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Review Article

Protein tyrosine phosphatase nonreceptor type 22 (PTPN22) gene R620W polymorphism is associated with inflammatory bowel disease risk

Xiangchen Li[1], Mingliao Niu[2], Huiju Yang[3], Fengrui Zhou[4], Zuowu Xi[2]

[1]General Surgery Ward 3 of Xinxiang Central Hospital, Xinxiang, Henan, China; [2]Anorectal Section of Henan Province Hospital of Traditional Chinese Medicine, Zhengzhou 450002, Henan, China; [3]Anorectal Section of The Third Hospital Affiliated to Henan University of Traditional Chinese Medicine, Zhengzhou, Henan, China; [4]Department of Liver Disease, The Sixth People's Hospital of Zhengzhou, Zhengzhou, Henan, China

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Abstract: Previous studies reported that Protein tyrosine phosphatase nonreceptor type 22 (PTPN22) R620W polymorphism may be associated with inflammatory bowel diseases (IBD) risk. However, the data are inconsistent. The aim of our study was to determine the association between PTPN22 R620W polymorphism and IBD in a meta-analysis. Online electronic databases were searched. The strength of the association between PTPN22 R620W polymorphism and IBD was measured by odds ratio (OR) and 95% confidence interval (CI). A total of ten studies with 16151 cases and 22360 controls were included in this meta-analysis. PTPN22 R620W polymorphism was significantly associated with the risk of IBD (OR=0.71; 95% CI, 0.56-0.90; I^2=81%). In the subgroup analysis, a significantly decreased CD risk were observed (OR=0.61; 95% CI, 0.44-0.84; I^2=78%). However, PTPN22 R620W polymorphism was not associated with the risk of UC (OR=0.85; 95% CI, 0.65-1.09; I^2=72%). This meta-analysis suggested that PTPN22 R620W polymorphism was significantly associated with the risk of CD in Caucasians.

Keywords: Inflammatory bowel diseases, PTPN22, meta-analysis

Introduction

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), which is a chronic relapsing and remitting inflammatory condition of the gastrointestinal tract, affect a large number of Europeans [1]. Despite the introduction of new treatments, many of these therapies have significant undesirable side effects [2].

Protein tyrosine phosphatase nonreceptor type 22 (PTPN22) located on chromosome 1p-13, encodes a lymphoid-specific phosphatase (Lyp). A non-synonymous SNP, R620W (also referred to as C1858T or rs2476601), located in the PTPN22 has been repeatedly associated with a wide range of autoimmune diseases [3]. Previous studies reported that PTPN22 R620W polymorphism may be associated with IBD risk. However, the data are inconsistent [4-11]. The aim of our study was to determine the association between PTPN22 R620W polymorphism and IBD in a meta-analysis.

Materials and methods

Publication search

Online electronic databases (PubMed, EMBASE, and Wanfang database) were searched using the search terms: ("Protein tyrosine phosphatase nonreceptor type 22" or PTPN22) and (polymorphism or variant orvariation) and ("inflammatory bowel diseases" or "IBD"). The reference lists of related articles were also manually examined. There was no language and time restriction.

Study selection

The inclusion criteria were as follows: (1) the study was a case-control study or a cohort study; (2) the study investigated the association between PTPN22 R620W polymorphism and

