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**Associations between *CD24* gene polymorphisms and inflammatory bowel disease: A meta-analysis**

Huang XL *et al*. CD24 polymorphisms and IBD

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**Abstract**

**AIM:** To evaluate the relationships between *CD24* gene polymorphisms and the risk of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn’s disease (CD).

**METHODS:** The PubMed, Web of Science and Cochrane Library databases were searched (up to May 30, 2014).The search terms “CD24”; “inflammatory bowel disease”, “Crohn’s disease”, “Ulcerative colitis”, “IBD”, “CD” or “UC”; and “polymorphism”, “mutation” or “variant” were used. Association studies were limited in to the English language, but no limitations in terms of race, ethnicity or geographic area were employed. Stata SE12 software was used to calculate the pooled odds ratios (ORs) with 95% confidence intervals (CIs). *P <* 0.05 was considered statistically significant. The information was independently extracted from each eligible study by two investigators. Two common polymorphisms, C170T (rs8734) and TG1527del (rs3838646), in the *CD24* gene were assessed.

**RESULTS:** A total of three case-control studies including 2342 IBD patients and 1965 healthy controls were involved in this meta-analysis. The patients and controls were from Caucasian cohorts. The three articles included in this meta-analysis all conformed to Hardy–Weinberg equilibrium. This meta-analysis revealed that there were no significant associations between the two *CD24* polymorphisms and the risk for IBD (all *P* > 0.05). However, in a disease subgroup analysis, we found that the *CD24* C170T polymorphism was associated with an increased risk of UC in a dominant model (OR = 1.79, 95%CI: 1.15-2.77, *P* = 0.009) and an additive model (OR = 1.87, 95%CI: 1.19-2.93, *P* = 0.007), but this relationship was not present for CD. The CD24 TG1570*del* polymorphism was significantly associated with CD in the additive model (OR = 1.24, 95%CI: 1.01-1.52, *P* = 0.037).

**CONCLUSION:** Our findings provide evidence that the *CD24* C170T polymorphism might contribute to the susceptibility to UC, and the CD24 TG1527del polymorphism might be associated with the risk of CD.

**Key words:**CD24; Polymorphism; Inflammatory bowel disease; rs8734; rs3838646; Meta-analysis

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**Core tip:** CD24 is a significant immune regulatory mediator of inflammatory bowel disease (IBD). Some recent studies have demonstrated that *CD24* gene polymorphisms are associated with the susceptibility to IBD, but the findings of other studies are contradictory. The present study sought to provide a more precise estimate of this potential association. A meta-analysis of Caucasian cohorts found that the *CD24* C170T polymorphism was associated with the susceptibility to UC and that the CD24 TG1527*del* polymorphism was associated with CD.

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**INTRODUCTION**

Inflammatory bowel disease (IBD) is a relapsing and chronic inflammatory disorder that is composed of two types of diseases, Crohn’s disease (CD) and ulcerative colitis (UC). The incidence of IBD is increasing worldwide. IBD places a heavy burden on patients because it reduces life quality and the ability to work and increases disability[[1](#_ENREF_1)]. The etiology of IBD is complicated and obscure but is primarily related to from genetic, environmental, immune and infectious factors and interactions between these factors. Based on assessments of familial clustering and the high concordance in monozygotic twins, it is well established that a genetic component is implicated in the pathogenesis of IBD [[2-4](#_ENREF_2)]. Recent studies have revealed that many gene variations are associated with the susceptibility to IBD, such as NOD2[[5-7](#_ENREF_5)],ATG16L1[[8](#_ENREF_8),[9](#_ENREF_9)], DLG5[[10](#_ENREF_10),[11](#_ENREF_11)] and IL23R[[12](#_ENREF_12)].

CD24 is a glycophosphatidylinositol (GPI)-anchored mucin-like cell surface glycoprotein that is expressed in a wide variety of cell types, including activated T cells[[13](#_ENREF_13)], B cells[[14](#_ENREF_14)], macrophages[[15](#_ENREF_15)], and dendritic cells[[16](#_ENREF_16)]. Human CD24 is encoded by a gene located on chromosome 6 and plays important roles in lymphocyte maturation[[13](#_ENREF_13),[17-19](#_ENREF_17)], neuronal development[[20](#_ENREF_20)], intercellular signal transmission and immune regulation. Some single nucleotide polymorphisms (SNPs) in the *CD24* gene have been shown to be associated with the susceptibilities to several chronic inflammatory and autoimmune diseases, such asmultiple sclerosis (MS)[[21](#_ENREF_21),[22](#_ENREF_22)], systemic lupus erythematous (SLE)[[23](#_ENREF_23),[24](#_ENREF_24)], and others. There are some studies of the correlations between *CD24* SNPs and risk factors for IBD pathogenesis[[25-27](#_ENREF_25)]. C170T (rs8734) and TG1527*del* (rs3838646) are two common CD24 genetic polymorphisms that are potentially related to IBD; however, the findings related to these polymorphisms are contradictory. To shed some light on the contradictory findings and provide a more precise estimate of the potential associations, we performed this meta-analysis to investigate whether the two *CD24* polymorphisms (C170T and TG1527del) contribute to the susceptibility to IBD.

**MATERIALS AND METHODS**

***Literature search***

We conducted a literature search forrelevant studies on the relationships between polymorphisms of *CD24* and IBD risk in the PubMed, Web of Science, and Cochrane Library databases (up to May 30, 2014).The following search terms were used: “CD24”; and “inflammatory bowel disease”, “Crohn’s disease”, “Ulcerative colitis”, “IBD”, “CD”, or “UC”; and “polymorphism”, “mutation”,or “variant”. The searched studies were limited to the English language.

***Inclusion and exclusion criteria***

Eligible studies were required to meet the following inclusion criteria: (1) case-control studies evaluating at least one polymorphism of the *CD24* gene; (2) studies containing original data; (3) studies with genotype or allelic distributions; (4) studies containing sufficient data to calculate odds ratios (ORs); and (5) studies in which the genotype distribution of the control population was in Hardy–Weinberg equilibrium (HWE). No limitations related to race, ethnicity or geographic area were utilized.

