Differential Association of Two *PTPN22* Coding Variants with Crohn's Disease and Ulcerative Colitis

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Background: The *PTPN22* gene is an important risk factor for human autoimmunity. The aim of this study was to evaluate for the first time the role of the R263Q *PTPN22* polymorphism in ulcerative colitis (UC) and Crohn's disease (CD), and to reevaluate the association of the R620W *PTPN22* polymorphism with both diseases.

Methods: A total of 1677 UC patients, 1903 CD patients, and 3111 healthy controls from an initial case–control set of Spanish Caucasian ancestry and two independent sample sets of European ancestry (Dutch and New Zealand) were included in the study. Genotyping was performed using TaqMan SNP assays for the R263Q (*rs33996649*) and R620W (*rs2476601*) *PTPN22* polymorphisms. Meta-analysis was performed on 6977 CD patients, 5695 UC patients, and 9254 controls to test the overall effect of the minor allele of R620W and R263Q polymorphisms.

Results: The *PTPN22* 263Q loss-of-function variant showed initial evidence of association with UC in the Spanish cohort (P = 0.026, odds ratio [OR] = 0.61, 95% confidence interval [CI]: 0.39–0.95), which was confirmed in the meta-analysis (P = 0.013 pooled, OR = 0.69, 95% CI: 0.51–0.93). In contrast, the 263Q allele showed no association with CD (P = 0.22 pooled, OR = 1.16, 95% CI: 0.91–1.47). We found in the pooled analysis that the PTPN22 620W gain-of-function variant was associated with reduced risk of CD (P = 7.4E-06 pooled OR = 0.81, 95% CI: 0.75–0.89) but not of UC (P = 0.88 pooled, OR = 0.98, 95% CI: 0.85–1.15).

Conclusions: Our data suggest that two autoimmunity-associated polymorphisms of the *PTPN22* gene are differentially associated with CD and UC. The R263Q polymorphism only associated with UC, whereas the R620W was significantly associated with only CD.

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Key Words: protein tyrosine phosphatase, nonreceptor type 22 (PTPN22) gene, inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (CD)

Additional supporting information may be found in the online version of this

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rohn's disease (CD) and ulcerative colitis (UC) are the main types of inflammatory bowel disease (IBD). They are relapsing and chronic inflammatory disorders that result from the complex interaction of genetic, immune, and environmental factors. It is estimated that the current number of loci associated with IBD only explain 10%–20% of the genetic risk attributed to UC and CD. Thus, additional genetic contributions clearly remain to be discovered.¹⁻⁴

The protein tyrosine phosphatase nonreceptor 22 (PTPN22) gene encodes the gatekeeper of T-cell receptor (TCR) signaling, protein tyrosine phosphatase (PTP, also known as LYP), and as such is a compelling candidate risk factor for IBD. In T cells, LYP (lymphoid tyrosine phosphatase) potently inhibits signaling through dephosphorylation of several substrates, including the Src-family kinases Lck and Fyn, as well as ZAP-70 and TCRzeta. Moreover, *PTPN22* has emerged as an important genetic risk factor for human autoimmunity. ⁵⁻⁸ Specifically, two missense single nucleotide polymorphisms (SNPs), both with functional influence, 6,8-12 have been associated with autoimmune diseases. The R620W (1858C>T, rs2476601) polymorphism in exon 14 of PTPN22 was first associated with type 1 diabetes (T1D), and subsequently with autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), IBD, and other autoimmune diseases. 13-16 The R620W variation disrupts the interaction between Lck and LYP, leading to reduced phosphorylation of LYP, which ultimately contributes to gain-of-function inhibition of T-cell signaling.¹⁷ The O minor allele of R263O (788G>A, rs33996649) in exon 10, within the catalytic domain of the enzyme, is a loss-of-function mutation that confers protection against development of SLE and RA. 12,18

In this study we sought first to determine whether the newly described amino acid substitution, R263Q (788G>A, rs33996649) is associated with altered susceptibility to CD and UC and, second, to reevaluate the influence of the R620W (1858C>T, rs2476601) polymorphism on these diseases by conducting a case—control study and meta-analysis.

MATERIALS AND METHODS

Case-Control Study

Study Population

A total of 1903 CD patients, 1677 UC patients, and 3111 healthy controls from an initial case–control set of Spanish Caucasian ancestry (699 CD patients, 658 UC patients, and 1685 healthy controls) and two independent sample sets of European ancestry from The Netherlands (694 CD patients, 548 UC patients, and 863 healthy controls) and New Zealand (510 CD patients, 471 UC patients, and 563 healthy controls) were included in the case–control study. All IBD patients were diagnosed according to standard clinical, endoscopic, radiologic, and histopathologic criteria. 19–21 Control individu-

als were matched by Caucasian origin, age, and gender. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of the Spanish and Dutch hospitals, and by the Upper (cases) and Lower (controls) South Regional Ethics Committees of New Zealand.

PTPN22 Genotyping

DNA from patients and controls was obtained using standard extraction methods. Samples were genotyped for SNP rs33996649 using a Custom TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA). The primer sequences were: forward 5' TTTGAACTAATGAAGGCCTCT GTGT 3' and reverse 5' ATTCCTGAGAACTTCAGTGTTTT CAGT 3'. The specific minor groove binder probe sequences were 5' TTGATCCGGGAAATG 3' and 5' TTGATCCAGGA AATG 3'. The samples were genotyped for rs2476601 polymorphism via TaqMan 5' allelic discrimination assay using a predesigned probe (Part number: C_16021387_20; Applied Biosystems). To verify the genotyping consistency 10% of samples from each studied cohort were genotyped twice. The concordance between original and repeat genotypes was 99%. The genotype call rate was >90% for all studied populations.

Data Analysis

Deviation from Hardy-Weinberg equilibrium (HWE) was tested by standard chi-square analysis. The differences in genotype distribution and allele frequency among cases and controls were calculated by contingency tables and when necessary by Fisher's exact test. An association was considered statistically significant if P < 0.05. Linkage disequilibrium (LD) measurements (r^2) between rs33996649 and rs2476601 were estimated by the expectation-maximization algorithm using HAPLOVIEW v. 4.1 (@ Broad Institute of MIT and Harvard 2008, Cambridge, MA). Case-control association analysis was performed using PLINK (v. 1.07) (http://pngu.mgh.harvard. edu/purcell/plink/) to estimate odds ratios (OR) and 95% confidence intervals (CI).²² To test for associations of the PTPN22 polymorphisms with clinical features, a univariate analysis using χ^2 or Fisher's exact test was applied. The Montreal Classification 19 criteria were used to determine the clinical variables. We compare each variable with the healthy controls and within cases (see Supporting Information Tables 1-4). Multiple testing was corrected by false discovery rate control (p_{FDR}). Analysis was conducted using PLINK (v. 1.07) and Stats Direct (v. 2.6.6 http://www.statsdirect.com) softwares.

