**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 11753**

**Columns:** **CASE CONTROL STUDY**

**Genetic association of apolipoprotein E polymorphisms with inflammatory bowel disease**

Al-Meghaiseeb ES *et al.* APOE polymorphism in IBD

Ebtissam Saleh Al-Meghaiseeb, Mulfi Mubarak Al-Otaibi, Abdulrahman Al-Robayan, Reem Al-Amro, Ahmd Saad Al-Malki, Misbahul Arfin, Abdulrahman K Al-Asmari

**Ebtissam Saleh Al-Meghaiseeb, Mulfi Mubarak Al-Otaibi, Abdulrahman K Al-Robayan, Reem Al-Amro, Ahmd Saad Al-Malki,** Department of Gasteroenterology, Prince Sultan Military Medical City, Riyadh 11159, Saudi Arabia

**Misbahul Arfin, Abdulrahman K Al-Asmari,** Research Centre, Prince Sultan Military Medical City, Riyadh 11159, Suadi Arabia

**Authors contributions:** Al-Meghaiseeb ES and Al-Robayan A performed clinical examination and collected demographic data; Al-Otaibi MM, Al-Amro R and Al-Malki AS performed clinical examination and searched the literature; Arfin M analyzed genotyping results and drafted the manuscript; Al-Asmari AK designed the study, supervised and edited the manuscript.

**Correspondence to: Abdulrahman K Al-Asmari, Senior Consultant and Director of Research Center,** Department of Gasteroenterology, Prince Sultan Military Medical City**,** P.O. Box 7897**,** Riyadh 11159, Saudi Arabia. abdulrahman.alasmari@gmail.com

**Telephone**: +966-1-4777714 **Fax**: +966-1-4777714

**Received:** June 2, 2014 **Revised:** August 28, 2014

**Accepted:** September 29, 2014

**Published online:**

**Abstract**

**AIM:** To study the association of apolipoprotein E (APOE) polymorphism with the susceptibility of inflammatory bowel disease (IBD) in Saudi patients.

**METHODS:** APOE genotyping was performed to evaluate the allele and genotype frequencies in 378 Saudi subjects including IBD patients (ulcerative colitis = 84, Crohn’s disease = 94) and matched controls (*n* = 200) using polymerase chain reaction and reverse-hybridization techniques.

**RESULTS**: The frequencies of the APOE allele ε2, genotypes ε2/ε3 and ε2/ε4 were significantly higher in the IBD patients than in controls suggesting that ε2 allele and its heterozygous genotypes may increase the susceptibility to IBD. On the contrary the frequencies of allele ε3 and genotype ε3/ε3 were lower in IBD patients as compared to controls suggesting a protective effect of APOE ε3 for IBD. The prevalence of ε4 allele was also higher in patient group compared to that in controls suggesting that ε4 allele may also increase the risk of IBD. Our results also indicated that APOE ε4 allele was associated with early age at onset of IBD. No effect of gender or type of IBD (familial or sporadic) on the frequency distribution of APOE alleles and genotypes was noticed in this study.

**CONCLUSION:** This study shows that APOE polymorphism is associated with risk of developing IBD and early age of onset in Saudi patients. However, this association of APOE polymorphisms with the risk of IBD warrants further studies on large-size population.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Apolipoprotein E;Inflammatory bowel disease; Polymorphism; Saudi

**Core tip:** This study shows that association of apolipoprotein E (APOE) polymorphism is associated with risk of developing inflammatory bowel disease (IBD) in Saudi patients. Allele ε2 and its heterozygous genotypes increase the susceptibility to IBD while ε3 allele and ε3/ε3 genotype are protective for IBD. APOE ε4 allele also increases the risk for IBD and is associated with early age at onset. The frequency distribution of APOE alleles and genotypes is not affected by gender or type of IBD (familial or sporadic).

Al-Meghaiseeb ES, Al-Otaibi MM, Al-Robayan A, Al-Amro R, Al-Malki AS, Arfin M, Al-Asmari AK. Genetic association of Apolipoprotein E polymorphisms with inflammatory bowel disease**.** *World J Gastroenterol* 2014; In press

**INTRODUCTION**

The inflammatory bowel diseases (IBDs), encompassing Crohn’s disease (CD, OMIM 266600) and ulcerative colitis (UC, OMIM 191390), are chronic inflammatory disorders of the gastrointestinal tract. IBD has emerged as a global disease with the increasing incidence and prevalence with time in different parts of the world[1-5]. The precise etiology of IBD is still unknown but available evidence suggests that it is a complex multifactorial disease in which immune dysregulation caused by genetic and/or environmental factors plays an important role[6-8]. IBD appears to be caused by immunogenic responses against environmental factors and/or microbes inhabiting distal ileum and colon of genetically susceptible hosts.