The exclusion criteria were as follows: (1) irrelevant and reviewarticles; (2) studies containing overlapping data; (3) articles that did not provide detailed genotype data; (4) investigations of the associations of other genes with IBD or the relationships between *CD24* gene polymorphisms and other diseases; and (5) studies in which family members were studied because the analyses were based on linkage considerations.

***Data extraction and synthesis***

The following information was extracted from each eligible study independently by two investigators: first author’s surname, year of publication, ethnicity of the study population, and the number of cases and controls for the *CD24* genotype. The allele and genotype frequencies of the *CD24* polymorphisms were calculated from each article by the allele counting method. Disagreements were resolved by discussion.

***Statistical analyses***

Stata SE12 software was used to calculate the pooled ORs with 95% confidence intervals (CIs) based on the available data from each article. *P* < 0.05 was considered statistically significant. The allelic model (A *vs* V or TEL *vs* del), recessive model (AA *vs* AV + VV or TGTG *vs* TG*del* + *deldel*), dominant model (AA + AV *vs* VV or TGTG + TG*del vs deldel*), and additive model (AA *vs* VV or TGTG *vs deldel*) were estimated for genotype comparisons. Cochran’s *Q*-statistic and the *I2* test were used to test the heterogeneity among the included studies, and *P* < 0.1 and *I2* > 50% suggested significant differences in study heterogeneity. When significant heterogeneity was observed across studies, the pooled results were based random effects models. The χ2 test was applied to assess whether the genotype distributions of the control populations conformed to HWE, and *P <* 0.05 was considered statistically significant. Begg’s funnel plotand Egger’s test were used to detect publication bias[[28](#_ENREF_28)].

**RESULTS**

***Literature search for eligible studies***

Based on the research criteria, a total of 49 articles were identified, and 29 of these articles were excluded because they were not relevant to *CD24* SNPs and the risk for IBD. Eight repetitive studies and 9 reviews were also excluded. Ultimately 3 case-control studies consisting of 2342 IBD patients (UC = 1148, CD = 1194) and 1965 controls were included into our paper. These articles were conducted with Spanish, Scottish and Israeli Caucasians. The characteristics of the 3 studies are summarized in Table 1. The distributions of the *CD24* genotypes and alleles among the IBD patients and controls are listed in Table 2.

***Association of the CD24 C170Tpolymorphism with IBD susceptibility***

Two studies including 806 IBD patients (CD = 397, UC = 409) and 733 controls were selected in this meta-analysis. A statistical test suggested that heterogeneity was present (for the allele: *I2* = 87.7%, *P* = 0.004; for the recessive model: *I2* = 92.8%, *P <* 0.001; for the additive model: *I2* = 73.9%, *P* = 0.051); therefore, the random effects model was used in these model analyses. No significant associations between the CD24 C170Tpolymorphism and the IBD risk were revealed (V *vs* A: OR = 1.39, 95%CI: 0.73-2.64, *P =* 0.314;VV *vs* AA: OR=1.32, 95%CI: 0.40-4.39, *P =* 0.654; VV + VA *vs* AA: OR = 0.64, 95%CI: 0.21-1.90, *P =* 0.420; VV *vs* AA + VA: OR=0.94, 95%CI: 0.62-1.43, *P =* 0.777). Subgroup analyses indicated no modifying effects of the *CD24* C170T polymorphism on the risk of CD (V *vs* A: OR = 1.16, 95%CI: 0.69-1.93, *P =* 0.583; VV *vs* AA: OR = 1.23, 95%CI: 0.76-1.99, *P =* 0.405; VV + VA *vs* AA: OR = 0.76, 95%CI: 0.28-2.07, *P =* 0.594; VV *vs* AA +VA: OR = 1.32, 95%CI: 0.83-2.11, *P =* 0.245). However, we observed a significant association between the *CD24* C170T polymorphism and UC risk for the dominant model (OR = 1.79, 95%CI: 1.15-2.77, *P =* 0.009) and the additive model (OR = 1.87, 95%CI: 1.19-2.93, *P =* 0.007) (Figure 1, Table 3).

***Association of*** ***the TG1527del polymorphism with IBD susceptibility***

Three studies consisting of 1625 IBD patients (UC = 759, CD = 866) and 1232 controls were included in this meta-analysis. A statistical test revealed that there was no heterogeneity between the studies (for the allele: *I2* = 0%, *P =* 0.803; for the recessive model: *I2* = 0%, *P =* 0.870; for the dominant model: *I2*=0%, *P =* 0.436; for the additive model: *I2* = 0%, *P =* 0.439); hence, the fixed effect model was used. The results did not indicate any significant association of the allele in the overall sample or the subgroup analyses with the exception that the del allele was related to CD susceptibility (OR=1.24, 95%CI: 1.01-1.52, *P* = 0.037) (Figure 2, Table 3).

***Sensitivity analysis and publication bias***

A sensitivity analysis conducted *via* the omission of individual studies did not materially alter the pooled results (data not shown). Begg’s funnel plots did not reveal obvious asymmetries for any of the comparison models. However, Egger’s tests revealed that there were some publication biases for both of the genetic allele analyses (V *vs* A, *PEgger* = 0.022; VV *vs* AA + AV, *PEgger* = 0.010; *deldel* *vs* TGTG + TG*del*, *PEgger* = 0.011; *deldel* *vs* TGTG, *PEgger* = 0.012) (Table 4).

**DISCUSSION**

The etiology of IBD has not been completely elucidated, but the contributions of immunological and genetic factors have been demonstrated. IBD is believed to arise partly due to multiple genetic factors. Many reports have used the genome-wide association study (GWAS) approach to identify novel candidate single nucleotide polymorphisms(SNPs) for IBD[[12](#_ENREF_12),[29](#_ENREF_29),[30](#_ENREF_30)]. To date, 99 variants have been identified as associated with CD and/or UC. Among these, only 28 variants have been shown to overlap in their contributions to the susceptibilities to both diseases[[31](#_ENREF_31)]. Some risk loci for CD have no reported affect UC. Similarly, some risk loci for UC have been shown to have little effect on UC. Different mutations of the same gene might be associated with different IBD diseases. IBD is an autoimmune disease that is related to the innate and adaptive immune systems[[32](#_ENREF_32),[33](#_ENREF_33)]. Evidence from animal models indicates that the failure to suppress immunity to the abundant intestinal foreign antigen load can cause inflammation[[34](#_ENREF_34)]. Certain genetic variations andchanges in the immune system might contribute to the development of IBD,such as those related to macrophage migration inhibitory factor (MIF)[[35](#_ENREF_35),[36](#_ENREF_36)] and interleukin-10(IL-10)[[37](#_ENREF_37)].