Meta-analysis

Study Selection and Data Extraction

To estimate the common effect of the *PTPN22* R620W polymorphism on IBD we conducted a search on MEDLINE and PUBMED electronic databases up to April 2010 to identify available articles in which this polymorphism was genotyped in patients with CD or UC and healthy controls. The search strategy included Medical Subject Heading (MeSH) terms and text words as follows: "Inflammatory Bowel Disease" [MeSH] OR

TABLE 1. Genotype and Allele Frequencies for the R263Q PTPN22 (rs33996649) Polymorphism in Healthy Controls and
IBD Patients from Three Different Populations

Population		GG	%	GA	%	AA	%	Allele G	%	Allele A	%	P-value	OR	(95 %	% CI)
Spanish	CD patients $(n = 699)$	640	91.6	59	8.4	0	0.0	1339	95.8	59	4.2	0.073	1.34	0.97	1.85
	UC patients $(n = 658)$	632	96.0	26	4.0	0	0.0	1290	98.0	26	2.0	0.026	0.61	0.39	0.95
	Controls $(n = 1685)$	1580	93.8	103	6.1	2	0.1	3263	96.8	107	3.2				
Dutch	CD patients $(n = 694)$	658	94.8	36	5.2	0	0.0	1352	97.4	36	2.6	0.98	0.99	0.64	1.55
	UC patients $(n = 548)$	523	95.4	25	4.6	0	0.0	1071	97.7	25	2.3	0.58	0.87	0.53	1.43
	Controls $(n = 863)$	818	94.8	45	5.2	0	0.0	1681	97.4	45	2.6				
New Zealand	CD patients ($n = 510$)	490	96.1	20	3.9	0	0.0	1000	98.0	20	2.0	0.87	0.95	0.52	1.74
	UC patients $(n = 471)$	459	97.5	12	2.5	0	0.0	930	98.7	12	1.3	0.17	0.61	0.30	1.24
	Controls $(n = 559)$	536	95.9	23	4.1	0	0.0	1095	97.9	23	2.1				
Pooled	CD patients ($n = 1903$)	1788	94.0	115	6.0	0	0.0	3691	97.0	115	3.0	0.22^{a}	1.16	0.91	1.47
	UC patients ($n = 1677$)	1614	96.2	63	3.8	0	0.0	3291	98.1	63	1.9	0.013^{b}	0.69	0.51	0.93
	Controls ($n = 3107$)	2934	94.4	171	5.5	2	0.1	6039	97.2	175	2.8				

CD, Crohn's disease'. UC, ulcerative colitis. P-value for the minor allele.

"Crohn's Disease" [MeSH] OR "Colitis, Ulcerative" [MeSH] AND "PTPN22 protein, human "[Substance Name] OR PTPN22. References in the studies were reviewed to identify additional studies not indexed by MEDLINE.

Studies for the meta-analysis were selected if they met the following conditions: 1) diagnosis and phenotype was established by means of the Vienna or Montreal Classifications^{19–21}; 2) data were collected in Caucasian populations; 3) the study had a case–control design; 4) the SNPs genotyped were rs2476601 or rs6679677 (both are in complete linkage disequilibrium in Caucasian populations, http://www.hapmap.org); 5) the study supplied enough information to calculate the OR, or the authors provided the data by personal communication (the authors of articles which did not show complete data were contacted by email); 6) the study provided original data (independent of other studies included in the meta-analysis); and 7) the article was published in a peer-reviewed journal as a full article, not as an abstract or similar type of summary.

Our systematic review of the literature identified 28 potential studies for the meta-analysis of R620W in IBD. ^{13,16,23–47} A total of 15 studies were not included in our analysis. ^{13,27,28,31–36,38,39,41,44–46} Five of these were not case–control studies ^{31,34,35,38,41} and three did not genotype rs2476601 or rs6679677. ^{27,28,36} Another five did not supply enough information to calculate the OR. ^{13,32,44–46} One included some samples of our Spanish cohort ³³ and another was carried out only on patients with ileal CD. ³⁹

Data Analysis

The analysis of the combined data from all populations was performed using Stats Direct software, v. 2.6.6. The summarized ORs and CIs were obtained by means of both the random (DerSimonian-Laird) and the fixed (Mantel-Haenszel

meta-analysis) effect models. The heterogeneity of ORs among cohorts was calculated using Breslow-Day test. The statistical power of the R263Q and R620W meta-analysis was 97%, 99% for CD, and 96%, 99% for UC, respectively (assuming a P=0.01; disease prevalence of 0.1% and allele frequency of 5%; done using CaTS software http://www.sph.umich.edu/csg/abecasis/CaTS/index.html).

RESULTS

R263Q Polymorphism of PTPN22 Is Associated with Reduced Risk of UC

First we conducted an association study in a case–control set of Spanish Caucasian ancestry. The distribution of the allelic frequencies of the two polymorphisms, R263Q and R620W (Tables 1, 2) were in HWE both in patients and controls. As previously reported, 12,18 no LD between the *PTPN22* R263Q and R620W genetic variants was observed in any population ($r^2 < 0.03$ for each studied population).

We observed that the 263Q allele was significantly associated with UC (P=0.026, OR = 0.61, 95% CI: 0.39–0.95) but not with CD (P=0.07, OR = 1.34, 95% CI: 0.97–1.85) (Table 1).

We then conducted a follow-up study in two independent Caucasian populations. The case–control analysis in the Dutch and New Zealand cohorts did not show significant association with the R263Q polymorphism in either the CD (Dutch: P=0.98, OR = 0.99 95%, CI:0.64–1.55, New Zealand: P=0.87, OR = 0.95, 95% CI: 0.52–1.74) or the UC sample sets (Dutch: P=0.58, OR = 0.87, 95% CI: 0.53–1.43, New Zealand: P=0.17, OR = 0.61, 95% CI: 0.30–1.24) (Table 1).

^aMeta-analysis calculated through the fixed effects model. Breslow-Day P = 0.44.

^bMeta-analysis calculated through the fixed effects model. Breslow-Day P = 0.54.

