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**Inflammatory bowel disease serology in Asia and the West**

Prideaux L *et al.* IBD Serology, Asian and the West

Lani Prideaux,Michael A Kamm, Peter De Cruz, Daniel R van Langenberg, Siew C Ng, Iris Dotan

**Lani Prideaux, Michael A Kamm, Peter De Cruz,** Department of Gastroenterology, St Vincent’s Hospital, Fitzroy 3065, Melbourne, Australia

**Lani Prideaux, Michael A Kamm, Peter De Cruz,** Department of Medicine, University of Melbourne, Victoria 3053, Melbourne, Australia

**Michael A Kamm,** Department of Medicine, Imperial College, London SW7 2AZ, United Kingdom

**Daniel R van Langenberg,** Department of Gastroenterology, Box Hill Hospital, Box Hill 3128, Melbourne, Australia

**Siew C Ng,** Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong

**Iris Dotan,** Inflammatory Bowel Disease Center, Department of Gastroenterology, Sourasky Medical Center, Tel Aviv 64239, Israel

**Author contributions:** Prideaux L and Kamm MA designed the research, performed the analysis and wrote the paper; Ng, SC, De Cruz P and van Langenberg DR collected samples and critically appraised the manuscript; Dotan I processed the samples and critically appraised the manuscript.

**Correspondence to: Michael A** **Kamm**, **MD, PhD, FRACP, Professor,** Department of Gastroenterology, St Vincent’s Hospital, Victoria Parade, Fitzroy 3065, Melbourne, Australia. mkamm@unimelb.edu.au

**Telephone:** + 61-3-9417 5064 **Fax:** +61-3-9416 2485

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**Abstract**

**AIM:** To study serological antibodies in Caucasians and Asians, in health and inflammatory bowel disease (IBD), in Australia and Hong Kong (HK).

**METHODS:** Anti-glycan antibodies [anti-chitobioside (ACCA), anti-laminaribioside (ALCA)], and anti-mannobioside (AMCA), anti-*Saccharomyces cervisiae* (gASCA); and pANCA (atypical perinuclear anti-neutrophil cytoplasmic antibody) were tested in IBD patients, their unaffected relatives, and healthy controls in Australia and Hong Kong (HK). Antibody status (positive or negative) and titre was compared between subjects of different geography, ethnicity and disease state.

**RESULTS:** Ninety subjects were evaluated: 21 Crohn’s disease (CD), 32 ulcerative colitis (UC), 29 healthy controls, and 8 IBD patient relatives. Forty eight subjects were Australian (29 Caucasian and 19 ethnic Han Chinese) and 42 were from HK (all Han Chinese). Caucasian CD patients had a significantly higher antibody prevalence of gASCA (67% *vs* 3%, *P* < 0.001), ALCA (44% *vs* 6%, *P* = 0.005), and AMCA (67% *vs* 15%, *P* = 0.002), whereas HK CD patients had a higher prevalence of only AMCA (58% *vs* 25%, *P* = 0.035), when compared with UC and healthy subjects in both countries. Caucasian CD had significantly higher gASCA prevalence (67% *vs* 0%, *P* < 0.001) and titre (median 59 *vs* 9, *P* = 0.002) than HK CD patients. Prevalence and titres of ALCA, ACCA and AMCA did not differ between CD in the two countries. Presence of at least one antibody was higher in Caucasian than HK CD patients (100% *vs* 58%, *P* = 0.045). pANCA did not differ between countries or ethnicity.

**CONCLUSION:** Serologic CD responses differ between HK Asian and Australian Caucasian patients. Different genetic, environmental or disease pathogenic factors may account for these differences.

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**Key words***:* Crohn’s disease; Ulcerative colitis; Serological antibodies; Asia; Ethnic; Anti-*Saccharomyces cervisiae* antibodies; Anti-chitobioside antibodies; Anti-laminaribioside antibodies; Anti-mannobioside antibodies; Atypical perinuclear anti-neutrophil cytoplasmic antibodies

**Core tip:**Serological antibodies to enteric antigens are a hallmark of inflammatory bowel disease (IBD) and may carry pathogenic and prognostic significance. There is limited information about their role and prevalence in Asian patients. We evaluated anti-glycan antibodies (anti-chitobioside, anti-laminaribioside, and anti-mannobioside), anti-*Saccharomyces cervisiae*; and atypical perinuclear anti-neutrophil cytoplasmic antibody in IBD patients, their unaffected relatives, and healthy controls in Australia and Hong Kong. Serologic responses were found to differ between Asian and Caucasian patients. Different genetic, environmental or disease pathogenic factors may account for these differences.

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**INTRODUCTION**

Crohn’s disease (CD) and ulcerative colitis (UC) are related to a mucosal immune response to antigenic stimulation from the gut microbiota on a background of genetic susceptibility[1]. Serological antibodies for IBD have a role as diagnostic markers for IBD and assist in disease stratification[2].