CD24 has been reported to play an important role in the immune system and to be associated with autoimmune diseases, including IBD. CD24 has been shown to be ligand for P-selectin and to play an important role in recruiting leukocytes to inflamed tissue.CD24 has also been implicated in the activation and differentiation of B lymphocytes[[38](#_ENREF_38)], and it has been identified as an important mediator in a CD28-independent co-stimulatory pathway related to the activation of both CD4 and CD8 T cells[[39](#_ENREF_39)]. Ahmed *et al*[[40](#_ENREF_40)] found that *CD24* is upregulated by Wnt signaling in regenerating tissue in IBD and can confer enhanced colony forming abilities and enhanced cell motilities,which play an important roles in tissue healing. The association between *CD24* polymorphisms and the risk of IBD has been reported in recent studies[[25](#_ENREF_25),[26](#_ENREF_26)]. The *CD24* gene contains multiple SNPs, such as the C170T (rs8734), TG1527del (rs3838646), A1626G (rs1058881) and A1056G (rs1058818) polymorphisms. Among these SNPs, C170T and TG1527del have received much attention.However, the existing data are contradictory. Van Limbergen *et al*[[27](#_ENREF_27)] reported that the *CD24* TG1527*del* gene polymorphism is not an important determinant of genetic susceptibility to IBD. However, Diaz-Gallo *et al*[[26](#_ENREF_26)] demonstrated that a TG1527del SNP is associated with an increased risk of CD but not UC. To better understand of the associations between these two polymorphisms and IBD, a meta-analysis with a larger sample and subgroup analyses is necessary.

The present study is the first meta-analysis that has attempted to determine the potential roles of *CD24* polymorphisms in IBD. Our results revealed a significant association between the *CD24* C170T polymorphism and UC risk in the dominant (OR = 1.79, 95%CI: 1.15-2.77, *P* = 0.009) and additive models (OR = 1.87, 95%CI: 1.19-2.93, *P* = 0.007), but the *CD24* C170T polymorphism was not related to the risk for CD. Moreover, our results indicated the *CD24* TG1570*del* polymorphism was significantly associated with CD in the additive model (OR = 1.27, 95%CI: 1.01-1.58, *P* = 0.037).These results support the hypothesis that CD and UC are related by differ in terms of some immunologic mechanisms[[41](#_ENREF_41)]. Similar results have been reported for other autoimmune diseases. Zhou *et al*[[42](#_ENREF_42)] reported that the expression of *CD24* on the peripheral blood T cells of CD24V/V MS patients is higher than that of *CD24* A/A genotype patients. Sanchez *et al*[[24](#_ENREF_24)] demonstrated that the frequency of the CD24V/V genotype in SLE patients was higher than that in the controls in a Spanish cohort. The TG1527*del* genetic variant has been reported to reduce the constitutive levels of *CD24* mRNA by more than two-fold and to reduce the risks for MS and SLE[[43](#_ENREF_43)]. Diaz-Gallo[[26](#_ENREF_26)] also observed that the TG1527*del* genetic variant is a risk factor for CD, specifically for CD with an age of diagnosis between 17 and 40 years. Van Limbergen *et al*[27] did not have any association between the *CD24* TG1527*del* SNP and CD susceptibility, possibly due to a low number of subjects.

However, our study has some limitations that should be considered. First, heterogeneities among the studies involving *CD24* C170T were present and might have partially influenced the results of this study. Therefore, additional details are needed to analyze the source of the heterogeneity. Second,the numbers of included studies and patients were limited. We are looking forward to the availability of additional relevant studies to help us to understand this problem. Third, only studies published in English were selected for this meta-analysis, and these studies do not include unpublished documents. Thus, a selection bias might have been present. Finally, some publication bias was present because the population of included studies was not uniform. Therefore, additional studies with the same patient inclusion criteria or studies that perform analyses stratified by age, gender and race will help to decrease the publication bias.

In conclusion, this study suggests that the *CD24* C170T polymorphism is associated with an increased risk of UC and that the *CD24* TG1527*del* polymorphism has some influence on CD risk. A large number of cases and controls are required enable us to make a more precise risk estimate and minimize the bias in this meta-analysis.

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**COMMENTS**

***Background***

Inflammatory bowel disease (IBD) is a nonspecific chronic intestinal inflammatory disorder, and its etiology has not been completely elucidated. In the last three decades, the prevalence of IBD has increased both in developed and developing regions. However, increasing evidence indicates that environmental, genetic and immunological factors play important roles in the pathogenesis of IBD.

***Research frontiers***

CD24 is a GPI-anchored mucin-like cell surface glycoprotein and plays an important role in the immune system. Some studies have reported that polymorphisms of *CD24* are associated with the pathogeneses of autoimmune diseases. Recently, some studies have indicated that *CD24* polymorphisms are related to IBD. However, contradictory findings exist.

***Innovations and breakthroughs***

This is a first meta-analysis to focus on the association between *CD24* polymorphisms and IBD. Based on this meta-analysis, the *CD24* C170T polymorphism plays a significant role in the risk of UC, and the *CD24* TG1527*del* polymorphism exerts some influence on the CD risk.

***Applications***

The different loci of *CD24* polymorphisms might be associated with the phenotypes of IBD. An exploration of the mechanisms might be useful for reducing the risk of IBD.

***Terminology***

Stata SE12 software was used to calculate the pooled odds ratios with 95% confidence intervals based on the available data from each article. Cochran’s *Q*-statistic and the *I2* test were used to test the heterogeneity. Begg’s funnel plots and Egger’s tests were used to detect publication biases.

