Association of the interleukin-22 genetic polymorphisms with ulcerative colitis

Hong Gang Chi1†, Xue Bao Zheng1†, Zhu Guo Wu2, Shi Xue Dai3, Zheng Wan4 and Ying Zou1,4*

Abstract

Background: Interleukin-22 (IL-22) is a member of the IL-10 family of anti-inflammatory cytokines that mediates epithelial immunity. IL-22 expression was found to be increased in patients with ulcerative colitis (UC). Whether genetic polymorphisms of IL-22 also influence UC risk is still unknown. The purpose of this study was to investigate the association between the IL-22 gene polymorphisms (−429 C/T, +1046 T/A and +1995 A/C) and the risk of UC in Chinese Han patients.

Methods: This hospital-based case–control study comprised 180 patients with UC and 180 age- and gender-matched controls. Genotypes of 3 common polymorphisms of the IL-22 gene were determined by fluorogenic 5′ exonuclease assays (TaqMan).

Results: Patients with UC had a significantly higher frequency of IL-22 −429 TT genotype [odds ratio (OR) =2.43, 95% confidence interval (CI) = 1.35, 4.37; P =0.003] and −429 T allele (OR =1.54, 95% CI = 1.14, 2.07; P = 0.004) than controls. The findings are still emphatic by the Bonferroni correction. The IL-22 +1046 T/A and IL-22 +1995 A/C gene polymorphisms were not associated with a risk of UC. When stratifying by clinical type, location and disease severity of UC, no significant differences were found in any groups.

Conclusion: This is the first study to provide evidence for an association of IL-22 −429 C/T gene polymorphisms with UC risk. Additional well-designed large studies were required for the validation of our results.

Virtual Slides: The virtual slide(s) for this article can be found here: http://www.diagnosticpathology.diagnomx.eu/vs/13000_2014_183

Keywords: Interleukin-22, Gene polymorphism, Ulcerative colitis, Case–control study

Background

Ulcerative colitis (UC), as the most common form of inflammatory bowel disease (IBD), is a form of colitis that includes characteristic ulcers, or open sores [1]. Ulcerative colitis has an incidence of 1 to 20 cases per 100,000 individuals per year, and a prevalence of 8 to 246 per 100,000 individuals [2]. Patients with UC have an increased risk of developing colorectal cancer [3]. The pathogenesis of UC is not well defined, but it is proposed that genetic and environmental factors result in an aberrant immune response to a subset of commensal enteric bacteria [4,5]. Recent genome-wide association (GWA) studies and meta-analyses have identified many single-nucleotide polymorphisms (SNPs) associated with UC [6,7].

Interleukin-22 (IL-22) is a member of the IL-10 family of anti-inflammatory cytokines that mediates epithelial immunity [8]. IL-22 is synthesized by different cell types including T- and NK-cells, and has been reported to mediate the crosstalk between inflammatory cells and keratinocytes [9-11]. IL-22 expression was induced in several human inflammatory conditions, including IBD [12,13]. IL-22 expression was found to be increased in patients with UC [14]. Several SNPs have previously been identified in the IL-22 gene [15-22].

Whether genetic polymorphisms of IL-22 also influence UC risk is still unknown. The aim of this study was...
to investigate the association between the \textit{IL-22} gene polymorphisms (−429 C/T, +1046 T/A and +1995 A/C) and the risk of UC in Chinese Han patients.

\section*{Methods}

\subsection*{Study subjects}

This hospital-based case–control study comprised 180 patients with UC and 180 age- and gender-matched controls during the years 2009 to 2014. Diagnosis of UC was based on clinical, radiological, endoscopic and histological examinations [23]. To confirm the diagnosis, two physicians reviewed the hospital records and validated each case. The location of disease was defined according to the Montreal classification (ulcerative proctitis, left-sided colitis, and extensive colitis) [24]. The severity of UC was determined according to Truelove and Witts criteria (mild colitis, moderate colitis, and severe colitis) [25]. According to their clinical courses, UC cases were classified into one episode, relapsing and continuous phenotypes [26]. The control group was composed of age- and gender-matched subjects who had undergone an endoscopic examinations in the same recruitment period as the UC patients, without evidence of UC. In addition, similar to the cases the controls were all required to be born in China to native Chinese Han parents. Informed consent was obtained from all subjects after a full explanation of the project according to the Declaration of Helsinki, and the specimen collecting procedures were approved by the Institutional Ethical Committee of Guangdong Medical College.