Glycans are carbohydrate surface components, which can be found on immune cells, erythrocytes, tissue matrices and microorganisms. They likely reflect the interaction between the immune system and glycosylated cell wall components of microbiota such as fungi, yeast, and bacteria[3]. Anti-*Saccharomyces cerevisiae* (gASCA ASCA) (IgA and IgG) antibodies are directed against the cell wall mannan of the yeast *Saccharomyces* that shares homology with intestinal bacteria[4]. gASCA (antibodies against covalently immobilized mannan)[5] have been found to be comparable to ‘‘conventional’’ ASCA[6]. Anti-laminaribioside carbohydrate IgG antibodies (ALCA), anti-chitobioside carbohydrate IgA antibodies (ACCA), anti-mannobioside carbohydrate IgG antibodies (AMCA) were first reported in 2006[5] and discovered using GlycoChip glycan array technology[7]. These antibodies may allow differentiation of IBD from health, define between IBD subtypes, and have been associated with a more complicated CD behaviour[2,5]. Atypical perinuclear anti-neutrophil cytoplasmic antibody (pANCA) is regarded as a marker of UC, as it has a higher prevalence in UC than in CD or healthy controls[8].

Until two decades ago IBD was rare in Asia[9], but recent population-based and referral centre cohorts[10,11] have shown a rising incidence and prevalence of IBD in Asia[12]. These temporal trends in disease incidence and prevalence may provide insights into possible etiologic factors, such as genetic *vs* environmental. As serologic antibodies may represent an interface between a patient’s genetic make-up and their environment, we hypothesised that evaluation of serologic responses in areas of increasing incidence may provide an insight into these complex interactions. Most data on serological antibodies are derived from North American or European cohorts. There are no publications of the prevalence of the anti-glycan antibodies in Asian cohorts, either in Asia or in Asians abroad.

This study aimed to provide an initial insight into the prevalence and magnitude of the anti-glycan antibodies, and pANCA in IBD, compared to control groups, in Han Chinese (referred to as Asian) and Caucasian subjects in Australia and in Han Chinese subjects in Hong Kong (HK).

**MATERIALS AND METHODS**

***Patient population***

Serum samples were obtained from consented consecutive subjects, regardless of disease extent or duration, from IBD centres in Melbourne, Australia and Hong Kong.

IBD diagnosis and differentiation into UC and CD was made based on accepted clinical, endoscopic, histopathological, and radiological findings. Patient characteristics are shown in Table 1. The healthy subjects consisted of patients undergoing a colonoscopy for a family history of cancer or polyps, with a subsequent normal colonoscopy. Eight first degree relatives of IBD subjects (2 of UC, 6 of CD) who were undergoing a colonoscopy for cancer screening were also studied. Signed informed consent was obtained from all participants. The study was approved by the Ethics Committees of St Vincent’s Public and Private Hospitals Melbourne, and The Chinese University of Hong Kong.

***Serological analysis***

After blood was taken, serum was immediately separated by centrifugation and then frozen at -80 ℃ until use. All sera were processed anonymously.

The IBDX ELISA kit was used to detect gASCA IgG, ALCA IgG, ACCA IgA, AMCA IgG, following the manufacturer’s recommendations (Glycominds Ltd, Lod, Israel). The cutoff values were those supplied by the manufacturer: 50, 90, 60, 100 EUs for gASCA IgG, ACCA, ALCA, and AMCA, respectively. pANCA was performed using indirect immunofluorescence on ethanol and formalin-fixed neutrophil substrate slides.

For the titre of immune response of the anti-glycan antibodies, quartile scores for each serologic antibody were calculated, as described previously[6,13,14]. For each patient each antibody titre was assigned to a quartile score of 1 (lowest), 2, 3, or 4 (highest). By adding individual quartile scores for each glycan antigen a semi-quantitative quartile sum score (QSS) (range 4–16), representing the cumulative quantitative immune response toward all four antigens for each patient, was obtained.

***Statistical analysis***

Using the suggested cut-off values for each antibody, positive or negative status was determined for each subject. In addition, antibody titres were divided into four groups based on the quartiles (see description above). Discrete parameters were assessed as percentages and compared using Fisher’s exact or *χ2*test where appropriate. Continuous parameters were assessed as means if normally distributed (compared using one way ANOVA), and medians if not normally distributed (compared using Mann–Whitney *U*-test). The software Graphpad Prism 5 and SPSS 21 were used for analyses. *P* < 0.05 was considered statistically significant.

**RESULTS**

***Demographics***

Ninety participants (21 CD, 32 UC, 29 healthy controls, and 8 relatives of IBD patients) were divided according to geography, ethnicity and disease (Table 1). All Asian patients were Han Chinese. There was no significant difference when comparing age or gender distribution between countries (Australian *vs* HK subjects), or ethnicities (Asian *vs* Caucasian subjects).

***CD*** *vs* ***Non-CD (UC, healthy subjects and relatives)***

**Anti-glycan antibody prevalence and number of antibodies positive:** As the anti-glycan antibodies are known to be associated with CD, we compared each CD *vs* non-CD groups in combined Australian and HK cohorts. Three (gASCA, ALCA, AMCA) of the four anti-glycan antibodies were present in a significantly higher proportion of Australian Caucasian CD compared to all non-CD subjects combined [6/9 (67%) *vs* 2/69 (3%), *P* < 0.001; 4/9 (44%) *vs* 4/69 (6%), *P* = 0.005; and 6/9 (67%) *vs* 10/69 (15%), *P* = 0.002, respectively]. In contrast, in the HK Asian CD group only AMCA had a significantly higher proportion of subjects positive compared to all non-CD groups combined [7/12 (58%) *vs* 10/69 (15%), *P* = 0.002] (Table 2).