***Peer-review***

This is a well-performed meta-analysis of currently available studies about the associations between the *CD24* gene polymorphisms and IBD risk. The authors found that the *CD24* polymorphisms C170T (rs8734) and TG1527*del* (rs3838646) are associated with the risk of UC and CD. This meta-analysis utilized appropriate methods for the literature search, data extraction and quality assessment of the literature.

**REFERENCES**

1 **Stone CD**. The economic burden of inflammatory bowel disease: clear problem, unclear solution. *Dig Dis Sci* 2012; **57**: 3042-3044 [PMID: 23086111 DOI: 10.1007/s10620-012-2417-8]

2 **Park JB**, Yang SK, Byeon JS, Park ER, Moon G, Myung SJ, Park WK, Yoon SG, Kim HS, Lee JG, Kim JH, Il Min Y, Kim KY. Familial occurrence of inflammatory bowel disease in Korea. *Inflamm Bowel Dis* 2006; **12**: 1146-1151 [PMID: 17119389 DOI: 10.1097/01.mib.0000235094.01608.59]

3 **Elding H**, Lau W, Swallow DM, Maniatis N. Dissecting the genetics of complex inheritance: linkage disequilibrium mapping provides insight into Crohn disease. *Am J Hum Genet* 2011; **89**: 798-805 [PMID: 22152681 DOI: 10.1016/j.ajhg.2011.11.006]

4 **Thompson NP**, Driscoll R, Pounder RE, Wakefield AJ. Genetics versus environment in inflammatory bowel disease: results of a British twin study. *BMJ* 1996; **312**: 95-96 [PMID: 8555939]

5 **Bonen DK**, Ogura Y, Nicolae DL, Inohara N, Saab L, Tanabe T, Chen FF, Foster SJ, Duerr RH, Brant SR, Cho JH, Nuñez G. Crohn's disease-associated NOD2 variants share a signaling defect in response to lipopolysaccharide and peptidoglycan. *Gastroenterology* 2003; **124**: 140-146 [PMID: 12512038 DOI: 10.1053/gast.2003.50019]

6 **Ogura Y**, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nuñez G, Cho JH. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature* 2001; **411**: 603-606 [PMID: 11385577 DOI: 10.1038/35079114]

7 **Ogura Y**, Saab L, Chen FF, Benito A, Inohara N, Nuñez G. Genetic variation and activity of mouse Nod2, a susceptibility gene for Crohn's disease. *Genomics* 2003; **81**: 369-377 [PMID: 12676561]

8 **Achkar JP**. IL23R and ATG16L1 SNPs in IBD: alphabet soup or something more? *Am J Gastroenterol* 2008; **103**: 628-630 [PMID: 18341487 DOI: 10.1111/j.1572-0241.2007.01656.x]

9 **Hampe J**, Franke A, Rosenstiel P, Till A, Teuber M, Huse K, Albrecht M, Mayr G, De La Vega FM, Briggs J, Günther S, Prescott NJ, Onnie CM, Häsler R, Sipos B, Fölsch UR, Lengauer T, Platzer M, Mathew CG, Krawczak M, Schreiber S. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. *Nat Genet* 2007; **39**: 207-211 [PMID: 17200669 DOI: 10.1038/ng1954]

10 **Lin Z**, Hegarty JP, Berb A, Wang Z, Kelly AA, Wang Y, Poritz LS, Wu R, Koltun WA. DLG5 P1371Q is associated with inflammatory bowel disease and complementary to R30Q in disease susceptibility. *Swiss Med Wkly* 2011; **141**: w13290 [PMID: 22065243 DOI: 10.4414/smw.2011.13290]

11 **Russell RK**, Drummond HE, Nimmo ER, Anderson N, Wilson DC, Gillett PM, McGrogan P, Hassan K, Weaver LT, Bisset WM, Mahdi G, Satsangi J. The contribution of the DLG5 113A variant in early-onset inflammatory bowel disease. *J Pediatr* 2007; **150**: 268-273 [PMID: 17307543 DOI: 10.1016/j.jpeds.2006.12.010]

12 **Duerr RH**, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barmada MM, Rotter JI, Nicolae DL, Cho JH. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006; **314**: 1461-1463 [PMID: 17068223 DOI: 10.1126/science.1135245]

13 **Hubbe M**, Altevogt P. Heat-stable antigen/CD24 on mouse T lymphocytes: evidence for a costimulatory function. *Eur J Immunol* 1994; **24**: 731-737 [PMID: 8125140 DOI: 10.1002/eji.1830240336]

14 **Wenger RH**, Kopf M, Nitschke L, Lamers MC, Köhler G, Nielsen PJ. B-cell maturation in chimaeric mice deficient for the heat stable antigen (HSA/mouse CD24). *Transgenic Res* 1995; **4**: 173-183 [PMID: 7795661]

15 **Clements DJ**, Matveyeva M, McCoy KL. Delta9-tetrahydrocannabinol suppresses macrophage costimulation by decreasing heat-stable antigen expression. *Int J Immunopharmacol* 1998; **20**: 415-428 [PMID: 9778102]

16 **Mahnke K**, Bhardwaj RS, Luger TA, Schwarz T, Grabbe S. Interaction of murine dendritic cells with collagen up-regulates allostimulatory capacity, surface expression of heat stable antigen, and release of cytokines. *J Leukoc Biol* 1996; **60**: 465-472 [PMID: 8864130]

17 **Carsetti R**, Rosado MM, Wardmann H. Peripheral development of B cells in mouse and man. *Immunol Rev* 2004; **197**: 179-191 [PMID: 14962195]

18 **Park K**, He X, Lee HO, Hua X, Li Y, Wiest D, Kappes DJ. TCR-mediated ThPOK induction promotes development of mature (CD24-) gammadelta thymocytes. *EMBO J* 2010; **29**: 2329-2341 [PMID: 20551904 DOI: 10.1038/emboj.2010.113]

19 **Nielsen PJ**, Lorenz B, Müller AM, Wenger RH, Brombacher F, Simon M, von der Weid T, Langhorne WJ, Mossmann H, Köhler G. Altered erythrocytes and a leaky block in B-cell development in CD24/HSA-deficient mice. *Blood* 1997; **89**: 1058-1067 [PMID: 9028339]