\subsection*{Genotyping}

Whole blood (3–6 ml) was obtained by venepuncture using standard EDTA collection tubes. DNA was extracted using the QIAGEN Gentra Puregene blood kit (QIAGEN Inc., Valencia, CA, USA). Genotypes of 3 common polymorphisms of the \textit{IL-22} gene were determined by fluorogenic 5′-exonuclease assays (TaqMan). Primer and probe sequences for 5′-exonuclease assays for \textit{IL-22} polymorphisms were listed in Table 1. The polymerase chain reaction (PCR) was performed in a Primus 96 plus thermal cycler using a total volume of 5 μl containing 2.5 μl of Universal-MasterMix, 0.125 μl 40x Assay-by-Design mix, 0.375 μl H2O and 2 μl DNA. Reactions were overlaid with 15 μl of mineral oil. Cycling parameters were: 10 min at 94°C for primary denaturation, followed by 40 cycles of 20 s at 92°C and 1 min at 60°C. Fluorescence was measured in a lambda Fluoro 320 Plus plate reader (MWG Biotech AG, Germany).

\subsection*{Statistical analysis}

STATA program version 11.0 (StataCorp LP, TX) was used for statistical analyses. Continuous variables were analysed by \textit{t}-test and presented as mean ± standard deviation (SD). Categorical variables are presented as percentages and were compared by chi-squared test. Odds ratio (OR) and 95% confidence intervals (CI) were determined by logistic regression analysis. For a new work, we also use the Bonferroni correction for total number of independent comparisons. The Hardy-Weinberg equilibrium was tested for goodness-of-fit chi-square test with one degree of freedom to compare the observed genotype frequencies among the subjects with the expected genotype frequencies. The \(P\)-value less than 0.05 was considered statistically significant.

\section*{Results}

\subsection*{Characteristics of participants}

Demographic and clinical characteristics of study participants were showed in Table 2. No significant differences were found between the UC cases and controls in age, sex, body mass index (BMI), smoking status and family history of inflammatory bowel disease (IBD) (Table 2). The genotype were in agreement with the Hardy-Weinberg equilibrium.

\subsection*{\textit{IL-22} −429C/T polymorphisms and UC}

Patients with UC had a significantly higher frequency of \textit{IL-22} −429 TT genotype (OR =2.43, 95% CI = 1.35, 4.37; \(P = 0.003\)) and −429 T allele (OR =1.54, 95% CI = 1.14, 2.07; \(P = 0.004\)) than controls (Table 3). The findings are still emphatic by the Bonferroni correction. When stratifying by clinical type, location and disease severity of UC, no significant differences were found in any groups (Table 4).

\begin{table}[h]
\centering
\caption{Primer and probe sequences for 5′-exonuclease assays for \textit{IL-22} polymorphisms}
\begin{tabular}{lll}
\hline
\textbf{SNPs} & \textbf{rs2227485} & \textbf{rs1182844} & \textbf{rs1179246} \\
\hline
\textbf{Exchange} & −429 C/T & +1046 T/A & +1995 A/C \\
\textbf{Forward Primer} & AAAATGAGTCCGTGACCAAAATGC & CCACCTATGAGACTTCCCTATCAGT & GAAAAGGCTTCTTGCCCTATGG \\
\textbf{Reverse Primer} & ACACAATTGTTTTGTCTTAGTAGTCACTAG & CACTAAAGGAAAAAGGAAAGGCTGTGGTTT & GGTGCTGCTTTAAGTGCTAGA \\
\textbf{Wildtype-Probe} & FAM-CTCCTATAGTGACTGAGTAA-NFQ & VIC-AAACTTACTAGTAGGAATGACTC-NFQ & VIC-TGAACAGAGTTATCTGCTCCTC-NFQ \\
\textbf{Mutant-Probe} & VIC-CTCCTATAGTGAGCTAGTAGTAA-NFQ & FAM-CTTACTAGTGAATGCTACTC-NFQ & FAM-AACAGAGTTAGCTGCTCTC-NFQ \\
\hline
\end{tabular}
\end{table}