TABLE 2. Genotype and Allele Frequencies for R620W PTPN22 (rs2476601) Polymorphism in Healthy Controls and IBD Patients from 14 Different Populations

CC % TT % Allele C % Allele T % P-value 9) 626 896 69 4 0.6 1321 94.5 7 5.5 0.11 8) 571 86.8 81 12.3 6 0.9 124.9 9.2 9.7 5.1 0.68 1 468 86.8 87.1 209 124.4 9.6 1343 92.9 93 7.1 0.68 9) 468 86.8 67 124.4 4 0.7 1003 93.0 75 7.0 0.015 9) 468 86.8 67 124.4 4 0.7 1003 93.0 75 0.015 10 468 86.8 67 124.4 4 0.7 1003 90.0 4 0.0 0.0 9.0 4 0.0 0.0 9.0 4 0.0 0.0 9.0 4 8 9.0 <	-															
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Controls ($n=448$) 366 81.7 76 17.0 6 1.3 808 90.2 88 9.8 9.8 0.93 In UC patients ($n=448$) 366 81.7 76 17.0 6 1.3 808 90.2 88 9.8 9.8 9.8 Controls ($n=243$) 2024 81.9 425 17.2 2 0.9 4473 90.5 469 9.5 0.74 an Controls ($n=248$) 225 90.0 23 9.6 1 0.4 468 94.8 90.3 81 9.7 Controls ($n=248$) 225 90.0 23 9.6 1 0.4 468 94.8 90.3 81 9.7 Controls ($n=248$) 225 90.0 23 9.6 1 0.4 468 94.8 90.3 81 9.7 Controls ($n=248$) 225 90.0 23 9.6 1 0.4 468 94.8 30 6.0 0.33 Detainents ($n=341$) 473 87.4 68 12.6 0.0 1014 93.7 68 6.3 0.03 Controls ($n=541$) 473 87.4 68 12.6 9.0 977 90.3 105 9.7 Controls ($n=541$) 473 87.4 68 12.6 9.0 97 97 90.3 105 9.7 Controls ($n=561$) 289 94.0 18 6.0 0.0 584 95.4 106 10.6 Controls ($n=560$) 289 94.0 18 6.0 0.0 584 95.4 106 10.6 Controls ($n=547$) 289 99.4 100 20.0 3 0.6 896 89.4 106 10.6 Controls ($n=247$) 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 Controls ($n=472$) 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 Controls ($n=472$) 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 Controls ($n=254$) 24 86.4 37 12.6 3 1.0 542 90.8 58 9.1 Controls ($n=254$) 258 85.3 10.8 11.1 0. 1893 90.0 211 10.0 0.08 Controls ($n=254$) 274 88.4 37 12.6 3 1.0 24.5 91.6 63 8.4 Controls ($n=254$) 275 89.8 2.5 12.0 9.9 410 8.3 This is a sian European UC patients ($n=254$) 271 84.4 38 14.9 17 0.7 4725 91.9 417 8.1 Controls ($n=254$) 288 85.5 63 13.8 3 0.7 841 92.4 69 7.6 6390 Controls ($n=254$) 288 85.5 63 13.8 3 0.7 841 92.4 69 7.6 6390 Controls ($n=254$) 288 85.5 63 13.8 3 0.7 841 92.4 69 7.6 6390 Controls ($n=254$) 288 85.5 63 13.8 3 0.7 841 92.4 69 7.6 6390 Controls ($n=254$) 288 85.5 63 13.8 3 0.7 841 92.4 69 7.6 6390 Controls ($n=254$) 288 85.5 63 13.8 3 0.7 841 92.4 69 7.8 10.9 83 The controls ($n=254$) 288 85.5 63 13.8 3 0.7 841 92.4 69 85 89.6 83 10.4 69 89.8 10.9 99.9 10.4 69 89.9 10.9 10.9 10.9 10.9 10.9 10.9 10.9 1	New Zealand		414	8.98	09	12.6	3 (9.(888	93.1	99	6.9	0.014	0.67	0.49	0.92
Controls $(n = 563)$ 454 80.6 106 18.8 3 0.5 1014 90.1 112 9.9 H UC patients $(n = 2471)$ 2024 81.9 425 17.2 2 0.9 4487 90.5 469 9.5 0.74 an Controls $(n = 2483)$ 225 90.0 23 9.6 10.4 468 95.9 16 9.5 Controls $(n = 207)$ 191 92.3 16 77.7 0 0.0 388 95.9 16 3.9 Controls $(n = 541)$ 473 87.4 68 12.6 0 0.0 1014 93.7 68 6.3 0.033 Controls $(n = 541)$ 471 81.5 95 17.6 5 0.9 977 90.3 105 9.7 Controls $(n = 541)$ 471 81.5 95 17.6 5 0.9 977 90.3 105 9.7 Controls $(n = 301)$ 283 94.0 18 6.0 0 0.0 884 95.4 106 10.6 Controls $(n = 300)$ 278 98. 28 9.2 0 0.0 884 95.4 106 10.6 Controls $(n = 342)$ 25. 80.8 28 9.2 0 0.0 884 95.4 106 10.7 Controls $(n = 342)$ 25. 80.8 89.9 10.9 10.7 10.7 Controls $(n = 342)$ 25. 80.8 89.9 10.9 10.7 10.7 Controls $(n = 342)$ 25. 80.8 89.9 10.9 10.7 10.7 Controls $(n = 342)$ 379 80.3 85 18.0 8 17 843 89.3 101 10.7 Controls $(n = 344)$ 312 83.4 61 16.3 1 0.3 548 95.4 28 46 0.70 Controls $(n = 374)$ 312 83.4 61 16.3 1 0.3 548 95.4 28 95.0 10.0 Controls $(n = 374)$ 312 83.4 61 16.3 1 0.3 548 95.9 10.8 10.7 Controls $(n = 374)$ 312 83.4 61 16.3 1 0.3 548 95.9 10.8 10.7 Controls $(n = 374)$ 312 83.4 61 16.3 1 0.3 548 95.4 28 95.0 10.0 Controls $(n = 2571)$ 2171 84.4 38.3 14.9 17 0.7 4725 91.9 417 8.1 dian Controls $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.3 10.4 Controls $(n = 254)$ 20.4 80.3 47 18.5 11 0.5 49.9 19.3 19.3 19.8 19.9 Controls $(n = 254)$ 20.4 80.3 47 18.5 11 2.5 40.8 19.3 19.3 19.3 19.3 19.3 19.8 19.9			366	81.7	9/	17.0	9	1.3	808	90.2	88	8.6	0.93	0.99	0.73	1.32
The UC patients $(n = 2471)$ 2024 81.9 425 17.2 22 0.9 4473 90.5 469 9.5 0.74 and Controls $(n = 2483)$ 2025 81.6 435 17.5 23 0.9 4485 90.3 481 9.7 and Controls $(n = 2483)$ 2025 81.6 435 17.5 23 0.9 4485 90.3 481 9.7 and European CD patients $(n = 244)$ 225 90.0 23 9.6 1 0.4 468 94.8 9.6 0.0 398 95.9 16 3.9 Controls $(n = 541)$ 441 81.5 87.4 68 12.6 0 0.0 1014 93.7 68 63 0.003 Controls $(n = 541)$ 441 81.5 87.4 66 19.1 4 1.2 616 89.3 74 10.7 0.92 Controls $(n = 541)$ 27.5 79.7 66 19.1 4 1.2 616 89.3 74 10.0 0.00 1014 93.7 68 9.4 106 10.6 Controls $(n = 541)$ 27.8 9.8 9.9 1 0.0 2.0 384 95.4 106 10.6 10.6 10.6 10.6 10.6 10.6 10.6		itrols $(n =$	454	9.08	106	18.8	3 (5.0	1014	90.1	112	6.6				
an Controls $(n = 2483)$ 2025 81.6 435 17.5 23 0.9 4485 90.3 481 9.7 Controls $(n = 2493)$ 225 90.0 23 9.6 1 0.4 468 94.8 96.0 5.3 9.6 Controls $(n = 241)$ 225 90.0 23 9.6 1 0.4 468 94.8 96.0 6.0 0.33 Controls $(n = 541)$ 471 81.4 87.4 68 12.6 0 0.0 1014 93.7 68 6.0 0.33 Controls $(n = 541)$ 473 87.4 68 12.6 0 0.0 1014 93.7 68 6.0 0.0 20 patients $(n = 541)$ 398 79.4 100 20.0 3 0.6 89.6 89.4 106 10.6 Controls $(n = 501)$ 398 79.4 100 20.0 3 0.6 89.6 89.4 106 10.6 Controls $(n = 501)$ 398 79.4 100 20.0 3 0.6 89.6 89.4 106 10.6 10.6 Controls $(n = 300)$ 278 90.8 28 92 0 0 0 584 97.0 18 3.0 0.31 Controls $(n = 300)$ 278 90.8 28 92 0 0 0 584 97.0 18 3.0 0.31 Controls $(n = 2472)$ 279 80.8 28 10.0 10 549 92.0 3 84 92.0 10 10.7 Controls $(n = 2472)$ 379 80.3 81 10.0 10.0 84 92 0 10.0 10.0 84 92 0 10.0 10.0 84 92 0 10.0 10.0 84 92 0 10.0 10.0 84 92 0 10.0 10.0 84 92 0 10.0 10.0 84 92 0 10.0 10.0 84 92 0 10.0 10.0 84 92 0 10.0 10.0 84 92 0 10.0 10.0 10.0 84 92 0 10.0 10.0 10.0 10.0 10.0 10.0 10.0 1	Anderson et al. (2009) British		2024	81.9	425	17.2	22 (6.0	4473	90.5	469	9.5	0.74	0.98	0.86	1.12