20 **Pruszak J**, Ludwig W, Blak A, Alavian K, Isacson O. CD15, CD24, and CD29 define a surface biomarker code for neural lineage differentiation of stem cells. *Stem Cells* 2009; **27**: 2928-2940 [PMID: 19725119 DOI: 10.1002/stem.211]

21 **Ronaghi M**, Vallian S, Etemadifar M. CD24 gene polymorphism is associated with the disease progression and susceptibility to multiple sclerosis in the Iranian population. *Psychiatry Res* 2009; **170**: 271-272 [PMID: 19896210 DOI: 10.1016/j.psychres.2009.01.002]

22 **Goris A**, Maranian M, Walton A, Yeo TW, Ban M, Gray J, Dubois B, Compston A, Sawcer S. CD24 Ala/Val polymorphism and multiple sclerosis. *J Neuroimmunol* 2006; **175**: 200-202 [PMID: 16631259 DOI: 10.1016/j.jneuroim.2006.03.009]

23 **Piotrowski P**, Lianeri M, Wudarski M, Łacki JK, Jagodziński PP. CD24 Ala57Val gene polymorphism and the risk of systemic lupus erythematosus. *Tissue Antigens* 2010; **75**: 696-700 [PMID: 20230526 DOI: 10.1111/j.1399-0039.2010.01447.x]

24 **Sánchez E**, Abelson AK, Sabio JM, González-Gay MA, Ortego-Centeno N, Jiménez-Alonso J, de Ramón E, Sánchez-Román J, López-Nevot MA, Gunnarsson I, Svenungsson E, Sturfelt G, Truedsson L, Jönsen A, González-Escribano MF, Witte T, Alarcón-Riquelme ME, Martín J. Association of a CD24 gene polymorphism with susceptibility to systemic lupus erythematosus. *Arthritis Rheum* 2007; **56**: 3080-3086 [PMID: 17763438 DOI: 10.1002/art.22871]

25 **Lisiansky V**, Kraus S, Naumov I, Kazanov D, Nabiochtchikov I, Toledano O, Leshno M, Avivi D, Dotan I, Arber N, Moshkowitz M. Role of CD24 polymorphisms in the susceptibility to inflammatory bowel disease. *Int J Biol Markers* 2014; **29**: e62-e68 [PMID: 24557789 DOI: 10.5301/jbm.5000072]

26 **Diaz-Gallo LM**, Medrano LM, Gómez-García M, Cardeña C, Rodrigo L, Mendoza JL, Taxonera C, Nieto A, Alcain G, Cueto I, López-Nevot MA, Urcelay E, Martin J. Analysis of the influence of two CD24 genetic variants in Crohn's disease and ulcerative colitis. *Hum Immunol* 2011; **72**: 969-972 [PMID: 21684315 DOI: 10.1016/j.humimm.2011.05.028]

27 **Van Limbergen J**, Geddes K, Henderson P, Russell RK, Drummond HE, Satsangi J, Griffiths AM, Philpott DJ, Wilson DC. Paneth cell marker CD24 in NOD2 knockout organoids and in inflammatory bowel disease (IBD). *Gut* 2015; **64**: 353-354 [PMID: 23704317 DOI: 10.1136/gutjnl-2013-305077]

28 **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634 [PMID: 9310563]

29 **Franke A**, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, Anderson CA, Bis JC, Bumpstead S, Ellinghaus D, Festen EM, Georges M, Green T, Haritunians T, Jostins L, Latiano A, Mathew CG, Montgomery GW, Prescott NJ, Raychaudhuri S, Rotter JI, Schumm P, Sharma Y, Simms LA, Taylor KD, Whiteman D, Wijmenga C, Baldassano RN, Barclay M, Bayless TM, Brand S, Büning C, Cohen A, Colombel JF, Cottone M, Stronati L, Denson T, De Vos M, D'Inca R, Dubinsky M, Edwards C, Florin T, Franchimont D, Gearry R, Glas J, Van Gossum A, Guthery SL, Halfvarson J, Verspaget HW, Hugot JP, Karban A, Laukens D, Lawrance I, Lemann M, Levine A, Libioulle C, Louis E, Mowat C, Newman W, Panés J, Phillips A, Proctor DD, Regueiro M, Russell R, Rutgeerts P, Sanderson J, Sans M, Seibold F, Steinhart AH, Stokkers PC, Torkvist L, Kullak-Ublick G, Wilson D, Walters T, Targan SR, Brant SR, Rioux JD, D'Amato M, Weersma RK, Kugathasan S, Griffiths AM, Mansfield JC, Vermeire S, Duerr RH, Silverberg MS, Satsangi J, Schreiber S, Cho JH, Annese V, Hakonarson H, Daly MJ, Parkes M. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet* 2010; **42**: 1118-1125 [PMID: 21102463 DOI: 10.1038/ng.717]

30 **Wellcome Trust Case Control C.** Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; **447**: 661-678 [PMID: 17554300 DOI: 10.1038/nature05911]

31 **Anderson CA,** Boucher G, Lees CW, Franke A, D'Amato M, Taylor KD, Lee JC, Goyette P, Imielinski M, Latiano A, Lagace C, Scott R, Amininejad L, Bumpstead S, Baidoo L, Baldassano RN, Barclay M, Bayless TM, Brand S, Buning C, Colombel JF, Denson LA, De Vos M, Dubinsky M, Edwards C, Ellinghaus D, Fehrmann RS, Floyd JA, Florin T, Franchimont D, Franke L, Georges M, Glas J, Glazer NL, Guthery SL, Haritunians T, Hayward NK, Hugot JP, Jobin G, Laukens D, Lawrance I, Lemann M, Levine A, Libioulle C, Louis E, McGovern DP, Milla M, Montgomery GW, Morley KI, Mowat C, Ng A, Newman W, Ophoff RA, Papi L, Palmieri O, Peyrin-Biroulet L, Panes J, Phillips A, Prescott NJ, Proctor DD, Roberts R, Russell R, Rutgeerts P, Sanderson J, Sans M, Schumm P, Seibold F, Sharma Y, Simms LA, Seielstad M, Steinhart AH, Targan SR, van den Berg LH, Vatn M, Verspaget H, Walters T, Wijmenga C, Wilson DC, Westra HJ, Xavier RJ, Zhao ZZ, Ponsioen CY, Andersen V, Torkvist L, Gazouli M, Anagnou NP, Karlsen TH, Kupcinskas L, Sventoraityte J, Mansfield JC, Kugathasan S, Silverberg MS, Halfvarson J, Rotter JI, Mathew CG, Griffiths AM, Gearry R, Ahmad T, Brant SR, Chamaillard M, Satsangi J, Cho JH, Schreiber S, Daly MJ, Barrett JC, Parkes M, Annese V, Hakonarson H, Radford-Smith G, Duerr RH, Vermeire S, Weersma RK, Rioux JD. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nature genetics* 2011; **43**: 246-252 [PMID: 21297633 DOI: 10.1038/ng.764]