Abbreviations: SNP single nucleotide polymorphisms.
**Table 2** Demographic and clinical characteristics of study participants

|                        | UC          | Controls     | P     |
|------------------------|-------------|--------------|-------|
| Number of subjects     | 180         | 180          |       |
| Sex (Male/Female)      | 95/85       | 98/82        | 0.75  |
| Age (years, mean ± SD) | 39.7 ± 12.5 | 40.2 ± 13.1  | 0.71  |
| BMI (kg/m², mean ± SD) | 20.2 ± 3.7  | 19.8 ± 3.5   | 0.29  |
| Smoking status (Ever/Never) | 79/101     | 75/105       | 0.67  |
| Family history of IBD (Positive/Negative) | 14/166 | 11/169 | 0.54 |

**Clinical type**
- One episode: 16
- Relapsing: 70
- Continuous: 94

**Location**
- Proctitis (E1): 73
- Left side (E2): 64
- Extensive (E3): 43

**Disease severity**
- Mild: 76
- Moderate: 95
- Severe: 9

**Abbreviations:** UC ulcerative colitis, BMI body mass index, IBD inflammatory bowel disease.

---

**IL-22 +1046 T/A polymorphisms and UC**

The IL-22 +1046 T/A gene polymorphisms were not associated with a risk of UC (Table 3). When stratifying by clinical type, location and disease severity of UC, no significant differences were found in any groups (Table 5).

---

**Table 3** Genotype and allele frequencies of IL-22 gene polymorphisms among ulcerative colitis cases and healthy controls

| Genotypes     | UC (n = 150) | Controls (n = 150) | OR (95% CI) | P     |
|---------------|--------------|-------------------|------------|-------|
| −429 CC       | 57(31.7)     | 68(37.8)          | 1.00(Reference) |
| −429 CT       | 70(38.9)     | 86(47.8)          | 0.97(0.61,1.56) | 0.90  |
| −429 TT       | 53(29.4)     | 26(14.4)          | 2.43(1.35,4.37) | 0.003 |
| −429 C allele frequency | 184(51.1) | 222(61.7) | 1.00(Reference) |
| −429 T allele frequency | 176(48.9) | 138(38.3) | 1.54(1.14,2.07) | 0.004 |
| +1046 TT      | 88(48.9)     | 94(52.2)          | 1.00(Reference) |
| +1046 TA      | 63(35.0)     | 61(33.9)          | 1.10(0.70,1.74) | 0.67  |
| +1046 AA      | 29(16.1)     | 25(13.9)          | 1.24(0.67,2.28) | 0.49  |
| +1046 T allele frequency | 239(66.4) | 249(69.2) | 1.00(Reference) |
| +1046 A allele frequency | 121(33.6) | 111(30.8) | 1.14(0.83,1.55) | 0.34  |
| +1995 AA      | 76(42.2)     | 81(45.0)          | 1.00(Reference) |
| +1995 AC      | 65(36.1)     | 63(35.0)          | 1.10(0.69,1.75) | 0.69  |
| +1995 CC      | 39(21.7)     | 36(20.0)          | 1.16(0.67,2.00) | 0.61  |
| +1995 A allele frequency | 217(60.3) | 225(62.5) | 1.00(Reference) |
| +1995 C allele frequency | 143(39.7) | 135(37.5) | 1.10(0.81,1.48) | 0.54  |

**Abbreviations:** UC ulcerative colitis, OR odds ratio, CI confidence interval.
with increased UC risk [32]. A meta-analysis of nine studies indicated that the vitamin D receptor (VDR) polymorphisms were associated with increased UC risk [33]. A meta-analysis suggested that the migration inhibitory factor (MIF) gene −173 G/C polymorphism contributed to the susceptibility of UC [34]. A case–control study included 422 very-early-onset IBD subjects and 480 healthy subjects suggested that IL-10R polymorphisms were associated with very-early-onset ulcerative colitis ($P = 0.0002$) [35]. A case–control study included 171 UC and 213 healthy controls found that polymorphisms in XRCC1 Arg399Gln and APE1 Asp148Glu significantly increased the rate of apoptosis and risk of UC ($P = 0.0007$) [36]. A case–control study in a group of 200 Mexican patients with UC and 698 healthy unrelated individuals suggested that IL-1 RN and IL-1B polymorphisms were associated with the genetic susceptibility to develop UC and might be associated with the presence of steroid-dependence in UC patients ($P = 0.019$) [37]. A case–control study in a group of 200 Mexican Mestizo patients with UC and 698 healthy unrelated individuals with no family history of UC suggested that IL-19 polymorphisms (rs2243188 and rs2243193) might have a protective role in the development of UC ($P = 0.018$ and $P = 0.006$, respectively) in Mexican individuals [38].