The proportion of subjects with at least one, and at least two, antibodies positive was significantly higher in the Australian Caucasian CD group than all non-CD groups combined [9/9 (100%) *vs* 17/69 (25%), *P* < 0.001; 6/9 (67%) *vs* 5/69 (7%), *P* = 0.001]. The HK Asian CD group had a significantly higher proportion of subjects with at least one antibody positive compared to all non-CD groups combined, [7/12 (58%) *vs* 17/69 (25%),*P* = 0.035], however, only 2/12 (17%) had at least two antibodies positive. All subjects in the HK Asian CD group that had an antibody positive had AMCA as one of the antibodies.

**Anti-glycan antibody titres:** The titres of three of the four anti-glycan antibodies (gASCA, ALCA, and AMCA), and the quartile sum score (QSS), were significantly higher in the Australian Caucasian CD group than all non-CD groups combined (median titres 59 *vs* 9, *P* < 0.001; 45 *vs* 18, *P* = 0.002; 111 *vs* 67, *P* = 0.002; 14 *vs* 9, *P* < 0.001, respectively). Two of the four anti-glycan antibodies (ALCA, and AMCA), and the QSS, had significantly higher titres in the HK Asian Crohn’s group than all non-CD groups combined (median titres 27 *vs* 18, *P* = 0.029; 121 *vs* 67, *P* = 0.003, 13 *vs* 9, *P* = 0.022, respectively). HK relatives did not have a significantly higher number of antibodies positive, or a higher antibody titre, than other healthy subjects.

***CD in Australian Caucasians and Hong Kong Asians***

**Anti-glycan antibody prevalence and number of antibodies positive:** The proportion of subjects with positive gASCA was significantly higher in the Australian Caucasian CD group than the HK Asian CD group [6/9 (67%) *vs* 0/12 (0%), *P* < 0.001]. Prevalence of ALCA, ACCA and AMCA in Australian Caucasian CD patients [4/9 (44%), 2/9 (22%), and 6/9 (67%)] was not significantly different to the HK CD patients [1/12 (8%), 1/12 (8%) and 7/12 (58%)].The proportion of subjects with at least one antibody, or at least two antibodies, positive was significantly higher in Australian Caucasian CD patients than the HK Asian CD patients [9/9 (100%) *vs* 7/12 (58%), *P* = 0.045; 6/9 (67%) *vs* 2/12 (17%), *P* = 0.032].

**Anti-glycan antibody titres:** A significant difference was seen when comparing gASCA titres of Australian Caucasian CD to HK Asian CD patients (median titres 59 *vs* 9, *P* = 0.002). There was no significant difference in any other antibody titre, or the QSS, between the CD patients in the two countries.

***pANCA presence***

The proportion of subjects with a positive pANCA in the Australian Caucasian UC group (7/10, 70%) did not differ significantly from the Australian Asian UC (5/10, 50%) and the HK Asian UC (4/12, 33%) patients. pANCA was present in 3/12 (25%) of the HK Asian CD group, but was virtually absent from all other non-UC groups. When comparing the Australian Caucasian UC patients, Australian Asian UC patients, and the HK Asian UC patients, to all non-UC subjects combined, each UC group had a statistically higher proportion of subjects with a positive pANCA (*P* < 0.001, *P* = 0.002, *P* = 0.025, respectively).

**DISCUSSION**

There are very few studies reporting the prevalence of antibodies to microbial antigens in non-Western countries and between different ethnicities. This is the first report investigating anti-glycan antibodies in an Asian cohort, and the first report investigating pANCA in an Asian cohort residing in a country outside of Asia.

The prevalence of anti-glycan antibody in Australian Caucasian CD patients was consistent with previous published Western CD cohorts[14], and were more prevalent than in all other subjects studied. The exception was ACCA which had a high prevalence in the healthy Australian Asian (33%) and Caucasian (20%) subjects, in contrast to a previously reported lower prevalence (0.5%-12%) in other healthy cohorts[2].

gASCA was not present in any HK Asian CD subjects studied. This is in contrast to Asian data showing a similar prevalence of ASCA in Japanese[15] and Korean[16,17] CD patients to that of Caucasian CD cohorts. A low gASCA titre was present in HK subjects. Chinese patients in HK may not raise an antibody response to this antigen, or may do it only in low titre. Lawrence et al. directly compared a HK IBD cohort with an Australian Caucasian IBD cohort and found ASCA IgG detection was similar but IgA was lower in Chinese CD patients[18]. This IgG detection may differ from the gASCA IgG we measured, although the two antibody measurements have been said to correlate well[6].

Differences in prevalence of the anti-glycan antibodies may reflect true pathogenic differences in different populations. However they may still be present in some populations in low titre; this may need to be taken into account in non-Caucasian ethnicities.