an CD patients $(n = 249)$ 225 90.0 23 9.6 1 0.4 468 94.8 30 6.0 0.33 Ordrols $(n = 207)$ 191 92.3 16 77.7 0 0.0 398 95.9 16 3.9 Controls $(n = 541)$ 44.1 81.5 95 17.6 5 0.9 1014 93.7 68 6.3 0.003 Controls $(n = 541)$ 44.1 81.5 95 17.6 5 0.9 1014 93.7 68 6.3 0.003 Controls $(n = 541)$ 44.1 81.5 95 17.6 5 0.9 97.7 90.3 105 9.7 Controls $(n = 541)$ 38.7 94.1 10. 28.3 94.0 10. 28.4 106 10.6 CD patients $(n = 301)$ 28.3 94.0 18 6.0 0.0 584 97.0 18 3.0 0.31 UC patients $(n = 306)$ 278 90.8 28 92.0 0.0 584 97.0 18 3.0 0.31 Controls $(n = 256)$ 235 91.8 21 82 0.0 0.0 584 97.0 18 3.0 0.31 Controls $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 Controls $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 Controls $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 Controls $(n = 374)$ 312 84.4 31.3 14.1 10.3 68.5 91.6 11.1 10.1 10.3 Controls $(n = 4571)$ 312 84.4 38 11.1 10.1 1893 90.0 211 10.0 0.008 Controls $(n = 4571)$ 21.1 84.4 38 3 19.3 10.1 10.7 10.0 8.3 man CD patients $(n = 460)$ 20.8 84.2 90.1 11.0 10.7 10.0 8.3 10.4 10.5 Controls $(n = 2541)$ 20.4 80.3 41.8 3 12.4 42.8 89.5 10.9 41.7 81.4 10.0 Controls $(n = 2541)$ 20.4 80.3 41.8 3 12.4 42.8 89.6 53 13.8 3 10.4 40.5 10.8 40.5 1		Controls $(n = 2483)$	2025	81.6	435	17.5	23 (6.0	4485	90.3	481	6.7				
Controls $(n=207)$ 191 92.3 16 7.7 0 0.0 398 95.9 16 3.9 Controls $(n=541)$ 473 874 68 12.6 0 0.0 1014 93.7 68 6.3 0.003 Controls $(n=541)$ 441 81.5 95 17.6 5 0.9 977 90.3 105 9.7 Controls $(n=541)$ 348 7.4 10 20.0 3 0.6 896 89.4 106 10.6 Controls $(n=501)$ 289 7.4 10 20.0 3 0.6 896 89.4 106 10.6 Controls $(n=501)$ 289 7.4 10 20.0 3 0.6 889 89.4 106 10.6 Controls $(n=256)$ 235 91.8 21 8.2 0 0.0 584 97.0 18 3.0 0.31 Controls $(n=256)$ 235 91.8 21 82 0 0.0 584 97.0 18 3.0 0.31 Controls $(n=256)$ 235 91.8 21 82 0 0.0 584 97.0 18 3.0 0.31 Controls $(n=254)$ 26 82.5 52 16.5 3 1.0 572 90.8 58 9.2 0.33 Controls $(n=2472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 Controls $(n=271)$ 211 844 88 14 0 1 0 0 2.0 491 95.9 21 4.1 Controls $(n=251)$ 212 84.0 18 10 1 10 32.8 90.0 211 10.0 0.008 The adam of Controls $(n=251)$ 214 44 84 18 14 0 14 0 14 0 14 0 15 0 15	De Jager et al (2006) Canadian	CD patients $(n = 249)$	225	0.06	23	9.6	1	7.4	468	8.46	30	0.9	0.33	1.33	0.71	2.50
The composition of the controls (n = 541) and the controls (n = 542) and the controls (n = 256) and the controls (n = 256) and the controls (n = 256) and the controls (n = 254) and the controls (n = 254) and the controls (n = 2571) and the controls (n = 254) and the control (n = 254) and t			191	92.3	16	7.7	0	0.0	398	95.9	16	3.9				
Controls $(n = 541)$ 441 81.5 95 17.6 5 0.9 977 90.3 105 9.7 CD patients $(n = 345)$ 275 79.7 66 19.1 4 1.2 616 89.3 74 10.7 0.92 Controls $(n = 501)$ 398 79.4 100 20.0 3 0.6 896 89.4 106 10.6 CD patients $(n = 306)$ 278 90.8 28 9.2 0 0.0 584 95.4 28 4.6 0.70 Controls $(n = 256)$ 235 91.8 21 8.2 0 0.0 491 95.9 21 4.1 CD patients $(n = 256)$ 235 91.8 21 8.2 0 0.0 491 95.9 21 4.1 CD patients $(n = 242)$ 379 80.3 85 16.5 3 1.0 575 90.8 58 9.2 0.33 CONTROLS $(n = 374)$ 312 83.4 61 16.3 1 0.3 685 91.6 63 8.4 CONTROLS $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 CONTROLS $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 CONTROLS $(n = 254)$ 20.8 85.5 63 13.8 3 0.7 841 92.4 69 7.6 0.55 CONTROLS $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 55 89.6 53 10.4 CONTROLS $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 55 89.6 53 10.4 CD patients $(n = 2005)$ 1703 84.9 291 14.5 11 0.5 3697 92.2 313 7.8 0.00 CONTROLS $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 CD patients $(n = 2005)$ 1703 84.9 291 14.5 11 0.5 3697 92.2 313 7.8 0.00 CD patients $(n = 603)$ 508 84.2 99 14.9 5 0.8 1106 91.7 100 8.3 CONTROLS $(n = 254)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 CD patients $(n = 697)$ 20.4 80.3 47 18.5 3 1.2 455 89.6 53 10.4 CD patients $(n = 697)$ 60.4 80.3 47 18.5 10.5 10.5 10.5 10.5 10.5 CD patients $(n = 6977)$ 60.4 14.5 16.6 17 10.7 16.0 17 10.7 10.0 10.0 10.0 10.0 10.0 10.0	Duerr et al. (2006) Caucasian European		473	87.4	89	12.6	0	0.0	1014	93.7	89	6.3	0.003	0.63	0.46	0.86
Controls $(n = 345)$ 275 79.7 66 19.1 4 1.2 616 89.3 74 10.7 0.92 Controls $(n = 501)$ 398 79.4 100 20.0 3 0.6 896 89.4 106 10.6 CD patients $(n = 301)$ 283 94.0 18 6.0 0 0.0 584 97.0 18 3.0 0.31 Controls $(n = 256)$ 235 91.8 21 82 0 0.0 584 95.4 28 4.6 0.70 Controls $(n = 256)$ 235 91.8 21 82 0 0.0 584 95.4 28 4.6 0.70 Controls $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 CD patients $(n = 294)$ 254 86.4 37 12.6 3 1.0 572 90.8 58 9.2 0.33 CD patients $(n = 2472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 CD patients $(n = 2472)$ 379 86.9 26 12.2 2 0.9 410 92.8 93 6.8 0.38 CONTROLS $(n = 374)$ 312 83.4 61 16.3 1 0.3 685 91.6 63 8.4 CONTROLS $(n = 4572)$ 389 85.5 81.0 189 18.0 11 10.1 189 18.0 11 10.1 189 18.0 11 10.0 10.008 CONTROLS $(n = 603)$ 80.8 84.2 90.1 14.9 17 0.7 4725 91.9 417 81 10.0 10.008 CONTROLS $(n = 254)$ 204 80.3 47 18.5 1 10.7 267 91.4 25 80.6 3.9 10.4 CONTROLS $(n = 2005)$ 1703 84.9 291 14.5 11 0.7 369 17.6 369 17.8 10.4 CONTROLS $(n = 2005)$ 1703 84.9 291 14.5 11 0.7 369 17.9 18.9 17.8 10.4 CONTROLS $(n = 2005)$ 1703 84.9 291 14.5 11 0.7 369 17.8 10.0 10.0 10.0 10.0 10.0 10.0 10.0 10		Controls $(n = 541)$	441	81.5	95	17.6	5 (6.0	214	90.3	105	6.7				