**Table 4 Stratification analysis of IL-22 −429 C/T polymorphisms in ulcerative colitis cases**

| Clinical type | Cases (n = 180) | CC | OR (95% CI) | P   | CT | OR (95% CI) | P   | TT | OR (95% CI) | P   |
|--------------|----------------|----|-------------|-----|----|-------------|-----|----|-------------|-----|
| One episode  | 180            | 57(31.7) | 1 (Reference) | 0.98 | 70(38.9) | 1 (Reference) | 0.80 | 53(29.4) | 1 (Reference) | 0.78 |
| Relapsing    | 70             | 24(34.3) | 1.08 (0.62, 1.88) | 0.78 | 26(37.1) | 0.96 (0.56, 1.62) | 0.87 | 20(28.6) | 0.97 (0.54, 1.74) | 0.92 |
| Continuous   | 94             | 28(29.8) | 0.94 (0.56, 1.58) | 0.82 | 37(39.4) | 1.01 (0.63, 1.62) | 0.96 | 29(30.8) | 1.05 (0.63, 1.76) | 0.86 |
| Location     | 180            | 57(31.7) | 1 (Reference) | 0.98 | 70(38.9) | 1 (Reference) | 0.80 | 53(29.4) | 1 (Reference) | 0.78 |
| Proctitis (E1) | 73        | 24(32.9) | 1.04 (0.60, 1.80) | 0.89 | 27(37.0) | 0.95 (0.57, 1.60) | 0.85 | 22(30.1) | 1.02 (0.58, 1.80) | 0.94 |
| Left side (E2) | 64        | 20(31.3) | 0.99 (0.55, 1.77) | 0.97 | 26(40.6) | 1.05 (0.61, 1.78) | 0.87 | 18(28.1) | 0.96 (0.52, 1.75) | 0.88 |
| Extensive (E3) | 43        | 13(30.2) | 0.96 (0.48, 1.90) | 0.89 | 17(39.6) | 1.02 (0.54, 1.90) | 0.96 | 13(30.2) | 1.03 (0.51, 2.05) | 0.94 |
| Disease severity | 180   | 57(31.7) | 1 (Reference) | 0.98 | 70(38.9) | 1 (Reference) | 0.80 | 53(29.4) | 1 (Reference) | 0.78 |
| Mild         | 76             | 25(32.9) | 1.04 (0.61, 1.79) | 0.89 | 28(38.6) | 0.95 (0.57, 1.58) | 0.84 | 23(30.3) | 1.03 (0.59, 1.80) | 0.92 |
| Moderate     | 95             | 29(30.5) | 0.96 (0.58, 1.61) | 0.89 | 38(40.0) | 1.03 (0.65, 1.64) | 0.91 | 28(29.5) | 1.00 (0.59, 1.68) | 0.99 |
| Severe       | 9              | 3(33.3)  | 1.05 (0.28, 4.02) | 0.94 | 4(44.5)  | 1.14 (0.34, 3.83) | 0.83 | 2(22.2)  | 0.76 (0.16, 3.60) | 0.72 |