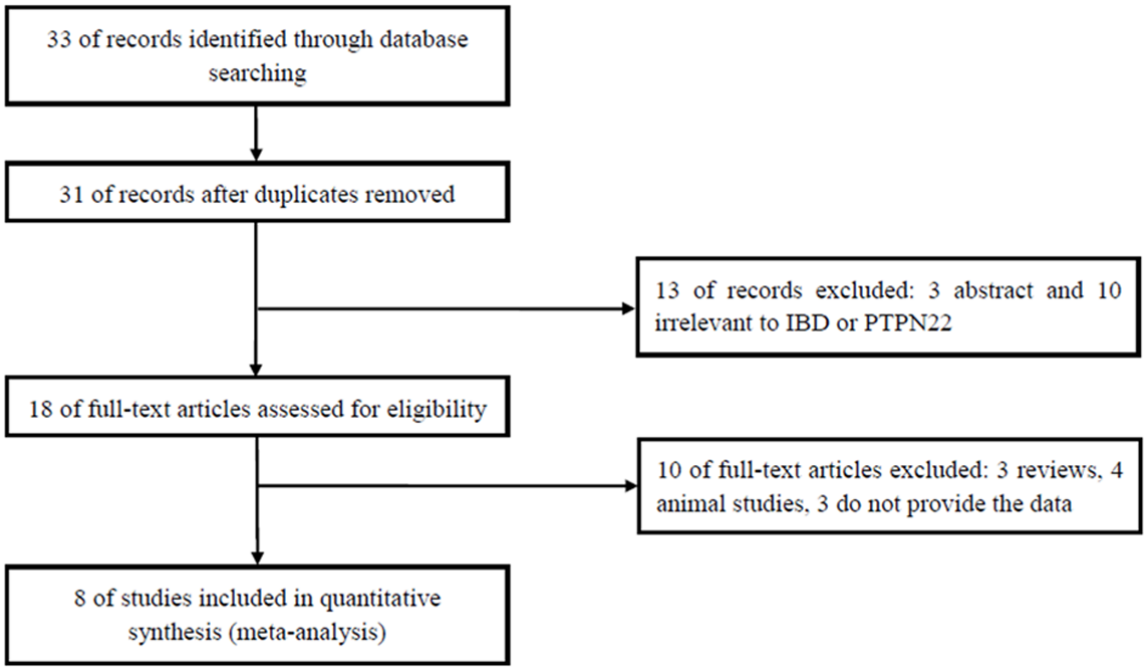

Figure 1. Flow of study identification, inclusion, and exclusion.

IBD; (3) sufficient published data about sample size, odds ratio (OR), and 95% confidence interval (CI). Studies were excluded when they were: (1) duplicate publication; (2) meta-analyses, letters, reviews, or editorial articles.

Quality score assessment

The quality of the studies was independently assessed by two investigators according to a set of predetermined criteria which was extracted and modified from previous studies [12]. These scores were based on traditional epidemiological considerations, as well as cancer genetic issues. Any disagreement was resolved by discussion between the two investigators. Scores ranged from the lowest zero to the highest 18. Articles scoring <12 were classified as "low quality", and those ≥12 as "high quality".

Data extraction

Two investigators extracted the data independently. Data on first author, year of publication, race, age, gender, type of IBD, numbers of case and control, and Hardy-Weinberg equilibrium (HWE) were extracted.

Statistical analysis

The strength of the association between PTPN22 R620W polymorphism and IBD risk was calculated with the ORs and respective 95% CIs. The significance of the pooled OR was determined by the Z test, and *P*-values of less than 0.05 were considered significant. Statistical heterogeneity among studies was assessed with the I^2 statistics. This value ranges from 0% (complete consistency) to 100% (complete inconsistency). IBD is commonly classified into UC and CD. Thus we did a subgroup analysis by the type of IBD. The Galbraith plot was used to find the source of the heterogeneity. The random-effects model was chosen to calculate the pooled OR. The presence of publication bias was assessed by a visual inspection of a funnel plot. All statistical tests were used by the Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and STATA 11.0 software (Stata Corporation, College Station, TX).

Results

Eligible studies

The literature search and study selection procedures are shown in **Figure 1**. Eight eligible literatures were enrolled in this meta-analysis. Two studies reported two case-control studies. Thus, a total of ten studies with 16151 cases and 22360 controls were included in this meta-

Table 1. Characteristics of included studies

First author	Year	Ethnicity	Age	Gender	Type of IBD	Source of controls	Case (n)	Control (n)	Hardy-Weinberg equilibrium	Genotying Type	Quality scores
Criswell	2005	Caucasian	NA	Mixed	IBD	Hospital-based	41	705	Yes	PCR-RFLP	8
Martin	2005	Caucasian	NA	Mixed	Both	Population-based	1113	812	Yes	PCR-RFLP	10
Prescott	2005	Caucasian	NA	Mixed	Both	Hospital-based	514	374	Yes	PCR-RFLP	11
Sfar 1	2010	Caucasian	36	Mixed	CD	Hospital-based	105	100	Yes	PCR-RFLP	9
Sfar 2	2010	Caucasian	36	Mixed	UC	Hospital-based	59	100	Yes	PCR-RFLP	8
Diaz-Gallo 1	2011	Caucasian	NA	Mixed	CD	Population-based	6977	9254	Yes	TaqMan SNP Genotyping Assay	16
Diaz-Gallo 2	2011	Caucasian	NA	Mixed	UC	Population-based	5695	8766	Yes	TaqMan SNP Genotyping Assay	16
Skieceviciene	2013	Caucasian	44.4	Mixed	UC	Population-based	447	1154	Yes	TaqMan SNP Genotyping Assay	14
Chen	2013	Asian	41.3	Mixed	UC	Hospital-based	165	300	NA	PCR-RFLP	14
Bank	2014	Caucasian	43	Mixed	Both	Population-based	1035	795	Yes	PCR	16

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis; NA, not available.