Controls $(n = 501)$ 398 79.4 100 20.0 3 0.6 896 89.4 106 10.6 CD patients $(n = 301)$ 283 94.0 18 6.0 0 0 584 97.0 18 3.0 0.31 CD patients $(n = 301)$ 283 94.0 18 6.0 0 0 584 97.0 18 3.0 0.31 COntrols $(n = 256)$ 235 91.8 21 82 0 0.0 584 95.4 28 4.6 0.70 COntrols $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 COntrols $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 COntrols $(n = 374)$ 312 84.4 38.1 12.6 3 1.0 545 92.7 43 7.3 0.46 UC patients $(n = 247)$ 312 84.4 38.1 10.0 88.5 91.6 63 84.4 31.0 10.0 10.0 10.0 10.0 10.0 10.0 10.0	Hradsky et al (2008) Czech		275	79.7	99	19.1	4	1.2	616	89.3	74	10.7	0.92	1.02	0.74	1.39
Copatients $(n = 301)$ 283 94.0 18 6.0 0 0.0 584 97.0 18 3.0 0.31 UC patients $(n = 366)$ 278 90.8 28 9.2 0 0.0 584 95.4 28 4.6 0.70 Controls $(n = 256)$ 235 91.8 21 8.2 0 0.0 584 95.4 28 4.6 0.70 Controls $(n = 472)$ 260 82.5 52 16.5 3 1.0 572 90.8 58 9.2 0.33 Controls $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 CD patients $(n = 294)$ 254 86.4 37 12.6 3 1.0 545 92.7 43 7.3 0.46 UC patients $(n = 274)$ 312 83.4 61 16.3 1 0.3 685 91.6 63 8.4 Controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 CD patients $(n = 254)$ 208 85.5 63 13.8 3 0.7 841 92.4 69 7.6 0.55 and Controls $(n = 254)$ 208 84.2 90 14.9 5 0.8 1106 91.7 100 8.3 man CD patients $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 CD patients $(n = 254)$ 204 80.3 47 18.5 3 1.0 5 60.3 10.3 10.4 CD patients $(n = 254)$ 204 80.3 41.4 10.5 50.5 10.5 10.3 10.3 10.3 10.3 10.3 10.3 10.3 10.3		Controls $(n = 501)$	398	79.4	100	20.0	3 (9.0	968	89.4	106	10.6				
Controls $(n = 306)$ 278 90.8 28 9.2 0 0.0 584 95.4 28 4.6 0.70 controls $(n = 256)$ 235 91.8 21 8.2 0 0.0 491 95.9 21 4.1 controls $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 cD patients $(n = 294)$ 254 86.4 37 12.6 3 1.0 549 92.7 43 7.3 0.46 UC patients $(n = 274)$ 312 84.6 37 12.6 3 1.0 549 92.7 43 7.3 0.46 Controls $(n = 374)$ 312 84.6 16.3 1 0.3 685 91.6 63 84 controls $(n = 2571)$ 2171 84.4 381 14.9 17 0.7 4725 91.9 417 81. dian CD patients $(n = 165)$ 38 85.5 63 13.8 3 0.7 841 92.4 69 7.6 0.55 and Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 45 89.6 53 1.3 7.8 10.4 CD patients $(n = 254)$ 247 81.5 53 17.7 24 0.8 542 90.3 17.8 17.8 17.8 17.8 18.5 27.1 10.5 3697 92.2 313 7.8 10.4 CD patients $(n = 603)$ 247 81.5 533 17.7 24 0.8 5427 90.3 14.6 57 17.8 17.8 17.8 18.5 18.5 18.5 18.5 18.5 18.5 18.5 18	Latiano et al. (2007)Italian		283	94.0	18	0.9	0	0.0	584	97.0	18	3.0	0.31	0.73	0.39	1.37
Controls $(n = 256)$ 235 91.8 21 8.2 0 0.0 491 95.9 21 4.1 ealand CD patients $(n = 315)$ 260 82.5 52 16.5 3 1.0 572 90.8 58 9.2 0.33 Controls $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 CD patients $(n = 294)$ 254 86.4 37 12.6 3 1.0 545 92.7 43 7.3 0.46 UC patients $(n = 374)$ 312 86.9 26 12.2 2 0.9 410 92.8 30 6.8 0.38 Controls $(n = 374)$ 312 83.4 61 16.3 1 0.3 685 91.6 63 8.4 Controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 dian CD patients $(n = 455)$ 389 85.5 63 13.8 3 0.7 841 92.4 69 7.6 0.55 and Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 2697)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a Controls $(n = 9074)$ 7718 83.4 1467 15.0 60.7 16903 91.3 1605 87			278	8.06	28	9.2	0	0.0	584	95.4	28	4.6	0.70	1.10	0.63	1.96
Controls $(n = 315)$ 260 82.5 52 16.5 3 1.0 572 90.8 58 9.2 0.33 Controls $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 CD patients $(n = 294)$ 254 86.4 37 12.6 3 1.0 545 92.7 43 7.3 0.46 UC patients $(n = 224)$ 254 86.4 37 12.6 3 1.0 545 92.7 43 7.3 0.46 Controls $(n = 374)$ 312 83.4 61 16.3 1 0.3 685 91.6 68 91.8 8.4 axisin European UC patients $(n = 1052)$ 852 81.0 189 18.0 11 1.0 1893 90.0 211 10.0 0.008 Controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 2054)$ 204 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 12.4 E-06a Controls $(n = 2054)$ 218 83.4 14.5 15.9 69 0.7 15003 91.3 1605 87		Controls $(n=256)$	235	91.8	21	8.2	0	0.0	491	626	21	4.1				
Controls $(n = 472)$ 379 80.3 85 18.0 8 1.7 843 89.3 101 10.7 CD patients $(n = 294)$ 254 86.4 37 12.6 3 1.0 545 92.7 43 7.3 0.46 UC patients $(n = 220)$ 192 86.9 26 12.2 2 0.9 410 92.8 30 6.8 0.38 Controls $(n = 374)$ 312 83.4 61 16.3 1 0.3 685 91.6 63 8.4 Controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 Controls $(n = 603)$ 508 84.2 90 14.9 5 0.8 1106 91.7 100 8.3 man CD patients $(n = 146)$ 122 83.6 23 15.8 1 0.7 267 91.4 25 89.6 53 10.4 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 CD patients $(n = 6977)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a Controls $(n = 9074)$ 7718 83.4 1467 15.9 69 74 1603 813 1605 87	Morgan et al. (2010) New Zealand		260	82.5	52	16.5	3	0.1	572	8.06	28	9.2	0.33	0.85	09.0	1.19
CD patients $(n = 294)$ 254 864 37 12.6 3 1.0 545 92.7 43 7.3 0.46 UC patients $(n = 220)$ 192 86.9 26 12.2 2 0.9 410 92.8 30 6.8 0.38 Controls $(n = 374)$ 312 83.4 61 16.3 1 0.3 685 91.6 63 8.4 3.8 Controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 Controls $(n = 603)$ 508 84.2 90 14.9 5 0.8 1106 91.7 100 8.3 man CD patients $(n = 455)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 10.3 10.4 CD patients $(n = 6077)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 103 7.2 7.4E-06a		Controls $(n = 472)$	379	80.3	85	18.0	~	1.7	843	89.3	101	10.7				