The incidence of IBD is higher in North America and Europe than in Asia and Africa possibly due to the variation in environmental factors and genetic makeup. The hygiene hypothesis was suggested to be responsible for the rising prevalence of various autoimmune and inflammatory disorders in developed populations, which are thought to result from the lack of early exposure to bacterial infections due to good sanitary conditions[9]. The changes in dietary and intestinal microbial milieu has been suggested to play a key pathogenic role in the etiology of IBD, however the precise environmental factors influencing the IBD prevalence have not been determined yet[10]. Intriguingly, the characteristics of western and Asian IBD patients differ in epidemiology, phenotype and genetic susceptibility[11-14] highlighting ethnic variations.

Various epidemiological and population-based studies have indicated that genetic factors contribute to the pathogenesis of IBD[15-17]. Apolipoprotein E (APOE) has an important role in cholesterol and lipid metabolism, and has also been shown to alter both innate and adaptive immune responses[18]. Several studies have indicated that APOE inhibits the production of T lymphocytes and regulates immune reactions by interacting with several cytokines[19-21]. Further, it has been suggested that APOE plays a key role in regulating immune response in various autoimmune diseases[22-24].

The gene encoding APOE is located on chromosome 19. It has 3 polymorphic allleles (ε2, ε3 and ε4) differing from one another by the presence of either C or T nucleotide at codons 112 and 158. These alleles encode three different isoproteins differing significantly in structure and function including receptor binding capacity and lipid metabolism[25].By different combinations of these three alleles, six genotypes (ε2/ε2, ε3/ε3, ε2/ε3, ε3/ε4, ε2/ε4, and ε4/ε4) are formed[26,27]. Though the frequency of these alleles/genotypes vary significantly among different ethnic populations, however APOE ε3/ε3 is the most common genotype and ε3 the most predominant allele in majority of population[28-29]. Several studies have indicated an association between APOE alleles and genotypes with onset and severity of various autoimmune diseases[24,30-33]. Recently association of APOE allele/genotype with UC has been reported in Chinese[34,35]. In this study we examined the APOE allele/genotype frequencies in Saudi CD and UC patients and matched controls.

**MATERIALS AND METHODS**

***Subjects***

A total of 378 Saudi subjects including 178 IBD patients visiting Gastroenterology Clinic and 200 age and sex matched healthy donors visiting community health clinic of Prince Sultan Military Medical City, Riyadh were recruited in this study. Venous blood was collected from all the patients and controls. IBD patients were divided into familial (20) and sporadic forms (158). They were grouped into patients with CD (94 including 56 male, 38 female) aged 17-65 years, with a mean age of 32 years, and patients with UC (84 including 34 male, 50 female) aged 22-68 years, with mean age of 34 years. Two hundred healthy Saudis (120 male and 80 female) were included in the study as controls. None of the controls had any history of IBD, diabetes, rheumatoid arthritis, systemic lupus erythematosus or other autoimmune diseases. The diagnoses of IBD (CD and UC) was based on the conventional endoscopic, radiological, and histological criteria as describe by Lennard-Jones[36]. Patients Information such as age at diagnosis, disease location, disease characteristics, and extraintestinal location were used to divide the patients into groups. Patients with any other autoimmune disease or having clinical features of both UC and CD (intermediate colitis) were excluded from the study. Patients with CD were also assessed on the basis of Montreal classification[37]. This study was approved by the ethical committee of PSMMC and written informed consent was obtained from all the subjects.

***DNA extraction and genotyping***

Genomic DNA was extracted from the blood of IBD patients and controls using QIAampR DNA mini kit (Qiagen CA, United States). APOE genotyping was performed using APOE StripAssayTM kit based on polymerase chain reaction (PCR) and reverse-hybridization technique (ViennaLab Labordiagnostika GmbH, Vienna, Austria). To cross-check the results, the APOE genotyping was also performed by PCR and restriction fragment length polymorphism (RFLP) technique as described earlier[38].