AMCA was prevalent in Asian IBD patients and healthy Asian subjects. This antibody has low specificity for differentiating IBD from health in an Asian population. Bernstein *et al*[19] demonstrated a similar lack of specificity in a Canadian study of Caucasian and First Nations cohorts. He found a relatively high prevalence of IBD associated antibodies (pANCA, ASCA, anti-OmpC, anti-I2, and anti-CBir-1) in all First Nations cohorts (including controls). They concluded that these antibodies are unlikely to be of pathogenic significance.

pANCA was less prevalent in Asian UC than Caucasian UC patients. The lack of significance may relate to the small number of subjects studied and the modest difference observed. These findings are consistent with Asian UC studies from Japan (35%)[20], South Korea (22%)[21], and HK (44%)[18]. The prevalence in our Caucasian UC cohort was consistent with other Western UC cohorts[2].

Our study included 8 first-degree relatives of IBD patients (all Asian from HK), six related to CD patients, and 2 to UC patients. The only 2 relatives with a positive anti-glycan antibody were related to a CD patient, and for both it was a positive AMCA. There have been no studies of antibodies in relatives of IBD patients in Asian cohorts, however several studies have shown ASCA is present in 20%-56% of Caucasian healthy relatives of patients with CD[22-28].None of the 8 relatives had a positive pANCA. Early studies of Caucasians demonstrated pANCA presence in 15%-30% of first degree relatives of patients with UC[29,30], however this has not been replicated[31-36], or not been significant when comparing to healthy non-related controls[37].

This study has a number of limitations. Sample sizes were small; however these data provide a basis for larger confirmatory studies. Australian Caucasian CD patients had more severe disease than Hong Kong Asian CD patients which could be contributing to differences in antibodies[38], however, because of the small numbers, comparisons between antibodies and CD phenotype were not made, but should be considered in further studies. Our lack of Australian Asian CD subjects limited our ability to separately determine the effects of ethnicity and geography. A cross sectional study on serological antibodies may be limited by changes in antibody status over time, although it appears that seropositive / seronegative antibody status remains relatively stable over time for the individual antibodies ASCA[13,14,23,38-41], ALCA, ACCA and AMCA[14,38,42].

In conclusion serological antibodies associated with IBD appear to differ in their presence and titre between the West and Chinese IBD patients. Caution should therefore be exercised in attributing pathogenic importance or using them as prognostic markers in different ethnic and geographic patient populations[43-45].

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**COMMENTS**

***Background***

Serological antibodies to enteric antigens are a hallmark of inflammatory bowel disease (IBD) and may carry pathogenic and prognostic significance.

***Research frontiers***

Until two decades ago IBD was rare in Asia, but recent population-based and referral centre cohorts have shown a rising incidence and prevalence of IBD in Asia.

***Innovations and breakthroughs***

Although there has been previous research on serological antibodies in Caucasian patients with IBD, there is limited information about their role and prevalence in Asian patients in Asia, or in Asian migrants to the West.

***Applications***

This study has found that serological antibodies associated with IBD appear to differ in their presence and titre between Western and Chinese IBD patients. Caution should therefore be exercised in attributing pathogenic importance or using them as prognostic markers in different ethnic and geographic patient populations.

***Terminology***

Anti-*Saccharomyces cervisiae* antibodies, which are directed against the cell wall mannan of the yeast *Saccharomyces*, that shares homology with intestinal bacteria; Antiglycan antibodies, which are directed against carbohydrates found on immune cells, erythrocytes, tissue matrices and microorganisms, and likely reflect the interaction between the immune system and glycosylated cell wall components of microbiota. The anti-glycan antibodies include: anti-chitobioside, anti-laminaribioside and anti-mannobioside; pANCA: atypical perinuclear anti-neutrophil cytoplasmic antibody, which is widely regarded as a marker of ulcerative colitis.

***Peer review***

This is interesting data of a little studied area in inflammatory bowel disease. The subject matter may be a spring board to further studies and understanding of the pathogenesis and prognosis of IBD.

**References**

1 **Danese S**, Fiocchi C. Etiopathogenesis of inflammatory bowel diseases. *World J Gastroenterol* 2006; **12**: 4807-4812 [PMID: 16937461]

2 **Prideaux L**, De Cruz P, Ng SC, Kamm MA. Serological antibodies in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2012; **18**: 1340-1355 [PMID: 22069240 DOI: 10.1002/ibd.21903]

3 **Dotan N**, Altstock RT, Schwarz M, Dukler A. Anti-glycan antibodies as biomarkers for diagnosis and prognosis. *Lupus* 2006; **15**: 442-450 [PMID: 16898180 DOI: 10.1191/0961203306lu2331oa]

4 **Sendid B**, Colombel JF, Jacquinot PM, Faille C, Fruit J, Cortot A, Lucidarme D, Camus D, Poulain D. Specific antibody response to oligomannosidic epitopes in Crohn's disease. *Clin Diagn Lab Immunol* 1996; **3**: 219-226 [PMID: 8991640]