**Table 5 Stratification analysis of IL-22 +1046 T/A polymorphisms in ulcerative colitis cases**

| Clinical type | Cases (n = 180) | TT | OR (95% CI) | P   | TA | OR (95% CI) | P   | AA | OR (95% CI) | P   |
|--------------|----------------|----|-------------|-----|----|-------------|-----|----|-------------|-----|
| One episode  | 180            | 88(48.9) | 1 (Reference) | 0.81 | 63(35.0) | 1 (Reference) | 0.89 | 29(16.1) | 1 (Reference) | 0.82 |
| Relapsing    | 70             | 33(47.1) | 0.96 (0.59, 1.57) | 0.88 | 26(37.2) | 1.06 (0.62, 1.81) | 0.83 | 11(15.7) | 0.98 (0.46, 2.06) | 0.95 |
| Continuous   | 94             | 48(51.1) | 1.04 (0.68, 1.61) | 0.84 | 31(33.0) | 0.94 (0.57, 1.55) | 0.82 | 15(15.9) | 0.99 (0.51, 1.94) | 0.98 |
| Location     | 180            | 88(48.9) | 1 (Reference) | 0.81 | 63(35.0) | 1 (Reference) | 0.89 | 29(16.1) | 1 (Reference) | 0.82 |
| Proctitis (E1) | 73        | 37(50.7) | 1.04 (0.65, 1.66) | 0.88 | 25(34.2) | 0.98 (0.57, 1.67) | 0.94 | 11(15.1) | 0.94 (0.44, 1.97) | 0.86 |
| Left side (E2) | 64        | 33(51.6) | 1.06 (0.65, 1.72) | 0.83 | 21(32.8) | 0.94 (0.53, 1.66) | 0.82 | 10(15.6) | 0.97 (0.45, 2.10) | 0.94 |
| Extensive (E3) | 43        | 18(41.9) | 0.86 (0.47, 1.57) | 0.62 | 17(39.5) | 1.13 (0.60, 2.12) | 0.70 | 8(18.6)  | 1.16 (0.49, 2.70) | 0.74 |
| Disease severity | 180   | 88(48.9) | 1 (Reference) | 0.81 | 63(35.0) | 1 (Reference) | 0.89 | 29(16.1) | 1 (Reference) | 0.82 |
| Mild         | 76             | 35(46.1) | 0.94 (0.59, 1.51) | 0.81 | 28(36.8) | 1.05 (0.63, 1.77) | 0.85 | 13(17.1) | 1.06 (0.52, 2.15) | 0.87 |
| Moderate     | 95             | 48(50.5) | 1.03 (0.67, 1.59) | 0.88 | 32(33.7) | 0.96 (0.59, 1.58) | 0.88 | 15(15.8) | 0.98 (0.50, 1.92) | 0.95 |
| Severe       | 9              | 5(55.6)  | 1.14 (0.37, 3.49) | 0.82 | 3(33.3)  | 0.95 (0.25, 3.63) | 0.94 | 1(11.1)  | 0.69 (0.08, 5.65) | 0.73 |

**Abbreviations:** OR odds ratio, CI confidence interval.
rhinosinusitis ($P = 0.0014$) [16]. A case–control study in 194 patients and 287 normal controls suggested that polymorphism of IL-22 receptor alpha-1 was associated with the development of childhood IgA nephropathy ($P = 0.002$) [22]. IL-22 deficiency may contribute to the pathogenesis of certain chronic disorders as postulated in this paper for acne inversa [39]. A study included 94 patients for acne inversa [39]. A study included 94 patients [39]. A study included allergic asthma (n = 18), controlled asthma (n = 17) and healthy controls (n = 12) [41]. A study in 18 cases and 21 controls suggested that increased expression of $IL-22$ was associated with disease activity in Behcet’s disease [42]. $IL-22$ has been reported to be involved in systemic sclerosis lesions [43]. A study included allergic asthma (n = 18), controlled asthma (n = 17) and healthy controls (n = 12) [41]. A study in 18 cases and 21 controls suggested that increased expression of $IL-22$ was associated with disease activity in Behcet’s disease [42]. $IL-22$ has been reported to be involved in systemic sclerosis lesions [43]. A study included allergic asthma (n = 18), controlled asthma (n = 17) and healthy controls (n = 12) [41]. A study in 18 cases and 21 controls suggested that increased expression of $IL-22$ was associated with disease activity in Behcet’s disease [42].

Our results should be taken with caution for some limitations. First of all, the numbers of subjects included in this study were small, and may not have been sufficient to reveal the associations between the $IL-22$ gene polymorphisms ($-429$ C/T, +1046 T/A and +1995 A/C) and the risk of UC. Secondly, our investigation was not based on genome wide screening, but UC was induced by multiple genes and environmental factors, which were not explored in the present study. Thirdly, the participants in our research are only from Han Chinese ethnic group. It would be interesting to conduct similar studies in different populations for comparison. Finally, this is a hospital based case control study, so the selection bias cannot be avoided and the subjects may not be representative of the general population.

