 1.22 (1.17, 1.27) |
| Meggyesi    | 2010 | 1.22 (1.17, 1.28) |
| Arai        | 2011 | 1.23 (1.18, 1.28) |

### Table 2

| Firstauthor | Year | OR (95%CI) |
|-------------|------|------------|
| Fisher      | 2008 | 1.19 (1.08, 1.31) |
| Franke      | 2008 | 1.25 (1.16, 1.34) |
| Weersma     | 2009 | 1.21 (1.14, 1.29) |
| Tanaka      | 2009 | 1.22 (1.16, 1.30) |
| Meggyesi    | 2010 | 1.23 (1.16, 1.30) |
| Meggyesi    | 2010 | 1.24 (1.17, 1.31) |
| Arai        | 2011 | 1.25 (1.18, 1.32) |

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Conceived and designed the experiments: L.X.C., L.L.X. Performed the experiments: L.X.C., T.L.I., L.K. Analyzed the data: L.X.C., Z.Y.I., Z.P.L. Contributed reagents/materials/analysis tools: L.X.C., T.L.I., T.Y. Wrote the paper: L.X.C., L.L.X.

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