Table 2. Scale for quality assessment

Criterion	Score
Source of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathology archives, but without description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based	1
Not described	0
Case-control match	
Matched by age and gender	3
Not matched by age and gender	0
Specimens used for determining genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Total sample size	
>1000	3
>500 and <1000	2
>200 and <500	1
<200	0

analysis. One study included Asians. All of the rest studies were Caucasians. In addition, all the studies were in HWE. The characteristics of the studies are listed in **Table 1**. The Scale for quality assessment is listed in **Table 2**. Quality scores for the individual studies ranged from 8 to 16.

Quantitative data synthesis

PTPN22 R620W polymorphism was significantly associated with the risk of IBD (OR=0.71; 95% CI, 0.56-0.90; I^2=81%; **Figure 2**). In the subgroup analysis, a significantly decreased CD risk were observed (OR=0.61; 95% CI, 0.44-0.84; I^2=78%; **Figure 2**). However, PTPN22 R620W polymorphism was not associated with the risk of UC (OR=0.85; 95% CI, 0.65-1.09; I^2=72%; **Figure 3**). The study by Chen et al. [11] was not in meta-analysis since the distribution of PTPN22 R620W frequencies did not differ between UC patients and the healthy controls.

Funnel plot was performed to assess the publication bias of literatures. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (P=0.187; **Figure 4**). The Galbraith plot was used to find the source of the heterogeneity. As shown in **Figure 5**, four studies were the outliers. After excluding these studies, the between-study heterogeneity decreased (I^2=0%). In addition, when we excluded these studies, the result was not changed (OR=0.79; 95% CI, 0.71-0.88; I^2=0%).

Discussion

In this meta-analysis, we found that PTPN22 R620W polymorphism was significantly associated with the risk of IBD. In the subgroup analysis, we also observed that this polymorphism was significantly associated with CD risk, but not UC risk. It was possible that different genetic factors may account for this discrepancy. Additionally, the heterogeneity may also influence the results.

The R620W polymorphism disrupts the interaction between Lck and LYP, leading to reduced phosphorylation of LYP, which ultimately contributes to gain-of-function inhibition of T-cell activation [13]. Thus, it is plausible that this genetic discrepancy in PTPN22 influences a range of diseases. Lester et al. suggested that PTPN22 R620W minor allele is a genetic risk factor for giant cell arteritis [14]. Goulielmos et al. demonstrates that PTPN22 was associated with increased risk of juvenile idiopathic arthritis in Greek sample [15]. Salinas-Santander et al. suggested the possible involvement of the T allele of the PTPN22 C1858T SNP as a genetic risk factor for this type of alopecia areata [16]. Xiong et al. shows a significant association between PTPN22 R620W polymorphism and myasthenia gravis risk [17].

This study had some advantages. First, this meta-analysis included 16151 cases and 22360 controls. Therefore, the statistical power was enough. Second, funnel plots did not find publication bias. Finally, the heterogeneity was decreased in the Galbraith plot.

Our meta-analysis had some limitations. First, the numbers of published studies were not suf-