Conclusions
In conclusion, this study provides evidence for an association of $IL-22$ –$429$ C/T gene polymorphisms with UC risk. To the best of our knowledge this is the first study to provide evidence about the role of $IL-22$ polymorphisms in the development of UC. Additional well-designed large-scale multicenter studies were required for the validation of our results.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
HGC and YZ carried out the molecular genetic studies and drafted the manuscript. XBZ carried out the genotyping. ZGW and SXD participated in the design of the study and performed the statistical analysis. HGC, XBZ, ZGW, SXD, ZW and YZ conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Authors’ information
Hong Gang Chi and Xue Bao Zheng are joint first authors.

Acknowledgment
This investigation was funded by the National Natural Science Foundation of China (NSFC, No. 81173240), Science and Technology Planning Project of Guangdong Province (No. 2013B032500019), China and the PhD Start-up Fund of Guangdong Medical College (No. B2013005, B2013006).

Author details
1Department of Traditional Chinese Medicine, The Second Clinical Medical College, Guangdong Medical College, 1 Xincheng Road, Songshan LakeSci. &Tech, Industry Park, Dongguan, Guangdong 523808, China. 2The Second Clinical Medical College, Guangdong Medical College, Dongguan 523808, China. 3Emergency Department of Nanfang Hospital, Southern Medical University, Guangzhou 510515, China. 4Sino-American Cancer Research Institute, Guangdong Medical College, Dongguan 523808, China.
References

1. Tyler AD, Milgrom R, Stempar JM, Xu W, Brummell JH, Miseu AM, Sehgal R, Cohen Z, Koster W, Shen B, Silverberg MS. The NO2insC polymorphism is associated with worsening outcome following ileal pouch-anal anastomosis for ulcerative colitis. Gut 2013, 62:1433–1439.

2. Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med 2011, 365:1713–1725.

3. Tess J, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. Clin Gastroenterol Hepatol 2012, 10:639–645.

4. Sartor RB. Mechanisms of disease: pathogenesis of Crohn’s disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol 2006, 3:390–407.

5. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleyen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Aloncova A, Ackhar JP, Ahmad T, Aminnejadi L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balchunis R, Baptista PR, Piton A, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 2012, 491:119–124.

6. Beaudoin M, Goyette P, Boucher G, Lo KS, Rivas MA, Stevens C, Alikashani A, Ladouceur M, Ellinghaus D, Fehrmann RS, Floyd JA, Florin T, Franchimont D, Torkvist L, Goel G, Lagacé C, Annese V, Bitton A, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar J, Thomas HC, Thursz M, Hill AV: Polymorphisms in the interleukin-22 receptor alpha-1 is associated with the development of childhood IgA nephropathy. J Interferon Cytokine Res 2013, 33:571–577.

7. Podolsky DK. Inflammatory bowel disease. N Engl J Med 2002, 347:417–429.

8. Satgani J, Silverberg MS, Verriere S, Colombel JF: The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006, 55:749–753.

9. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1953, 2:1041–1048.

10. Langhoft E, Mushkolt P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology 1994, 107:193–11.

11. Sivaram G, Tiwari SK, Bardia A, Anjum F, Vishnupriya S, Habeeb A, Khan AA: Macrophage migration inhibitory factor, Toll-like receptor 4, and CD14 polymorphisms with altered expression levels in patients with ulcerative colitis. Hum Immunol 2012, 73:201–205.

12. Mo JS, Ko KS, Yu Ji, Chae SC: Identification of the polymorphisms in IFITM1 gene and their association in a Korean population with ulcerative colitis. Innate Immunol 2013, 15:119–122.

13. Yamamoto-Furusho JK, De-Leon-Rendon JL, de la Torre MG, Alvarez-Leon E, Vargas-Alarcon G: Genetic polymorphisms of interleukin 20 (IL-20) in patients with ulcerative colitis. Immunol Lett 2013, 149:50–53.

14. Shiota A, Kusunoki H, Kimura Y, Ishii M, Imamura H, Tanumi K, Manabe N, Komada T, Hata J, Haruma K: S100A expression and interleukin-10 polymorphisms are associated with Ulcerative colitis and diarrhea predominant irritable bowel syndrome. Dig Dis Sci 2013, 58:2314–2323.

15. Yu Ji, Kang H, Seo GS, Choi SC, Yun KL, Chae SC: Promoter polymorphism of the EED gene is associated with the susceptibility to Ulcerative colitis. Dig Dis Sci 2012, 57:1537–1543.