5 **Dotan I**, Fishman S, Dgani Y, Schwartz M, Karban A, Lerner A, Weishauss O, Spector L, Shtevi A, Altstock RT, Dotan N, Halpern Z. Antibodies against laminaribioside and chitobioside are novel serologic markers in Crohn's disease. *Gastroenterology* 2006; **131**: 366-378 [PMID: 16890590 DOI: 10.1053/j.gastro.2006.04.030]

6 **Papp M**, Altorjay I, Dotan N, Palatka K, Foldi I, Tumpek J, Sipka S, Udvardy M, Dinya T, Lakatos L, Kovacs A, Molnar T, Tulassay Z, Miheller P, Norman GL, Szamosi T, Papp J, Lakatos PL. New serological markers for inflammatory bowel disease are associated with earlier age at onset, complicated disease behavior, risk for surgery, and NOD2/CARD15 genotype in a Hungarian IBD cohort. *Am J Gastroenterol* 2008; **103**: 665-681 [PMID: 18047543 DOI: 10.1111/j.1572-0241.2007.01652.x]

7 **Schwarz M**, Spector L, Gargir A, Shtevi A, Gortler M, Altstock RT, Dukler AA, Dotan N. A new kind of carbohydrate array, its use for profiling antiglycan antibodies, and the discovery of a novel human cellulose-binding antibody. *Glycobiology* 2003; **13**: 749-754 [PMID: 12851287 DOI: 10.1093/glycob/cwg091]

8 **Quinton JF**, Sendid B, Reumaux D, Duthilleul P, Cortot A, Grandbastien B, Charrier G, Targan SR, Colombel JF, Poulain D. Anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut* 1998; **42**: 788-791 [PMID: 9691915 DOI: 10.1136/gut.42.6.788]

9 **Loftus EV**. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; **126**: 1504-1517 [PMID: 15168363 DOI: 10.1053/j.gastro.2004.01.063]

10 **Molodecky NA**, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; **142**: 46-54.e42; quiz e30 [PMID: 22001864]

11 **Ng SC**, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, Wong TC, Leung VK, Tsang SW, Yu HH, Li MF, Ng KK, Kamm MA, Studd C, Bell S, Leong R, de Silva HJ, Kasturiratne A, Mufeena MN, Ling KL, Ooi CJ, Tan PS, Ong D, Goh KL, Hilmi I, Pisespongsa P, Manatsathit S, Rerknimitr R, Aniwan S, Wang YF, Ouyang Q, Zeng Z, Zhu Z, Chen MH, Hu PJ, Wu K, Wang X, Simadibrata M, Abdullah M, Wu JC, Sung JJ, Chan FK. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. *Gastroenterology* 2013; **145**: 158-165.e2 [PMID: 23583432]

12 **Prideaux L**, Kamm MA, De Cruz PP, Chan FK, Ng SC. Inflammatory bowel disease in Asia: a systematic review. *J Gastroenterol Hepatol* 2012; **27**: 1266-1280 [PMID: 22497584 DOI: 10.1111/j.1440-1746.2012.07150.x]

13 **Landers CJ**, Cohavy O, Misra R, Yang H, Lin YC, Braun J, Targan SR. Selected loss of tolerance evidenced by Crohn's disease-associated immune responses to auto- and microbial antigens. *Gastroenterology* 2002; **123**: 689-699 [PMID: 12198693 DOI: 10.1053/gast.2002.35379]

14 **Rieder F**, Schleder S, Wolf A, Dirmeier A, Strauch U, Obermeier F, Lopez R, Spector L, Fire E, Yarden J, Rogler G, Dotan N, Klebl F. Association of the novel serologic anti-glycan antibodies anti-laminarin and anti-chitin with complicated Crohn's disease behavior. *Inflamm Bowel Dis* 2010; **16**: 263-274 [PMID: 19653286]

15 **Hisabe T**, Matsui T, Sakurai T, Murakami Y, Tanabe H, Matake H, Yao T, Kamachi S, Iwashita A. Anti-Saccharomyces cerevisiae antibodies in Japanese patients with inflammatory bowel disease: diagnostic accuracy and clinical value. *J Gastroenterol* 2003; **38**: 121-126 [PMID: 12640524 DOI: 10.1007/s005350300020]

16 **Kim BG**, Kim YS, Kim JS, Jung HC, Song IS. Diagnostic role of anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic antibodies in patients with inflammatory bowel disease. *Dis Colon Rectum* 2002; **45**: 1062-1069 [PMID: 12195191 DOI: 10.1007/s10350-004-6361-3]

17 **Kim BC**, Park S, Han J, Kim JH, Kim TI, Kim WH. Clinical significance of anti-Saccharomyces cerevisiae antibody (ASCA) in Korean patients with Crohn's disease and its relationship to the disease clinical course. *Dig Liver Dis* 2007; **39**: 610-616 [PMID: 17531556 DOI: 10.1016/j.dld.2007.03.006]

18 **Lawrance IC**, Murray K, Hall A, Sung JJ, Leong R. A prospective comparative study of ASCA and pANCA in Chinese and Caucasian IBD patients. *Am J Gastroenterol* 2004; **99**: 2186-2194 [PMID: 15555001 DOI: 10.1111/j.1572-0241.2004.40486.x]