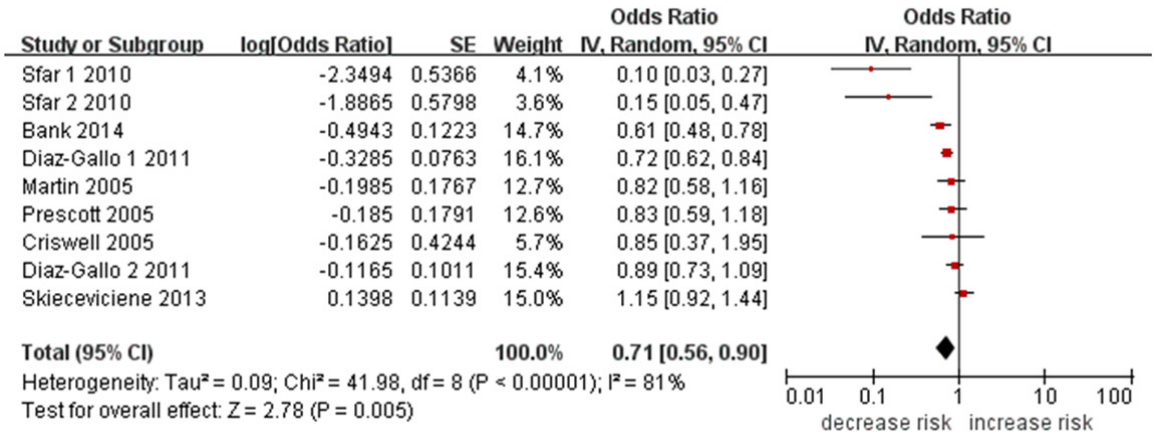

Figure 2. Meta-analysis of the association between PTPN22 R620W polymorphism and IBD risk.

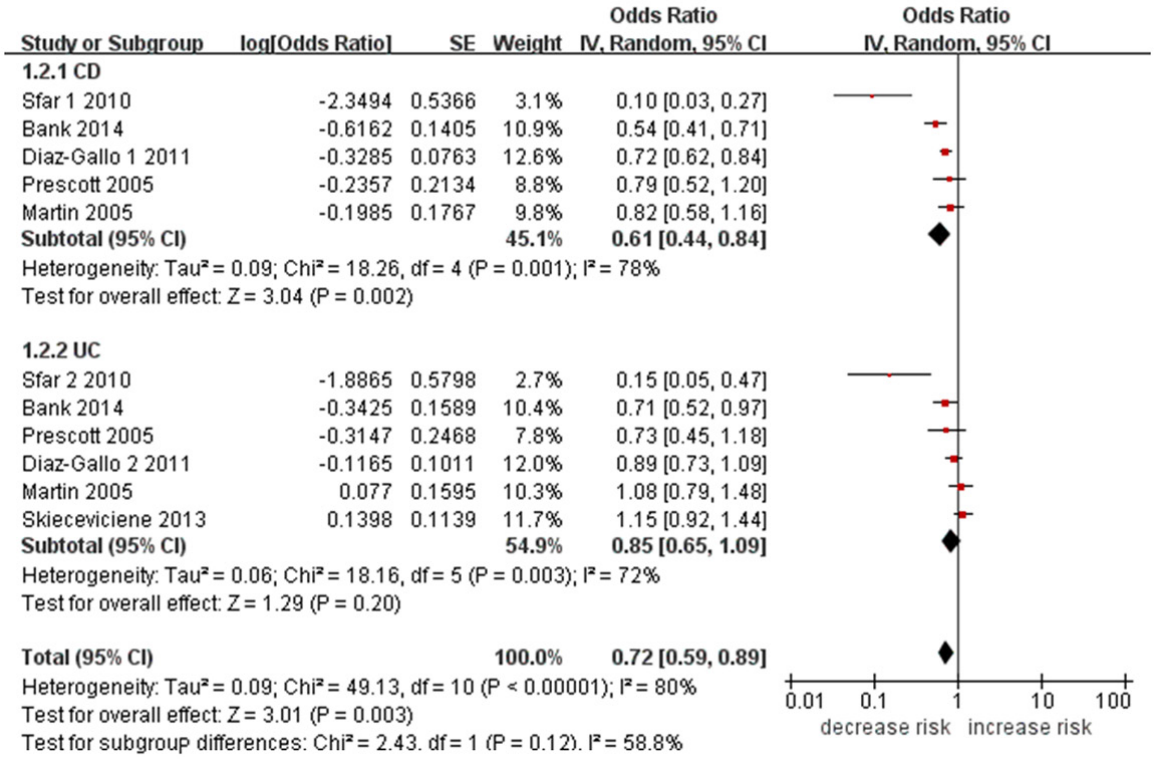

Figure 3. Subgroup analysis of the association between PTPN22 R620W polymorphism and IBD risk.

ficient for a comprehensive analysis, particularly for Asians and Africans. Second, lack of the original data of the reviewed studies limited our further evaluation of potential interactions, because the interactions between gene-to-gene and gene-to-environment may modulate IBD risk.

In conclusion, this meta-analysis suggested that PTPN22 R620W polymorphism was significantly associated with the risk of CD in Caucasians.

Disclosure of conflict of interest

None.