16. Zhang JX, He JH, Wang JQ, Song J, Lei HB, Wang J, Dong WG: Associations between PTNP2 polymorphisms and susceptibility to ulcerative colitis. Inflamm Res 2014, 63:71–79.

17. Xue LN, Xu QX, Zhang W, Wang Q, Wu J, Wang XY: Associations between vitamin D receptor polymorphisms and susceptibility to Ulcerative colitis and Crohn’s disease: a meta-analysis. Inflamm Bowel Dis 2013, 19:54–60.

18. Wang B, Zhao XP, Fan YC, Zhang Ji, Zhao J, Wang K: IL-17A but not IL-22 suppresses the replication of hepatitis B virus mediated by over-expression of MxA and OAS mRNA in the HepG2.2.15 cell line. Antiviral Res 2013, 97:285–292.

19. Moran CJ, Walters TD, Guo CH, Kugathasan S, Klein C, Turner D, Wolters VM, Bandsma RH, Mouzaki M, Zachos M, Langer JC, Cutz E, Benseler SM, Roifman CM, Silverberg MS, Griffiths AM, Snapper SB, Muehe AM: IL-10R polymorphisms are associated with very-early-onset Ulcerative colitis. Inflamm Bowel Dis 2013, 19:115–123.

20. Baidar A, Tiwari SK, Gunisetty S, Anjum F, Nallari P, Habeeb AM, Khan AA: Functional polymorphisms in XRCC1 and APE1 contribute to increased apoptosis and risk of ulcerative colitis. Inflamm Res 2012, 61:359–365.

21. Yamamoto-Furusho JK, Santiago-Hernandez JJ, Perez-Hernandez N, Ramirez-Fuentes S, Frasgo JM, Vargas-Alarcon G: Interleukin 1 beta (IL-1B) and IL-1 antagonist receptor (IL-1RN) gene polymorphisms are associated with the genetic susceptibility and steroid dependence in patients with Ulcerative colitis. J Clin Gastroenterol 2011, 45:531–533.

22. Yamamoto-Furusho JK, Alvarez-Leon E, Frasgo JM, Gozalishvili A, Vallejo M, Vargas-Alarcon G: Protective role of interleukin-19 gene polymorphisms in patients with ulcerative colitis. Hum Immunol 2011, 72:1029–1032.

23. Wolk K, Warszawka K, Hoeflich C, Witte E, Schneider-Burrus S, Witte K, Kunz S, Buss A, Roewert HJ, Krause M, Lukovsky A, Volk HD, Sterny W, Sabat R:
Deficiency of IL-22 contributes to a chronic inflammatory disease: pathogenetic mechanisms in acne inversa. *J Immunol* 2011, 186:1228–1239.

40. Zhang L, Cheng Z, Liu W, Wu K: Expression of interleukin (IL)-10, IL-17A and IL-22 in serum and sputum of stable chronic obstructive pulmonary disease patients. *COPD* 2013, 10:659–665.

41. Luo Z, Wang H, Sun Z, Luo W, Wu Y: Expression of IL-22, IL-22R and IL-23 in the peri-implant soft tissues of patients with peri-implantitis. *Arch Oral Biol* 2013, 58:523–529.

42. Cai T, Wang Q, Zhou Q, Wang C, Hou S, Qi J, Kijlstra A, Yang P: Increased expression of IL-22 is associated with disease activity in Behcet’s disease. *PLoS One* 2013, 8:e59009.

43. Mathian A, Parizot C, Dorcham K, Trad S, Arnaud L, Larsen M, Miyara M, Hie M, Piette JC, Frances C, Yssel H, Amoura Z, Gorochov G: Activated and resting regulatory T cell exhaustion concurs with high levels of interleukin-22 expression in systemic sclerosis lesions. *Ann Rheum Dis* 2012, 71:1227–1234.

44. Zhu J, Cao Y, Li K, Wang Z, Zuo P, Xiong W, Xu Y, Xiong S: Increased expression of aryl hydrocarbon receptor and interleukin 22 in patients with allergic asthma. *Asian Pac J Allergy Immunol* 2011, 29:266–272.

doi:10.1186/s13000-014-0183-y

Cite this article as: Chi et al: Association of the interleukin-22 genetic polymorphisms with ulcerative colitis. *Diagnostic Pathology* 2014 9:183.