19 **Filippelli A**, Marrazzo R, Susanna V, Losasso C, De Santis D, De Novellis V, Marmo E. Opiate peptidergic neurotransmission and cardiovascular and respiratory apparatus: experimental research with beta-endorphin and dermorphin on normotensive and hypertensive rats. *Acta Physiol Hung* 1990; **75 Suppl**: 105-106 [PMID: 2164746]

20 **Kaneko K**, Suzuki Y, Shimizu T, Yamashiro Y, Yabuta K, Lifschitz CH. Anti-neutrophil cytoplasmic antibodies in Japanese children with ulcerative colitis. *J Paediatr Child Health* 1995; **31**: 336-338 [PMID: 7576894 DOI: 10.1111/j.1440-1754.1995.tb00823.x]

21 **Lee JH**, Cheon JH, Kim ES, Chung MJ, Kang W, Kim DH, Ha YJ, Park JJ, Kim TI, Kim WH. The prevalence and clinical significance of perinuclear anti-neutrophil cytoplasmic antibody in Korean patients with ulcerative colitis. *Dig Dis Sci* 2010; **55**: 1406-1412 [PMID: 19507028]

22 **Sendid B**, Quinton JF, Charrier G, Goulet O, Cortot A, Grandbastien B, Poulain D, Colombel JF. Anti-Saccharomyces cerevisiae mannan antibodies in familial Crohn's disease. *Am J Gastroenterol* 1998; **93**: 1306-1310 [PMID: 9707056 DOI: 10.1111/j.1572-0241.1998.00415.x]

23 **Vermeire S**, Peeters M, Vlietinck R, Joossens S, Den Hond E, Bulteel V, Bossuyt X, Geypens B, Rutgeerts P. Anti-Saccharomyces cerevisiae antibodies (ASCA), phenotypes of IBD, and intestinal permeability: a study in IBD families. *Inflamm Bowel Dis* 2001; **7**: 8-15 [PMID: 11233666 DOI: 10.1097/00054725-200102000-00002]

24 **Seibold F**, Stich O, Hufnagl R, Kamil S, Scheurlen M. Anti-Saccharomyces cerevisiae antibodies in inflammatory bowel disease: a family study. *Scand J Gastroenterol* 2001; **36**: 196-201 [PMID: 11252413 DOI: 10.1080/00365520120969]

25 **Annese V**, Andreoli A, Andriulli A, Dinca R, Gionchetti P, Latiano A, Lombardi G, Piepoli A, Poulain D, Sendid B, Colombel JF. Familial expression of anti-Saccharomyces cerevisiae Mannan antibodies in Crohn's disease and ulcerative colitis: a GISC study. *Am J Gastroenterol* 2001; **96**: 2407-2412 [PMID: 11513182 DOI: 10.1111/j.1572-0241.2001.04043.x]

26 **Glas J**, Török HP, Vilsmaier F, Herbinger KH, Hoelscher M, Folwaczny C. Anti-saccharomyces cerevisiae antibodies in patients with inflammatory bowel disease and their first-degree relatives: potential clinical value. *Digestion* 2002; **66**: 173-177 [PMID: 12481163 DOI: 10.1159/000066760]

27 **Sutton CL**, Yang H, Li Z, Rotter JI, Targan SR, Braun J. Familial expression of anti-Saccharomyces cerevisiae mannan antibodies in affected and unaffected relatives of patients with Crohn's disease. *Gut* 2000; **46**: 58-63 [PMID: 10601056 DOI: 10.1136/gut.46.1.58]

28 **Hadrich I**, Vandewalle P, Cheikhrouhou F, Makni F, Krichen MS, Sendid B, Standaert-Vitse A, Ayadi A, Poulain D. Ethnic and socio-cultural specificities in Tunisia have no impact on the prevalence of anti-Saccharomyces cerevisiae antibodies in Crohn's disease patients, their relatives or associated clinical factors. *Scand J Gastroenterol* 2007; **42**: 717-725 [PMID: 17505994 DOI: 10.1080/00365520601083625]

29 **Seibold F**, Slametschka D, Gregor M, Weber P. Neutrophil autoantibodies: a genetic marker in primary sclerosing cholangitis and ulcerative colitis. *Gastroenterology* 1994; **107**: 532-536 [PMID: 8039629]

30 **Shanahan F**, Duerr RH, Rotter JI, Yang H, Sutherland LR, McElree C, Landers CJ, Targan SR. Neutrophil autoantibodies in ulcerative colitis: familial aggregation and genetic heterogeneity. *Gastroenterology* 1992; **103**: 456-461 [PMID: 1634063]

31 **Lee JC**, Lennard-Jones JE, Cambridge G. Antineutrophil antibodies in familial inflammatory bowel disease. *Gastroenterology* 1995; **108**: 428-433 [PMID: 7835584 DOI: 10.1016/0016-5085(95)90070-5]

32 **Folwaczny C**, Noehl N, Endres SP, Loeschke K, Fricke H. Antineutrophil and pancreatic autoantibodies in first-degree relatives of patients with inflammatory bowel disease. *Scand J Gastroenterol* 1998; **33**: 523-528 [PMID: 9648993 DOI: 10.1080/00365529850172106]