Address correspondence to: Zuowu Xi, Anorectal Section of Henan Province Hospital of Traditional Chinese Medicine, No.6, Dongfeng Road, Zhengzhou

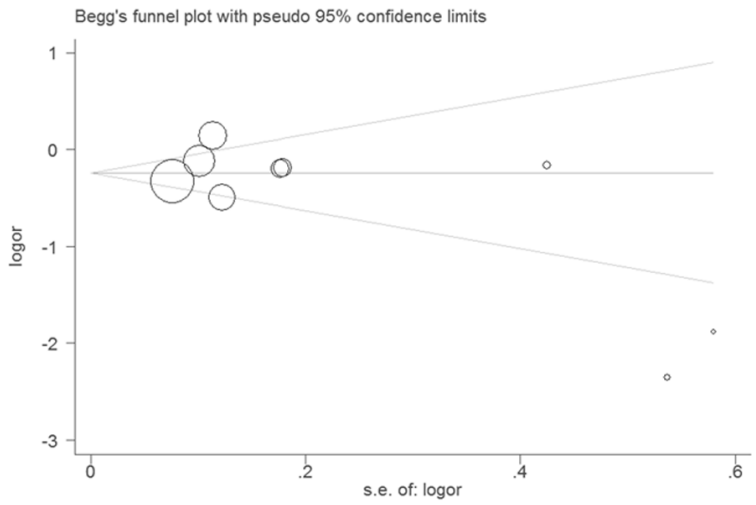

Figure 4. Funnel plot analysis to detect publication bias.

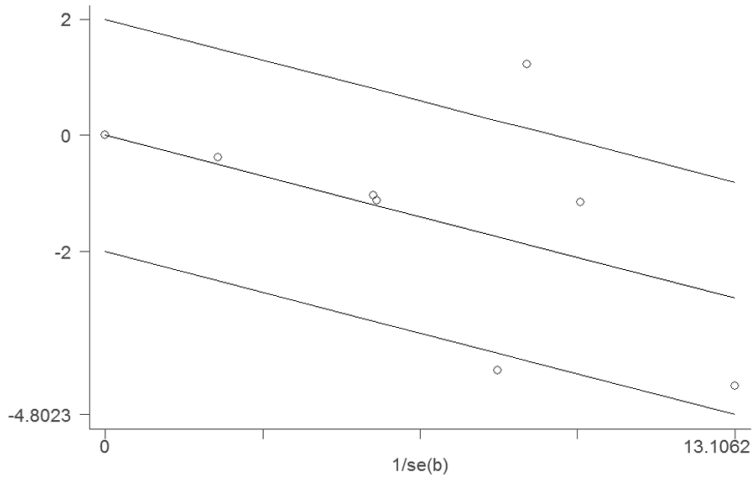

Figure 5. Galbraith plots for heterogeneity test.

450002, Henan, China. Tel: 86-0371-60905547; E-mail: a04jnk@163.com

References

[1] Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW and Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012; 142: 46-54.

[2] Baumgart DC and Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet 2007; 369: 1627-40.

[3] Stanford SM and Bottini N. PTPN22: the archetypal non-HLA autoimmunity gene. Nat Rev Rheumatol 2014; 10: 602-11.

[4] Criswell LA, Pfeiffer KA, Lum RF, Gonzales B, Novitzke J, Kern M, Moser KL, Begovich AB, Carlton VE, Li W, Lee AT, Ortmann W, Behrens TW and Gregersen PK. Analysis of families in the multiple autoimmune disease genetics consortium (MADGC) collection: the PTPN22 620W allele associates with multiple autoimmune phenotypes. Am J Hum Genet 2005; 76: 561-71.

[5] Martín MC, Oliver J, Urcelay E, Orozco G, Gómez-Garcia M, López-Nevot MA, Piñero A, Brieva JA, de la Concha EG, Nieto A and Martín J. The functional genetic variation in the PTPN22 gene has a negligible effect on the susceptibility to develop inflammatory bowel disease. Tissue Antigens 2005; 66: 314-7.

[6] Prescott NJ, Fisher SA, Onnie C, Pattni R, Steer S, Sanderson J, Forbes A, Lewis CM and Mathew CG. A general autoimmunity gene (PTPN22) is not associated with inflammatory bowel disease in a British population. Tissue Antigens 2005; 66: 318-20.