Briefly, genomic DNA (200–300 ng) was amplified in 25 μL reaction tubes for 40 cycles of 94 °C for 30 s, 68 °C for 10 s, 72 °C for 1 min; PCR products obtained were separated by electrophoresis on 1.5% agarose gel in TAE buffer, visualized by ethidium bromide fluorescence. Fragments with the expected size were cut from the gel, purified using GFX PCR DNA Gel band purification kit (GE Healthcare, United Kingdom). Purified DNA was digested with *Hha* I enzyme, separated by agarose gel electrophoresis to identify the genotype. The frequencies of various genotypes in patients and controls were determined and compared. Both the above mentioned procedures yielded completely matching results.

***Statistical analysis***

Frequencies of various alleles and genotypes for APOE polymorphism were analyzed by Fisher’s exact test and the *P*-values < 0.05 were considered as significant. The strength of the association of disease with respect to a particular allele/genotype is expressed by odd ratio interpreted as *relative risk* (RR) according to the method of Woolf as outlined by Schallreuter *et al*[39]. The RR was calculated only for those alleles and genotype which were increased or decreased in IBD patients as compared to normal Saudis. RR was calculated using the following formula:

 RR =

(a) = number of patients expressing the allele or genotype

(b) = number of patients without allele or genotype expression

(c) = number of controls expressing the allele or genotype

(d) = number of controls without allele or genotype expression

The etiologic fraction (EF) indicates the hypothetical genetic component of the disease. EF values of > 0.00-0.99 are significant. It is calculated for positive associations (RR > 1) using the following formula proposed by Savejgaard *et al*[40]:

EF = $\frac{(RR-1)f}{RR}$ $\frac{(RR-1)f}{RR}$, where $f=\frac{a}{a+b}$

Preventive fraction (PF) indicates the hypothetical protective effect of one allele/genotype for a disease. It is calculated for negative associations (RR < 1) using the following formula[40]. Values of < 1.0 indicate the protective effect of an allele/genotype against the manifestation of disease.

PF = $\frac{(1-RR)f}{RR\left(1-f\right)+f } $, where $f=\frac{a}{a+b}$

**RESULTS**

The results of APOE genotyping in the IBD patients and the healthy controls are summarized in Tables 1-5. In both, IBD patient and control groups the genotype distributions were in Hardy-Weinberg equilibrium. The ε2 allele was present in the 7.59% of IBD patients while altogether absent in controls (*P* = 0.0001). The frequency of allele ε4 was also significantly higher in patients compared with that in controls (10.11% *vs* 4.25%, *P* = 0.002, RR = 2.531, EF = 0.411) indicating that allele ε4 is positively associated with IBD with relative risk of 2.53. The frequency of ε3 alleles was significantly lower in the IBD patients (82.30%) than in controls (95.75%, *P* = 0.0001, RR = 0.206, PF = 0.549) (Table 1). The frequency of various genotypes of APOE also showed variations in patient and control groups. The prevalence of genotypes ε2/ε3, and ε2/ε4 was 13.48, and 6.18% in patients while totally absent in control group (*P* = 0.0001, *P* = 0.001, respectively). The difference in the frequencies of the genotype ε3/ε4 was not statistically significant between the patient and control groups (*P* = 0.10, RR = 1.759, EF = 0.256) albeit that there is a trend towards a higher frequency in IBD patients. The frequency of ε3/ε3 genotype was significantly higher in controls than that in IBD patients (*P* = 0.0001, RR = 0.183, PF = 0.637). The genotypes ε2/ε2 and ε4/ε4 were absent in both patients and controls (Table 2). Our results showed that allele ε2, ε4 and genotype ε2/ε3 and ε2/ε4 were associated with IBD and could be a risk factor while allele ε3 and genotype ε3/ε3 might be protective for IBD in Saudis. The frequencies of alleles and genotypes of APOE polymorphism were not significantly different in male and female patients except the frequencies of allele ε3 and homozygous genotype ε3/ε3 which were higher in female patients than male patients. These results indicate that gender plays no significant role in genotype/allele distributions among Saudi patients with IBD (Table 3).