33 **Bansi DS**, Lo S, Chapman RW, Fleming KA. Absence of antineutrophil cytoplasmic antibodies in relatives of UK patients with primary sclerosing cholangitis and ulcerative colitis. *Eur J Gastroenterol Hepatol* 1996; **8**: 111-116 [PMID: 8723413 DOI: 10.1097/00042737-199602000-00004]

34 **Reumaux D**, Delecourt L, Colombel JF, Noël LH, Duthilleul P, Cortot A. Anti-neutrophil cytoplasmic autoantibodies in relatives of patients with ulcerative colitis. *Gastroenterology* 1992; **103**: 1706 [PMID: 1426894]

35 **Papo M**, Quer JC, Pastor RM, García-Pardo G, Prats E, Mirapeix E, Rodríguez R, Richart C. Antineutrophil cytoplasmic antibodies in relatives of patients with inflammatory bowel disease. *Am J Gastroenterol* 1996; **91**: 1512-1515 [PMID: 8759652]

36 **Osangthamnont C**, Manatsathit S, Pongprasopchai S, Viriyataveekul R, Chaihirunkarn S, Leelakusolvong S, Boonyapisit S. Antibodies to neutrophil cytoplasma in patients with ulcerative colitis and their first-degree relatives in Thailand. *J Gastroenterol Hepatol* 2001; **16**: 866-871 [PMID: 11555099 DOI: 10.1046/j.1440-1746.2001.02546.x]

37 **Yang P**, Järnerot G, Danielsson D, Tysk C, Lindberg E. P-ANCA in monozygotic twins with inflammatory bowel disease. *Gut* 1995; **36**: 887-890 [PMID: 7615278 DOI: 10.1136/gut.36.6.887]

38 **Rieder F**, Schleder S, Wolf A, Dirmeier A, Strauch U, Obermeier F, Lopez R, Spector L, Fire E, Yarden J, Rogler G, Dotan N, Klebl F. Serum anti-glycan antibodies predict complicated Crohn's disease behavior: a cohort study. *Inflamm Bowel Dis* 2010; **16**: 1367-1375 [PMID: 20024902 DOI: 10.1002/ibd.21179]

39 **Desir B**, Amre DK, Lu SE, Ohman-Strickland P, Dubinsky M, Fisher R, Seidman EG. Utility of serum antibodies in determining clinical course in pediatric Crohn's disease. *Clin Gastroenterol Hepatol* 2004; **2**: 139-146 [PMID: 15017619 DOI: 10.1016/S1542-3565(03)00321-5]

40 **Israeli E**, Grotto I, Gilburd B, Balicer RD, Goldin E, Wiik A, Shoenfeld Y. Anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies as predictors of inflammatory bowel disease. *Gut* 2005; **54**: 1232-1236 [PMID: 16099791 DOI: 10.1136/gut.2004.060228]

41 **Müller S**, Styner M, Seibold-Schmid B, Flogerzi B, Mähler M, Konrad A, Seibold F. Anti-Saccharomyces cerevisiae antibody titers are stable over time in Crohn's patients and are not inducible in murine models of colitis. *World J Gastroenterol* 2005; **11**: 6988-6994 [PMID: 16437604]

42 **Rieder F**, Lopez R, Franke A, Wolf A, Schleder S, Dirmeier A, Schirbel A, Rosenstiel P, Dotan N, Schreiber S, Rogler G, Klebl F. Characterization of changes in serum anti-glycan antibodies in Crohn's disease--a longitudinal analysis. *PLoS One* 2011; **6**: e18172 [PMID: 21573154 DOI: 10.1371/journal.pone.0018172]

43 **Devlin SM**, Yang H, Ippoliti A, Taylor KD, Landers CJ, Su X, Abreu MT, Papadakis KA, Vasiliauskas EA, Melmed GY, Fleshner PR, Mei L, Rotter JI, Targan SR. NOD2 variants and antibody response to microbial antigens in Crohn's disease patients and their unaffected relatives. *Gastroenterology* 2007; **132**: 576-586 [PMID: 17258734 DOI: 10.1053/j.gastro.2006.11.013]

44 **Cruyssen BV**, Peeters H, Hoffman IE, Laukens D, Coucke P, Marichal D, Cuvelier C, Remaut E, Veys EM, Mielants H, De Vos M, De Keyser F. CARD15 polymorphisms are associated with anti-Saccharomyces cerevisiae antibodies in caucasian Crohn's disease patients. *Clin Exp Immunol* 2005; **140**: 354-359 [PMID: 15807862 DOI: 10.1111/j.1365-2249.2005.02759.x]

45 **Mow WS**, Vasiliauskas EA, Lin YC, Fleshner PR, Papadakis KA, Taylor KD, Landers CJ, Abreu-Martin MT, Rotter JI, Yang H, Targan SR. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. *Gastroenterology* 2004; **126**: 414-424 [PMID: 14762777 DOI: 10.1053/j.gastro.2003.11.015]

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**S-Editor** Zhai HH **L-Editor E-Edito**r