[7] Diaz-Gallo LM, Espino-Paisán L, Fransen K, Gómez-García M, van Sommeren S, Cardeña C, Rodrigo L, Mendoza JL, Taxonera C, Nieto A, Alcain G, Cueto I, López-Nevot MA, Bottini N, Barclay ML, Crusius JB, van Bodegraven AA, Wijmenga C, Ponsioen CY, Gearry RB, Roberts RL, Weersma RK, Urcelay E, Merriman TR, Alizadeh BZ and Martin J. Differential association of two PTPN22 coding variants with Crohn's disease and ulcerative colitis. Inflamm Bowel Dis 2011; 17: 2287-94.

[8] Skieceviciene J, Kiudelis G, Ellinghaus E, Balschun T, Jonaitis LV, Zvirbliene A, Denapiene G, Leja M, Pranculiene G, Kalibatas V, Saadati H, Ellinghaus D, Andersen V, Valantinas J, Irnius A, Derovs A, Tamelis A, Schreiber S, Kupcinskas L and Franke A. Replication study of ulcerative colitis risk loci in a Lithuanian-Latvian case-control sample. Inflamm Bowel Dis 2013; 19: 2349-55.

[9] Bank S, Skytt Andersen P, Burisch J, Pedersen N, Roug S, Galsgaard J, Ydegaard Turino S, Brodersen JB, Rashid S, Kaiser Rasmussen B, Avlund S, Bastholm Olesen T, Jürgen Hoffmann H, Kragh Thomsen M, Ostergaard Thomsen V, Frydenberg M, Andersen Nexø B, Sode J, Vogel U and Andersen V. Polymorphisms in the inflammatory pathway genes TLR2, TLR4, TLR9, LY96, NFKBIA, NFKB1, TNFA, TNFRSF1A, IL6R, IL10, IL23R, PTPN22, and PPARG are associated with susceptibility of inflammatory bowel disease in a Danish cohort. PLoS One 2014; 9: e98815.

[10] Sfar I, Ben Aleya W, Mouelhi L, Aouadi H, Ben Rhomdhane T, Makhlouf M, Ayed-Jendoubi S, Gargaoui H, Najjar T, Ben Abdallah T, Ayed K and Gorgi Y. Lymphoid tyrosine phosphatase R620W variant and inflammatory bowel disease in Tunisia. World J Gastroenterol 2010; 16: 479-83.

[11] Chen Z, Zhang H, Xia B, Wang P, Jiang T, Song M and Wu J. Association of PTPN22 gene (rs2488457) polymorphism with ulcerative cols of PTPN22 mRNA in ulcerative colitis. Int J Colorectal Dis 2013; 28: 1351-8.

[12] Wang F, Sun G, Zou Y, Fan L, Song B. Lack of association of miR-146a rs2910164 polymorphism with gastrointestinal cancers: evidence from 10206 subjects. PLoS One 2012; 7: e39623.

[13] Zhang J, Zahir N, Jiang Q, Miliotis H, Heyraud S, Meng X, Dong B, Xie G, Qiu F, Hao Z, McCulloch CA, Keystone EC, Peterson AC and Siminovitch KA. The autoimmune disease-associated PTPN22 variant promotes calpain-mediated Lyp/Pep degradation associated with lymphocyte and dendritic cell hyperresponsiveness. Nat Genet 2011; 43: 902-7.

[14] Lester S, Hewitt AW, Ruediger CD, Bradbury L, De Smit E, Wiese MD, Black R, Harrison A, Jones G, Littlejohn GO, Merriman TR, Shenstone B, Smith MD, Rischmueller M, Brown MA and Hill CL. PTPN22 R620W minor allele is a genetic risk factor for giant cell arteritis. RMD Open 2016; 2: e000246.

[15] Goulielmos GN, Chiaroni-Clarke RC, Dimopoulou DG, Zervou MI, Trachana M, Pratsidou-Gertsi P, Garyfallos A and Ellis JA. Association of juvenile idiopathic arthritis with PTPN22 rs2476601 is specific to females in a Greek population. Pediatr Rheumatol Online J 2016; 14: 25.

[16] Salinas-Santander M, Sánchez-Domínguez C, Cantú-Salinas C, Gonzalez-Cárdenas H, Cepeda-Nieto AC, Cerda-Flores RM, Ortiz-López R and Ocampo-Candiani J. Association between PTPN22 C1858T polymorphism and alopecia areata risk. Exp Ther Med 2015; 10: 1953-8.

[17] Xiong X, Xiang M, Cheng X and Huang Y. PTPN22 R620W Polymorphism is associated with myasthenia gravis risk: a systematic review and meta-analysis. Med Sci Monit 2015; 21: 2567-71.