The difference in the frequencies of APOE alleles and genotypes in the CD and UC patients was not significant (Table 4, Figure 1). Moreover, when compared with controls separately, almost similar pattern was noticed for both UC and CD except that the frequency of allele ε3/ε4 was significantly higher in UC patients (*P* = 0.03) but not in CD patients (*P* = 0.66) as compared to that in controls. However, the relative risk values calculated for ε3/ε4 genotype in UC and CD being > 1.0 (RR = 2.34 and RR = 1.28, Table 4) indicated similar positive association for both. Similarly the stratification of IBD patients into familial and sporadic forms showed no significant difference in the frequency distribution of either alleles or genotypes of APOE in two forms of IBD (Table 5). APOE ε4 allele was significantly associated with the early age of onset in IBD (*P* = 0.05). The groups of patients with genotype ε3/ε4 (*n* = 25), and ε2/ε4 (*n* = 11) had lower age of onset than the patients with genotype ε3/ε3 and ε2/ε3.

**DISCUSSION**

Our results showed higher frequency of APOE ε2 allele and predominance of ε2/ε3, ε2/ε4 genotypes in the IBD patients in comparison with matched controls (Tables 1-2) suggesting that allele ε2 carriers are at a higher risk of developing IBD. The APOE ε2 isoprotein differs from the APOE ε3 isoprotein by one amino acid, at position 158, with ε2 containing cysteine, ε3 containing arginine. This single amino acid difference causes a marked reduction in binding capacity of APOE ε2 to the low density lipoprotein family of receptors[25], which in turn results in severe metabolic disturbances, particularly Type III hyperlipidemia. Additionally the two cysteines in APOE ε2 (positions 112 and 158) allow APOE ε2 to form disulfide-linked multimeric protein complexes[41]. These unique properties of APOE ε2 may contribute to its role in the etiology of IBD and other lipid associated diseases.

Disturbances in the lipid, apolipoprotein, lipoprotein profiles and cholesterol efflux in IBD patients have been reported[42-44]. Thus, genetic variations of apoproteins, essential in lipoprotein metabolism may affect susceptibility to IBD. APOE is involved in transport and metabolism of cholesterol, triglyceride and other lipids. The lipid transporting and catabolic activity in APOE-ε2 carriers is significantly slower as compared to ε3 and ε4 carriers due to lowest receptor binding affinity of ε2. Individual with APOE ε2 are unable to efficiently clear lipids from plasma/tissues which facilitates the accumulation of chylomicron, very low density lipoprotein and lipids[45]. It has been suggested that APOE protein might be involved in pathogenesis of diseases via the sequestration of lipids contributing to the epidermal barrier function[46].

Present study also observed a significantly higher frequency of genotype ε2/ε3 in Saudi IBD patients as compared to matched controls (*P* = 0.0001). The genotype ε2/ε3 has been associated with significant imbalance in lipids and lipoprotein metabolism. APOE ε2/ε3 genotype has also been associated with ischemic cerebrovascular diseases[47,48]. Parameters associated with atherosclerosis such as inflammation, carotid intima media thickness (cIMT), homocysteine and insulin resistance are increased in IBD as reported by several researchers[49-53]. In addition, several studies have suggested that IBD is a risk factor for ischaemic heart diseases including atherosclerosis[49,53,54]. Furthermore, it has also been reported that IBD is an independent predictor of hypertriglyceridemia[55] and hypocholesterolemia[56].

Results of this study showed higher frequency of ε4 allele in patient group compared to that in controls (*P* = 0.002, RR = 2.531, EF = 0.411) suggesting that ε4 allele may also increase the risk of IBD. Similarly higher frequency of ε4 allele has been reported in Chinese UC patients[42,43]. These authors suggested that APOE ε4 confers greater risk for the development of UC in Chinese[34]. Our results indicated that allele ε4 increases the risk for both UC and CD in Saudi patients. The allele ε4 of the APOE gene is an established risk factor for low bone mineral density (BMD)[57,58],and the high frequency of APOE ε4 in UC and CD patients may be responsible for low BMD in patients with UC[34,59]. To the best of our knowledge, no published report has indicated any association of APOE polymorphism with CD and this is the first report showing a significant association of APOE polymorphism with both CD and UC. APOE is a multifunctional in nature, and the presence of the APOE ε4 has been associated with an enhanced inflammatory immune response[60-62]. Though the exact mechanisms by which APOE ε4 regulates the innate immune response is far from clear. Significantly higher levels of the pro-inflammatory cytokines TNF-α and IL-6 have been reported in animals expressing the allele ε4 as compared with those with allele ε3[60]. Increased oxidative stress in the APOE ε4 cells has been suggested to contribute to higher cytokine production by enhancing the activation of the nuclear factor-kappa B (NF-κB)[63]. Moreover, increased expression of interleukin 1 beta, MIP-1α, and TNF-α as well as the transactivation of NF-κB have been observed in APOE ε4 macrophages[64]. Recently Li *et al*[34] postulated that the epistatic interaction of MIP-1α and APOE polymorphism may contribute to individual variation in MIP-1α levels in mucosa of UC patients.