UC patients $(n = 220)$ 192 86.9 26 12.2 2 0.9 410 92.8 30 6.8 0.38 Controls $(n = 374)$ 312 83.4 61 16.3 1 0.3 685 91.6 63 8.4 erg et al. (2009) Caucasian European UC patients $(n = 1052)$ 852 81.0 180 11 1.0 1893 90.0 211 10.0 0.008 controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 er et al. (2005) Canadian CD patients $(n = 603)$ 508 84.2 90 14.9 5 0.8 1106 9.7 100 8.3 leiter et al (2005) German CD patients $(n = 146)$ 122 83.6 23 15.8 1 0.7 267 91.4 25 8.6 0.390 (2007) Caucasian CD patients $(n = 254)$ 204 80.3 47 18.5 3 10.5 80.6 13.2 10.4 10.4 10.4 10.3 10.4 10.4 10.	Prescott et al. (2005) British		254	86.4	37	12.6	3	0.1	545	92.7	43	7.3	0.46	98.0	0.58	1.29
erg et al. (2009) Caucasian European UC patients $(n = 174)$ 312 83.4 61 16.3 1 0.3 685 91.6 63 8.4 Controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 Controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 Controls $(n = 603)$ 508 84.2 90 14.9 5 0.8 1106 91.7 100 8.3 leiter et al (2005) German CD patients $(n = 146)$ 122 83.6 23 15.8 1 0.7 267 91.4 25 8.6 0.390 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 Controls $(n = 977)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a			192	6.98	56	12.2	7	6.(410	92.8	30	8.9	0.38	0.83	0.53	1.30
erg et al. (2009) Caucasian European UC patients $(n = 1052)$ 852 81.0 189 18.0 11 1.0 1893 90.0 211 10.0 0.008 Controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 and et al. (2005) Canadian CD patients $(n = 455)$ 389 85.5 63 13.8 3 0.7 841 92.4 69 7.6 0.55 Controls $(n = 603)$ 508 84.2 90 14.9 5 0.8 1106 91.7 100 8.3 leiter et al (2005) German CD patients $(n = 146)$ 122 83.6 23 15.8 1 0.7 267 91.4 25 86 0.390 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 Controls $(n = 3004)$ 60.13 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a		Controls $(n = 374)$	312	83.4	61	16.3	1	3.3	685	91.6	63	8.4				
Controls $(n = 2571)$ 2171 84.4 383 14.9 17 0.7 4725 91.9 417 8.1 8.1 ene et al. (2005) Canadian CD patients $(n = 455)$ 389 85.5 63 13.8 3 0.7 841 92.4 69 7.6 0.55 Controls $(n = 603)$ 508 84.2 90 14.9 5 0.8 1106 91.7 100 8.3 Controls $(n = 24)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 Controls $(n = 6977)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a	Silverberg et al. (2009) Caucasian European		852	81.0	189	18.0	11	0.1	1893	0.06	211	10.0	0.008	1.27	1.06	1.50
ene et al. (2005) Canadian CD patients $(n = 455)$ 389 85.5 63 13.8 3 0.7 841 92.4 69 7.6 0.55 Controls $(n = 603)$ 508 84.2 90 14.9 5 0.8 1106 91.7 100 8.3 Leiter et al (2005) German CD patients $(n = 146)$ 122 83.6 23 15.8 1 0.7 267 91.4 25 80.6 53 10.4 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 Controls $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 Controls $(n = 6977)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a		Controls ($n = 2571$)	2171	84.4	383	14.9	17 (7.0	4725	91.9	417	8.1				
leiter et al (2005) German CD patients $(n = 603)$ 508 84.2 90 14.9 5 0.8 1106 91.7 100 8.3 Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 CD patients $(n = 2005)$ 1703 84.9 291 14.5 11 0.5 3697 92.2 313 7.8 0.001 CD patients $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 CD patients $(n = 6977)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a CD patients $(n = 6977)$ 6013 86.4 1467 15.9 69 0.7 16003 91.3 1605 8.7	Van Oene et al. (2005) Canadian	CD patients $(n = 455)$	389	85.5	63	13.8	3	7.(841	92.4	69	7.6	0.55	0.91	99.0	1.25
leiter et al (2005) German CD patients ($n = 146$) 122 83.6 23 15.8 1 0.7 267 91.4 25 8.6 0.390 Controls ($n = 254$) 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 CD patients ($n = 2005$) 1703 84.9 291 14.5 11 0.5 3697 92.2 313 7.8 0.001 Controls ($n = 3004$) 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 CD patients ($n = 6977$) 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a CD patients ($n = 6977$) 6013 83.4 1467 15.9 69 0.7 16003 91.3 1605 8.7			208	84.2	3	14.9	ς	8.	1106	91.7	100	8.3				
Controls $(n = 254)$ 204 80.3 47 18.5 3 1.2 455 89.6 53 10.4 (2007) Caucasian CD patients $(n = 2005)$ 1703 84.9 291 14.5 11 0.5 3697 92.2 313 7.8 0.001 Controls $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 CD patients $(n = 6977)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a	Wagenleiter et al (2005) German		122	83.6	23	15.8	-	7.(267	91.4	25	8.6	0.390	0.82	0.49	1.34
(2007) Caucasian CD patients $(n = 2005)$ 1703 84.9 291 14.5 11 0.5 3697 92.2 313 7.8 0.001 Controls $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 CD patients $(n = 6977)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a Controls $(n = 0.954)$ 7718 83.4 1467 15.9 69 0.7 16003 91.3 1605 8.7		Controls $(n = 254)$	204	80.3	47	18.5	3	1.2	455	9.68	53	10.4				
Controls $(n = 3004)$ 2447 81.5 533 17.7 24 0.8 5427 90.3 581 9.7 CD patients $(n = 6977)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a Controls $(n = 0.054)$ 7718 83.4 1467 15.9 69 07 16903 913 1605 8.7	WTCC (2007) Caucasian	CD patients $(n = 2005)$	1703	84.9	291	14.5		5.0	3697	92.2	313	7.8	0.001	0.79	0.69	0.91
CD patients $(n = 6977)$ 6013 86.2 925 13.3 39 0.6 12951 92.8 1003 7.2 7.4E-06a Controls $(n = 0.954)$ 7718 83.4 1467 15.9 69 0.7 16903 91.3 1605 8.7		Controls $(n = 3004)$	2447	81.5	533			8.(5427	90.3	581	6.7				
7718 83 4 1467 15 9 69 0.7 16903 913 1605	Pooled		6013	86.2	925			9.(12951	92.8	1003	7.2	7.4E-06a	0.81	0.75	0.89
		Controls $(n = 9254)$	7718	83.4	1467	15.9) 69	0.7	16903	91.3	1605	8.7				
UC patients $(n = 5695)$ 4751 83.4 893 15.7 51 0.9 10395 91.3 995 8.7 0.88 ^b (4751	83.4	893	15.7	Ī.	6.(10395	91.3	995	8.7	0.88^{b}	0.98	0.85	1.15
Controls $(n = 8766)$ 7347 83.8 1357 15.5 62 0.7 16051 91.6 1481 8.4			7347	83.8	1357			7.(16051	91.6	1481	8.4				