32 **Geremia A**, Biancheri P, Allan P, Corazza GR, Di Sabatino A. Innate and adaptive immunity in inflammatory bowel disease. *Autoimmun Rev* 2014; **13**: 3-10 [PMID: 23774107 DOI: 10.1016/j.autrev.2013.06.004]

33 **Sartor RB**. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol* 2006; **3**: 390-407 [PMID: 16819502 DOI: 10.1038/ncpgasthep0528]

34 **Xavier RJ**, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; **448**: 427-434 [PMID: 17653185 DOI: 10.1038/nature06005]

35 **Oliver J**, Márquez A, Gómez-Garcia M, Martinez A, Mendoza JL, Vilchez JR, López-Nevot MA, Piñero A, de la Concha EG, Nieto A, Urcelay E, Martín J. Association of the macrophage migration inhibitory factor gene polymorphisms with inflammatory bowel disease. *Gut* 2007; **56**: 150-151 [PMID: 17172590 DOI: 10.1136/gut.2006.107649]

36 **Zhang H**, Ma L, Dong LQ, Shu C, Xu JL. Association of the macrophage migration inhibitory factor gene--173G/C polymorphism with inflammatory bowel disease: a meta-analysis of 4296 subjects. *Gene* 2013; **526**: 228-231 [PMID: 23707797 DOI: 10.1016/j.gene.2013.05.012]

37 **Marrakchi R**, Moussa A, Ouerhani S, Bougatef K, Bouhaha R, Messai Y, Rouissi K, Khadimallah I, Khodjet-el-Khil H, Najar T, Benammar-Elgaaeid A. Interleukin 10 promoter region polymorphisms in inflammatory bowel disease in Tunisian population. *Inflamm Res* 2009; **58**: 155-160 [PMID: 19184348 DOI: 10.1007/s00011-008-8265-5]

38 **Lim SC**. CD24 and human carcinoma: tumor biological aspects. *Biomed Pharmacother* 2005; **59 Suppl 2**: S351-S354 [PMID: 16507407]

39 **Liu Y**, Jones B, Aruffo A, Sullivan KM, Linsley PS, Janeway CA. Heat-stable antigen is a costimulatory molecule for CD4 T cell growth. *J Exp Med* 1992; **175**: 437-445 [PMID: 1346270]

40 **Ahmed MA**, Jackson D, Seth R, Robins A, Lobo DN, Tomlinson IP, Ilyas M. CD24 is upregulated in inflammatory bowel disease and stimulates cell motility and colony formation. *Inflamm Bowel Dis* 2010; **16**: 795-803 [PMID: 19998456 DOI: 10.1002/ibd.21134]

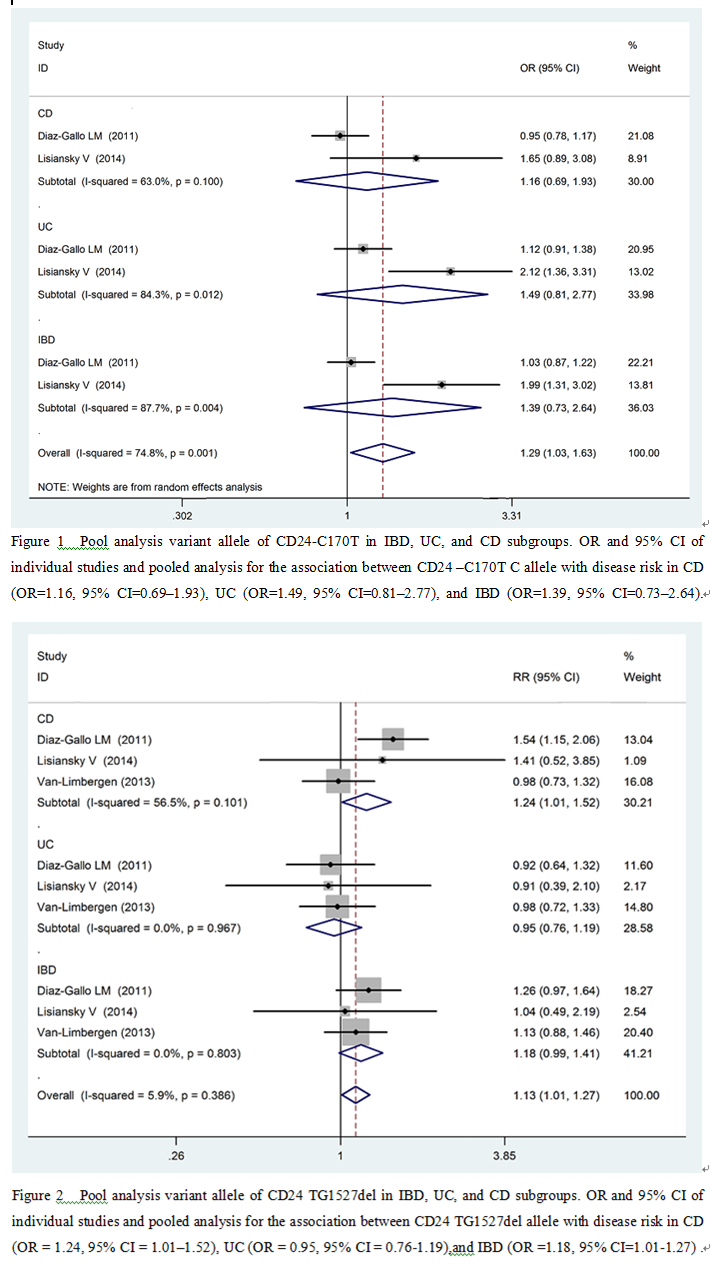
41 **Wang K**, Baldassano R, Zhang H, Qu HQ, Imielinski M, Kugathasan S, Annese V, Dubinsky M, Rotter JI, Russell RK, Bradfield JP, Sleiman PM, Glessner JT, Walters T, Hou C, Kim C, Frackelton EC, Garris M, Doran J, Romano C, Catassi C, Van Limbergen J, Guthery SL, Denson L, Piccoli D, Silverberg MS, Stanley CA, Monos D, Wilson DC, Griffiths A, Grant SF, Satsangi J, Polychronakos C, Hakonarson H. Comparative genetic analysis of inflammatory bowel disease and type 1 diabetes implicates multiple loci with opposite effects. *Hum Mol Genet* 2010; **19**: 2059-2067 [PMID: 20176734 DOI: 10.1093/hmg/ddq078]