Our results also indicated that APOE ε4 allele was associated with early age at onset of IBD, and patients with genotype ε3/ε4 and ε2/ε4 had significantly lower age of onset than the patients with genotype ε3/ε3, ε2/ε3. Polymorphism in APOE gene has been defined as a modifying factor for age at onset in neurodegenerative and autoimmune diseases[30,65,66]. Our results of APOE ε4 allele association with early onset of IBD is in accordance with various reports showing association of allele ε4 with early onset of some autoimmune and neurodegenerative diseases[30,64,67,68]. The APOE ε4 allele is believed to be responsible for reducing the high-density lipoprotein (HDL) and increasing the low-density lipoprotein (LDL) in the high-fat intake individuals[69] which are critical risk factor for occlusive lipid disorders. The implication of APOE ε4 in lipid metabolism and developing of immunologic responses to lipid antigens may contribute to IBD in Saudis with high-fat intake as reported earlier for psoriasis[70-72]. The APOE ε4 has also been linked to lower C-reactive protein (CRP), and it has been suggested that the effect on CRP is a consequence of intrinsic functional differences among the ε2, ε3, and ε4 APOE proteins in the plasma[73]. Our results also showed that association of APOE polymorphism was not affected by the sex of the host and the association was similar in both CD and UC.

In conclusion, this study shows a significant relation between APOE polymorphisms and IBD. Allele 𝜀2 is associated with increased susceptibility for IBD, whereas allele 𝜀3 may be protective for IBD in Saudis. In addition, allele 𝜀4 may be a risk factor of severity or early onset of IBD. However, this association of APOE polymorphisms with the risk of IBD warrants further studies with larger population. Similar studies on different ethnic populations will be helpful in defining the role of APOE as a putative pharmacological target for IBD.

**ACKNOWLEDGMENT**

The authors thank S. Sadaf Rizvi and Mohammad Al-Asmari for their help with laboratory work.

**COMMENTS**

***Background***

The inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn’s disease (CD) are chronic inflammatory disorders of the gastrointestinal tract. The precise etiology of IBD is still unknown but available data suggests a definite role of immune dysregulation caused by genetic and/or environmental factors. Association of apolipoprotein E (APOE) plays a pivotal role in immunogenic response by interacting with several cytokines and regulating macrophage functions. In view of the above fact, the role of APOE polymorphism was studied in Saudi patients with IBD.

***Research frontiers***

The gene encoding APOE is located on chromosome 19 and has three polymorphic alleles (ε2, ε3 and ε4) differing from one another by the presence of either C or T nucleotide at codons 112 and 158. Alleles ε2, ε3 and ε4 encode different APOE isoproteins which not only differ in structure but also in function including receptor binding capacity and lipid metabolism.The frequency of APOE alleles vary significantly among different ethnic populations.Several studies have indicated an association between APOE alleles and genotypes with onset and severity of various autoimmune diseases. Such association studies will help in the better prognosis and treatment of various autoimmune diseases.

***Innovations and breakthroughs***

Saudi population with sedentary life style, lack of exercise, unique dietary habits of rich fat, sugar and red meat diet has an increasing prevalence of obesity and lipid disorders. Being a closed society with high rate of consanguinity, it is ideal for genetic association studies however, the genetic studies on IBD/other autoimmune disorder in KSA and other Arab countries are scanty and inconclusive. This is the first report from Saudi population showing the role of APOE polymorphism in the etiology of UC and CD.

***Applications***

The study results suggest that APOE polymorphism is associated with risk of developing IBD in Saudi patients. Allele ε2 and its heterozygous genotypes increase the susceptibility to IBD while ε3 allele and ε3/ε3 genotype are protective for IBD. APOE å4 allele also increases the risk for IBD and is associated with early age at onset. Similar studies on different ethnic populations will be helpful in defining the role of APOE as a putative pharmacological target for IBD. Understanding this relationship may be potentially useful for predicting the vulnerability of individuals/population to various autoimmune diseases.