CD, Crohn's disease. UC, ulcerative colitis. P-value for the minor allele "Meta-analysis calculated through the fixed effects model. Breslow-Day P=0.18. bMeta-analysis calculated through the random effects model. Breslow-Day P=0.03.

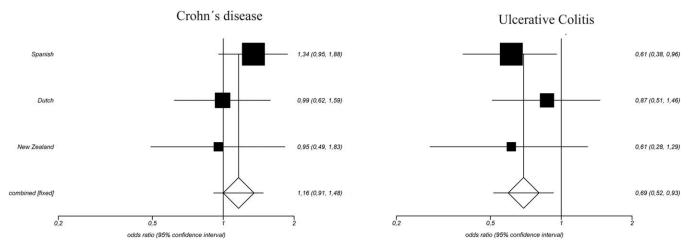


FIGURE 1. Forest plots for the meta-analyses of the PTPN22 R263Q (G788A; rs33996649) polymorphism in CD and UC. The analyses correspond to the frequency of the minor (A) allele in the three Caucasian IBD sample sets.

Our combined analysis of the three studied Caucasian sample sets did not reveal a significant association between the R263Q polymorphism and CD (P=0.22 pooled, OR = 1.16, 95% CI: 0.91–1.47) but it did strengthen the initial association observed in UC in the Spanish sample set (P=0.013 pooled, OR = 0.69, 95% CI: 0.51–0.93) (Table 1; Fig. 1), suggesting that the 263Q variant of the *PTPN22* gene may reduce the risk of UC.

620W Allele of PTPN22 Is Associated with Reduced Risk of CD

In order to reevaluate the role of the R620W polymorphism of the PTPN22 gene on IBD, we conducted a case-control study in the three Caucasian cohorts. We did not observe a significant difference in genotype or in the minor allele frequency (MAF) between CD patients and healthy controls in the Spanish sample set (P = 0.11, OR)= 0.81, 95% CI: 0.62–1.1). In contrast, we observed that the R620W variant was associated with reduced risk of CD in the Dutch sample set (P = 0.036, OR = 0.76, 95% CI): 0.58-0.98) and in the New Zealand sample set (P = 0.014,OR = 0.67, 95% CI: 0.49-0.92) (Table 2). For the UC analysis, we did not observe a significant difference in either the Spanish or the New Zealand sample sets for the R620W polymorphism (Spanish: P = 0.68, OR = 1.05, 95% CI: 0.82–1.35, New Zealand: P = 0.93, OR = 0.99, 95% CI: 0.73-1.32). However, the 620W allele was associated with a reduced risk of UC in the Dutch sample set (P = 0.015, OR = 0.70, 95% CI = 0.52-0.93) (Table 2).