42 **Zhou Q**, Rammohan K, Lin S, Robinson N, Li O, Liu X, Bai XF, Yin L, Scarberry B, Du P, You M, Guan K, Zheng P, Liu Y. CD24 is a genetic modifier for risk and progression of multiple sclerosis. *Proc Natl Acad Sci U S A* 2003; **100**: 15041-15046 [PMID: 14657362 DOI: 10.1073/pnas.2533866100]

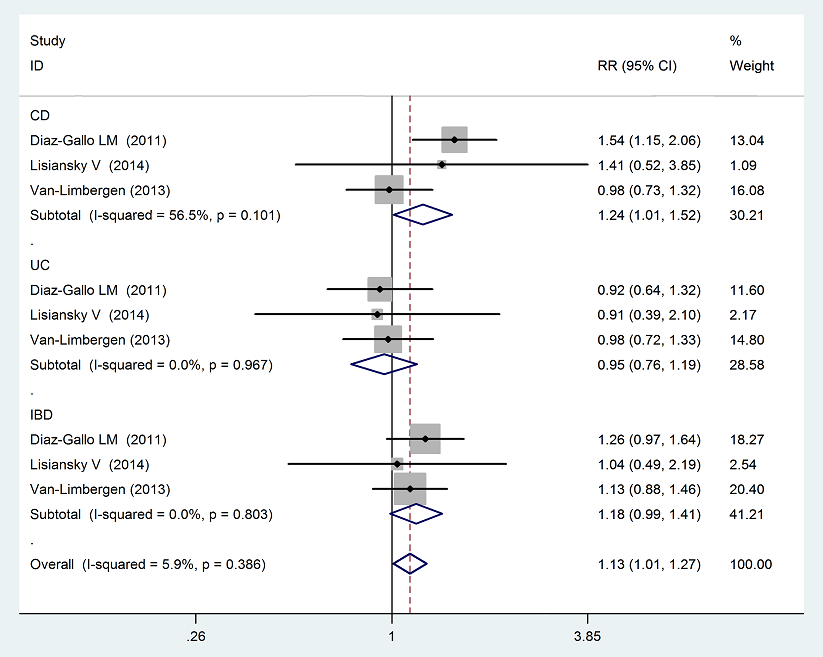
43 **Wang L**, Lin S, Rammohan KW, Liu Z, Liu JQ, Liu RH, Guinther N, Lima J, Zhou Q, Wang T, Zheng X, Birmingham DJ, Rovin BH, Hebert LA, Wu Y, Lynn DJ, Cooke G, Yu CY, Zheng P, Liu Y. A dinucleotide deletion in CD24 confers protection against autoimmune diseases. *PLoS Genet* 2007; **3**: e49 [PMID: 17411341 DOI: 10.1371/journal.pgen.0030049]

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**Figure 1 Pooled analysis of the variant allele *CD24*-C170T in the IBD, UC, and Crohn’s disease subgroups.** ORs and 95%CIs of the individual studies and pooled analyses of the associations between the *CD24* C170T C allele and the disease risks for Crohn’s disease (CD) (OR = 1.16, 95%CI: 0.69–1.93), ulcerative colitis (UC) (OR = 1.49, 95%CI: 0.81–2.77), and inflammatory bowel disease (IBD) (OR = 1.39, 95%CI = 0.73–2.64). OR: Odds ratio.



**Figure 2 Pooled analyses of the variant allele CD24 TG1527del in the IBD, UC and Crohn’s disease subgroups.** ORs and 95% CIs of the individual studies and the pooled analyses of the associations between the *CD24* TG1527*del* allele and the disease risks for Crohn’s disease (CD) (OR = 1.24, 95%CI: 1.01–1.52), ulcerative colitis (UC) (OR = 0.95, 95%CI: 0.76-1.19) and inflammatory bowel disease (IBD) (OR =1.18, 95%CI: 0.99-1.41). OR: Odds ratio.

**Table 1 Characteristics of the studies included in the meta-analysis**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author** | **Year** | **Country** | **Ethnicity** | **Sample size** | | | **Polymorphisms** | **Genotype**  **method** |
| **UC** | **CD** | **Control** |
| Diaz-Gallo LM | 2011 | Spain | Caucasian | 632 | 737 | 1257 | P170 P1527 | PCR |
| Van Limbergen | 2013 | Scottish | Caucasian | 342 | 395 | 498 | P1527 | PCR |
| Lisiansky V | 2014 | Israel | Caucasian | 174 | 62 | 210 | P170 P1527 | PCR-RFLP |

UC: Ulcerative colitis; CD: Crohn’s disease; RFLP: Restricted fragment length polymorphisms; PCR: Polymerase chain reaction.