***Peer review***

In this study the authors studied the association between APOE polymorphism and IBD in a Saudi Arabian Population.

**REFERENCES**

|  |
| --- |
| 1 **Cosnes J,** Gower–Rousseau C, Seksik P, Cortot A. Epidemiology and Natural History of Inflammatory Bowel diseases. G*astroenterology* 2011; **140**:1785-1794 [PMID: 21530745]2 **Fadda MA**, Peedikayil MC, Kagevi I, Kahtani KA, Ben AA, Al HI, Sohaibani FA, Quaiz MA, Abdulla M, Khan MQ, Helmy A. Inflammatory bowel disease in Saudi Arabia: a hospital-based clinical study of 312 patients. *Ann Saudi Med* 2012; **32**: 276-282 [PMID: 22588439 DOI: 10.5144/0256-4947]3 **Gunisetty S**, Tiwari S, Bardia A, Phanibhushan M, Satti V, Habeeb M, Khan A. The epidemiology and prevalence of Ulcerative colitis in the South of India. *O J Immunol* 2012; **2**: 144-148 [DOI: 10.4236/oji.2012.24018]4 **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]5 **Zeng Z**, Zhu Z, Yang Y, Ruan W, Peng X, Su Y, Peng L, Chen J, Yin Q, Zhao C, Zhou H, Yuan S, Hao Y, Qian J, Ng SC, Chen M, Hu P. Incidence and clinical characteristics of inflammatory bowel disease in a developed region of Guangdong Province, China: a prospective population-based study. *J Gastroenterol Hepatol* 2013; **28**: 1148-1153 [PMID: 23432198 DOI: 10.1111/jgh.12164]6 **Podolsky DK**. Inflammatory bowel disease. *N Engl J Med* 2002; **347**: 417-429 [PMID: 12167685 DOI: 10.1056/NEJMra020831]7 **Strober W**, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. *J Clin Invest* 2007; **117**: 514-521 [PMID: 17332878 DOI: 10.1172/]8 **Xavier RJ**, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; **448**: 427-434 [PMID: 17653185 DOI: 10.1038/nature06005]9 **Gent AE**, Hellier MD, Grace RH, Swarbrick ET, Coggon D. Inflammatory bowel disease and domestic hygiene in infancy. *Lancet* 1994; **343**: 766-767 [PMID: 7907734 DOI: 10.1016/S0140-6736(94)91841-4]10 **Matricon J**, Barnich N, Ardid D. Immunopathogenesis of inflammatory bowel disease. *Self Nonself* 2010; **1**: 299-309 [PMID: 21487504 DOI: 10.4161/self.1.4.13560]11 **Yang SK**, Hong WS, Min YI, Kim HY, Yoo JY, Rhee PL, Rhee JC, Chang DK, Song IS, Jung SA, Park EB, Yoo HM, Lee DK, Kim YK. Incidence and prevalence of ulcerative colitis in the Songpa-Kangdong District, Seoul, Korea, 1986-1997. *J Gastroenterol Hepatol* 2000; **15**: 1037-1042 [PMID: 11059934 DOI: 10.1046/j.1440-1746.2000.02252.x]12 **Ling KL**, Ooi CJ, Luman W, Cheong WK, Choen FS, Ng HS. Clinical characteristics of ulcerative colitis in Singapore, a multiracial city-state. *J Clin Gastroenterol* 2002; **35**: 144-148 [PMID: 12172359]13 **Inoue N**, Tamura K, Kinouchi Y, Fukuda Y, Takahashi S, Ogura Y, Inohara N, Núñez G, Kishi Y, Koike Y, Shimosegawa T, Shimoyama T, Hibi T. Lack of common NOD2 variants in Japanese patients with Crohn's disease. *Gastroenterology* 2002; **123**: 86-91 [PMID: 12105836]14 **Leong RW**, Lau JY, Sung JJ. The epidemiology and phenotype of Crohn's disease in the Chinese population. *Inflamm Bowel Dis* 2004; **10**: 646-651 [PMID: 15472528 DOI: 10.1097/00054725-200409000-00022]15 **Kim ES**, Kim WH. Inflammatory bowel disease in Korea: epidemiological, genomic, clinical, and therapeutic