**Table 1 Subject demographics and disease characteristics**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Country | Group | Ethnicity | Group No. | Age (yr) | Female  | Never smoker  | Family history of IBD  | CD(severe behaviour ) | CD (ileocoloniclocation )  | UC proctitis  |
| Australia(*n* = 48) | Crohn’s | Caucasian | 9 | 29 ±12 | 4 (44) | 3 (33) | 0 (0) | 8 (89) | 7 (78) | - |
| UC | Caucasian | 10 | 37 ±11 | 5 (50) | 7 (70) | 1 (10) | - | - | 1 (10) |
| Asian | 10 | 45 ±14 | 2 (20) | 8 (80) | 0 (0) | - | - | 3 (10) |
| Healthy | Caucasian | 10 | 46 ±12 | 5 (50) | 4 (40) | 0 (0) | - | - | - |
| Asian | 9 | 51 ±11 | 4 (44) | 7 (78) | 1 (11) | - | - | - |
| Hong Kong(*n* = 42) | Crohn's | Asian | 12 | 38 ±15 | 7 (58) | 7 (58) | 1 (8) | 3 (25) | 9 (75) | - |
| UC | Asian | 12 | 43 ±12 | 5 (42) | 12 (100) | 0 (0) | - | - | 2 (17) |
| Healthy | Asian | 10 | 50 ±5 | 6 (60) | 7 (78) | 0 (0) | - | - | - |
| Relatives | Asian | 8 | 34 ±9 | 3 (38) | 6 (75) | 8 (100) | - | - | - |
|  | Total | 90 | 42 ±13 | 41 (46) | 61 (68) | 11 (12) | 11 (52) | 16 (76) | 6 (19) |

Data are expressed as absolute numbers (percentage) or mean ± SD.CD: Crohn’s disease; UC: Ulcerative colitis; Severe behaviour: Stricturing or penetrating disease.

**Table 2 Antibody Positivity and titre according to geography, ethnicity and disease**

|  |  |  |
| --- | --- | --- |
|   | Australia | Hong Kong (all Asian) |
|   | CD | UC | Healthy | CD | UC | Healthy | Relatives |
|   | Caucasian | Caucasian | Asian | Caucasian | Asian |
| Total | 9 | 10 | 10 | 10 | 9 | 12 | 12 | 10 | 8 |
| Antibody Positivity *n* (%) |
| gASCA | 6 (67)a,c | 0 (0) | 1 (10) | 1 (10) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| ALCA | 4 (44)a | 1 (10) | 0 (0) | 2 (20) | 0 (0) | 1 (8) | 1 (8) | 0 (0) | 0 (0) |
| ACCA | 2 (22) | 1 (10) | 0 (0) | 2 (20) | 3 (33) | 1 (8) | 1 (8) | 1 (10) | 0 (0) |
| AMCA | 6 (67)a | 0 (0) | 0 (0) | 1 (10) | 3 (33) | 7 (58)a | 2 (17) | 2 (20) | 2 (25) |
| pANCA | 0 (0) | 7 (70)e | 5 (50)e | 0 (0) | 1 (11) | 3 (25) | 4 (33)e | 0 (0) | 0 (0) |
| No. of positive antibodies *n* (%) |
| At least 1 | 9 (100)a,c | 2 (20) | 1 (10) | 2 (20) | 4 (44) | 7 (58)a | 4 (33) | 2 (20) | 2 (25) |
| At least 2  | 6 (67)a,c | 0 (0) | 0 (0) | 2 (20) | 2 (22) | 2 (17) | 0 (0) | 1 (10) | 0 (0) |
| Antibody/QSS titre median (range) |
| gASCA | 59(146)a,c | 10 (12) | 9 (47) | 17 (45) | 8 (21) | 9 (44) | 2 (39) | 11 (17) | 5 (46) |
| ALCA | 46(79)a | 17 (86) | 14 (38) | 23 (77) | 18 (34) | 27 (69)a | 17 (82) | 17 (18) | 24 (25) |
| ACCA | 50(188) | 39 (101) | 43 (56) | 60 (310) | 76 (135) | 50 (80) | 37 (87) | 46 (77) | 34 (62) |
| AMCA | 111(154)a | 63 (47) | 70 (60) | 79 (59) | 75 (116) | 121 (459)a | 60 (272) | 59 (145) | 74 (94) |
| QSS | 14(5)a | 9 (6) | 10 (6) | 12 (8) | 9 (10) | 13 (10)a | 8 (7) | 8 (10) | 10 (9) |

a*P* < 0.05 *vs* all non- Crohn’s disease (CD) groups combined; c*P* < 0.05 *vs* Hong Kong (HK) Asian CD; e*P* < 0.05 *vs* all non- ulcerative colitis (UC) groups combined. gASCA: Anti-*Saccharomyces cerevisiae*; ALCA: Anti-laminaribioside carbohydrate IgG antibodies;

ACCA: Anti-chitobioside carbohydrate IgA antibodies; AMCA: Anti-mannobioside carbohydrate IgG antibodies; pANCA: Atypical perinuclear anti-neutrophil cytoplasmic antibody; QSS: Quartile sum score.