**Table 2 Distributions of two *CD24* genotypes and alleles among the inflammatory bowel disease patients and controls**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Arms** | **C170T** | | | | | |  | **Arms** | **TG1570*del*** | | | | | |
| **A** | **V** | **AA** | **AV** | **VV** | **HWE** | **TG** | ***del*** | **TGTG** | **TG*del*** | ***deldel*** | **HWE** |
| Diaz-Gallo *et al*[26], 2011 | CD (*n =* 366) | 534 | 198 | 200 | 134 | 32 |  |  | CD (*n =* 371) | 662 | 80 | 301 | 60 | 10 |  |
|  | UC (*n =* 322) | 448 | 196 | 161 | 126 | 35 |  |  | UC (*n =* 310) | 580 | 40 | 270 | 40 | 0 |  |
|  | Control (*n =* 628) | 904 | 352 | 317 | 270 | 41 | 0.10 |  | Control (*n =* 629) | 1170 | 88 | 547 | 76 | 6 | 0.448 |
| Lisiansky *et al*[25], 2014 | CD (*n =* 31) | 42 | 20 | 12 | 18 | 1 |  |  | CD (*n =* 31) | 57 | 5 | 26 | 5 | 0 |  |
|  | UC (*n =* 87) | 108 | 66 | 29 | 50 | 8 |  |  | UC (*n =* 87) | 165 | 9 | 78 | 9 | 0 |  |
|  | Control (*n =* 105) | 163 | 47 | 63 | 37 | 5 | 0.884 |  | Control (*n =* 105) | 198 | 12 | 93 | 12 | 0 | 0.534 |
| Van Limbergen *et al*[27], 2013 | CD (*n =* 395) | - | - | - | - | - |  |  |  | 719 | 71 | 326 | 67 | 2 |  |
|  | UC (*n =* 310) | - | - | - | - | - |  |  |  | 623 | 61 | 283 | 57 | 2 |  |
|  | Control (*n =* 498) | - | - | - | - | - |  |  |  | 905 | 91 | 411 | 83 | 4 | 0.932 |

UC: Ulcerative colitis; CD: Crohn’s disease; HWE: Hardy–Weinberg equilibrium.

**Table 3 Meta-analysis of the associations between two promoter polymorphisms of *CD24* and inflammatory bowel disease**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Polymorphism** | **Disease** | **Test of association** | | | **Test of heterogeneity** | | |
| **OR** | **95%CI** | ***P value*** | **Model** | ***P* value** | ***I2*(%)** |
| P170V *vs* A | CD | 1.16 | 0.69-1.93 | 0.583 | R | 0.100 | 63.0 |
|  | UC | 1.49 | 0.81-2.77 | 0.203 | R | 0.012 | 84.3 |
|  | IBD | 1.39 | 0.73-2.64 | 0.314 | R | 0.004 | 87.7 |
| VV + AV *vs* AA | CD | 0.76 | 0.28-2.07 | 0.594 | R | 0.019 | 81.9 |
| (recessive) | UC | 0.59 | 0.21-1.70 | 0.330 | R | 0.001 | 90.5 |
|  | IBD | 0.64 | 0.21-1.90 | 0.420 | R | <0.001 | 92.8 |
| VV *vs* AA + AV | CD | 1.32 | 0.83-2.11 | 0.245 | F | 0.527 | 0.0 |
| (dominant) | UC | 1.79 | 1.15-2.77 | **0.009** | F | 0.816 | 0.0 |
|  | IBD | 0.94 | 0.62-1.43 | 0.777 | F | 0.287 | 11.8 |
| VV *vs* AA | CD | 1.23 | 0.76-1.99 | 0.405 | F | 0.888 | 0.0 |
| (additive) | UC | 1.87 | 1.19-2.93 | **0.007** | F | 0.272 | 17.1 |
|  | IBD | 1.32 | 0.40-4.39 | 0.654 | R | 0.051 | 73.9 |
| P1527*del vs* TG | CD | 1.24 | 1.01-1.52 | **0.037** | F | 0.101 | 56.5 |
|  | UC | 0.95 | 0.76-1.19 | 0.649 | F | 0.967 | 0.0 |
|  | IBD | 1.18 | 0.99-1.41 | 0.063 | F | 0.803 | 0.0 |
| *deldel* + TG*del* *vs* TGTG | CD | 0.80 | 0.63-1.02 | 0.068 | F | 0.207 | 36.5 |
| (recessive) | UC | 1.02 | 0.79-1.33 | 0.870 | F | 0.980 | 0 |
|  | IBD | 0.82 | 0.67-1.01 | 0.061 | F | 0.870 | 0 |
| *deldel* *vs* TGTG + TG*del* | CD | 1.87 | 0.81-4.32 | 0.143 | F | 0.133 | 55.7 |
| (dominant) | UC | 0.40 | 0.10-1.63 | 0.201 | F | 0.345 | 0 |
|  | IBD | 1.23 | 0.54-2.76 | 0.625 | F | 0.436 | 0 |
| *deldel* *vs* TGTG | CD | 1.93 | 0.84-4.47 | 0.123 | F | 0.121 | 58.4 |
| (additive) | UC | 0.40 | 0.10-1.64 | 0.203 | F | 0.348 | 0.0 |
|  | IBD | 1.27 | 0.56-2.86 | 0.572 | F | 0.439 | 0.0 |

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn’s disease.

**Table 4 Egger’s tests for C170 T and TG1527*del* of *CD24* and the inflammatory bowel disease risk in all of the included studies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Contrast models** | **Coefficient** | **95%CI** | **SE** | ***t*** | ***P* value** |
| C170T |  |  |  |  |  |
| V *vs* A | 3.902 | 0.912 to 6.891 | 1.077 | 3.62 | **0.022** |
| VV +AV *vs* AA | -4.527 | -5.832 to 3.075 | 1.969 | -0.70 | 0.501 |
| VV *vs* AA + AV | 0.200 | -7.276 to -1.779 | 0.990 | -4.57 | **0.010** |
| VV *vs* AA | 1.399 | -2.040 to 4.838 | 1.239 | 1.13 | 0.322 |
| TG1527*del* |  |  |  |  |  |
| *del* *vs* TG | -0.435 | -2.669 to 1.799 | 0.945 | -0.46 | 0.659 |
| *deldel* + TG*del vs* TGTG | 0.444 | -1.833 to 2.721 | 0.963 | 0.64 | 0.659 |
| *deldel* *vs* TGTG + TG*del* | -2.977 | -4.820 to -1.134 | 0.664 | -4.48 | **0.011** |
| *deldel vs* TGTG | -2.598 | -4.249 to -0.947 | 0.595 | -4.37 | **0.012** |

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn’s disease.