We performed a meta-analysis to reevaluate the role of the R620W polymorphism in IBD. From the remaining 13 studies, three studies fulfilled inclusion criteria for meta-analysis of the R620W *PTPN22* polymorphism in UC, ^{24,30,37} and Silverberg et al ⁴⁰ provided the minor allele frequencies of R620W in their initial cohort by personal

communication. In CD, eight studies fulfilled inclusion criteria for meta-analysis of the R620W *PTPN22* polymorphism, ^{23,25,29,30,37,42,43,47} and Duerr et al²⁶ provided the minor allele frequencies of R620W in their initial cohort by personal communication.

A strong association between the 620W variant and CD was demonstrated (P=7.4E-06 pooled, OR = 0.81, 95% CI: 0.75–0.89) (Table 2; Fig. 2). This confirms the association of the reduced risk observed between this allele and CD in our initial case–control study in the Dutch and New Zealand sample sets and in the previous meta-analysis reported by Barrett et al. ¹³ In contrast, no association was observed between the 620W allele and UC (P=0.88 pooled, OR = 0.98, 95% CI: 0.85–1.15) (Table 2; Fig. 2).

620W Allele of PTPN22 Is Associated with Reduced Risk of Ileal Location in CD

We evaluated the possible associations of the R263Q and R620W variants of PTPN22 with the clinical phenotypes of UC and CD (Supplementary Tables 1–4). Metanalysis revealed the 620W variant was significantly associated with reduced risk of ileal location of CD when compared to healthy controls ($P_{FDRcorrected} = 9E-03$) pooled OR = 0.64, 95% CI = 0.49-0.84, Supplementary Table 2). We observed no significant association of the R263Q polymorphism with CD or UC clinical manifestations.

DISCUSSION

This article reports for the first time the role of the newly identified R263Q polymorphism of *PTPN22* in IBD. In addition, we performed a case–control study in Spanish, Dutch, and New Zealand populations and a meta-analysis to assess the role of the R620W *PTPN22* polymorphism with CD and UC. Our results indicate that there is a differential association of the R263Q and R620W polymorphisms

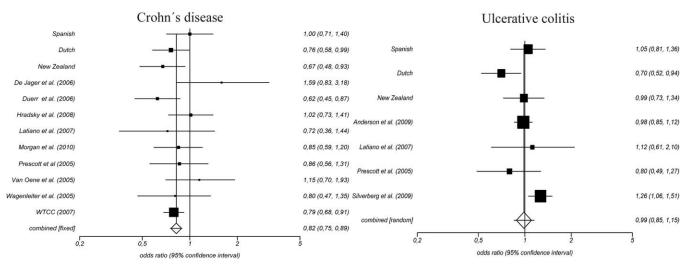


FIGURE 2. Forest plots for the meta-analyses of the *PTPN22* the R620W (C1858T; rs2476601) polymorphism in CD and UC. The analyses correspond to the frequency of the minor (T) allele in 12 Caucasian IBD sample sets.

with IBD. On the one hand, the PTPN22 263Q loss-offunction variant is a protective factor for UC, with no relationship to CD; on the other hand, the 620W gain-of-function variant confers protection against CD, while showing no association with UC. The effect size observed between the R263Q polymorphism and UC (0.69) is similar to that reported for SLE (i.e., 0.63) by Orru et al, 12,18 suggesting that this polymorphism could be another common genetic component in autoimmunity. In addition, we confirmed in the Dutch and New Zealand CD cohorts, together with a combined analysis, the previously reported protective role of the 620W allele in CD but not in UC. 12,13,23,26,32,39,45-47 Thus, there is support for the hypothesis that both outcomes of IBD have a partially different genetic component. On the other hand, we have reported evidence of a reduced risk factor of the 620W allele in the ileal location of CD. Nevertheless, these result should be taken cautiously, since we observed no significant difference when comparing the ileal location against colonic/ileocolonic location of the disease. This may be an artifact of low statistical power of these stratified analyses (i.e., 50%-65% power). Replication studies are needed to confirm this new finding. Increased emphasis has been placed in the recent years on predictive biomarkers to predict the onset or future course of disease. 48 In this regard, the present report supports the idea that subtle genetic differences combined with assessment of the pattern of critical mediators (i.e., presence of autoantibodies) may be useful for tracing progression of the disease.

To determine the immunological implications of the differential association of R263Q and R620W *PTPN22* polymorphisms with CD and UC, functional approaches are required. Nevertheless, there is strong evidence to suggest that the 263Q allele is a loss-of-function variant which

is less effective in reducing TCR signaling than 263R.¹² This supports the hypothesis that positive modulation of the TCR helps in reestablishing tolerance in at least a subset of autoimmune patients.^{6,49} This functional evidence, together with the significant association that we observed with UC, suggests that TCR signaling is more important in this disease than in CD. Actually, autoantibodies are more often detected in UC than in CD patients. It is estimated that 60%–70% of UC patients are positive for atypical antineutrophilic cytoplasmic antibodies, whereas only few CD patients present autoantibodies (atypical antineutrophilic cytoplasmic antibodies 5%–25%, pancreatic autoantibodies 27%–37%, and thrombophilia-associated antibodies 3%–37%).⁵⁰

The present study confirms that the 620W allele is associated with a reduced risk of developing CD, in contrast to the increasing risk that this genetic variant confers to other autoimmune diseases such as T1D, SLE, and RA. 6,14-16 Several authors have shown that 620W PTPN22 is a gain-of-function variant that reduces TCR signaling leading to decreased elimination of potentially autoreactive T cells and/or decreased production of natural regulatory T cells (Treg) (reviewed⁶). This could explain the loss of tolerance that takes place in autoimmune diseases like T1D, SLE, and RA, but not the protective role 620W allele appears to confer against CD. A possible explanation could be that IBD may represent an inappropriate immune response to the commensal microbiota in a genetically predisposed host,³ mimicking an infection process. This hypothesis is supported by the fact that the 620W allele confers protection towards some highly prevalent infectious diseases.⁶ Previous studies have reported a significant protective role of the 620W allele in tuberculosis (TB).^{51,52} Moreover, the R263Q polymorphism has been associated with increasing risk to develop TB,⁵² the opposite of the reported associations with SLE¹² and RA¹⁸ and UC in the present study. Our findings suggest that many of the genetic loci involved in autoimmunity may be under balanced selection due to antagonistic pleiotropic effects. Genetic variants such as R620W and R263Q with opposite effects in different diseases may facilitate the maintenance of common susceptibility alleles in human populations.^{6,46,53} Moreover, our results also support the idea that CD and UC differ in some genetic risk factors, thereby suggesting the involvement of different immunological mechanisms with a related nature.^{24,45,46,54,55}

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