characteristics. *Gut Liver* 2010; **4**: 1-14 [PMID: 20479907 DOI: 10.5009/gnl.2010.4.1.1]16 **Yun J**, Xu CT, Pan BR. Epidemiology and gene markers of ulcerative colitis in the Chinese. *World J Gastroenterol* 2009; **15**: 788-803 [PMID: 19230040 DOI: 10.3748/]17 **Waterman M**, Xu W, Stempak JM, Milgrom R, Bernstein CN, Griffiths AM, Greenberg GR, Steinhart AH, Silverberg MS. Distinct and overlapping genetic loci in Crohn's disease and ulcerative colitis: correlations with pathogenesis. *Inflamm Bowel Dis* 2011; **17**: 1936-1942 [PMID: 21830272 DOI: 10.1002/ibd.21579]18 **Laskowitz DT**, Lee DM, Schmechel D, Staats HF. Altered immune responses in apolipoprotein E-deficient mice. *J Lipid Res* 2000; **41**: 613-620 [PMID: 10744782]19 **Yin M**, Zhang L, Sun XM, Mao LF, Pan J. Lack of apoE causes alteration of cytokines expression in young mice liver. *Mol Biol Rep* 2010; **37**: 2049-2054 [PMID: 19644765 DOI: 10.1007/s11033-009-9660-x]20 **Baitsch D**, Bock HH, Engel T, Telgmann R, Müller-Tidow C, Varga G, Bot M, Herz J, Robenek H, von Eckardstein A, Nofer JR. Apolipoprotein E induces antiinflammatory phenotype in macrophages. *Arterioscler Thromb Vasc Biol* 2011; **31**: 1160-1168 [PMID: 21350196 DOI: 10.1161/ATVBAHA.111.222745]21 **Zhang H**, Wu LM, Wu J. Cross-talk between apolipoprotein E and cytokines. *Mediators Inflamm* 2011; **2011**: 949072 [PMID: 21772670 DOI: 10.1155/2011/949072]22 **Zhang HL**, Wu J. Apolipoprotein E4 and psoriasis. *Arch Dermatol Res* 2010; **302**: 151 [PMID: 20033191 DOI: 10.1007/s00403-009-1015-x]23 **Postigo J**, Genre F, Iglesias M, Fernández-Rey M, Buelta L, Carlos Rodríguez-Rey J, Merino J, Merino R. Exacerbation of type II collagen-induced arthritis in apolipoprotein E-deficient mice in association with the expansion of Th1 and Th17 cells. *Arthritis Rheum* 2011; **63**: 971-980 [PMID: 21225684 DOI: 10.1002/]24 **Song LJ**, Liu WW, Fan YC, Qiu F, Chen QL, Li XF, Ding F. The positive correlations of apolipoprotein E with disease activity and related cytokines in systemic lupus erythematosus. *Diagn Pathol* 2013; **8**: 175 [PMID: 24144108 DOI: 10.1186/1746-1596-8-175]25 **Artiga MJ**, Bullido MJ, Sastre I, Recuero M, García MA, Aldudo J, Vázquez J, Valdivieso F. Allelic polymorphisms in the transcriptional regulatory region of apolipoprotein E gene. *FEBS Lett* 1998; **421**: 105-108 [PMID: 9468288]26 **Utermann G**, Hees M, Steinmetz A. Polymorphism of apolipoprotein E and occurrence of dysbetalipoproteinaemia in man. *Nature* 1977; **269**: 604-607 [PMID: 199847]27 **Hatters DM**, Peters-Libeu CA, Weisgraber KH. Apolipoprotein E structure: insights into function. *Trends Biochem Sci* 2006; **31**: 445-454 [PMID: 16820298 DOI: 10.1016/j.tibs.2006.06.008]28 **Yin R**, Pan S, Wu J, Lin W, Yang D. Apolipoprotein E gene polymorphism and serum lipid levels in the Guangxi Hei Yi Zhuang and Han populations. *Exp Biol Med* (Maywood) 2008; **233**: 409-418 [PMID: 18367629 DOI: 10.3181/0709-RM-254]29 **Al-Dabbagh NM**, Al-Dohayan N, Arfin M, Tariq M. Apolipoprotein E polymorphisms and primary glaucoma in Saudis. *Mol Vis* 2009; **15**: 912-919 [PMID: 19421411]30 **Pertovaara M**, Lehtimäki T, Rontu R, Antonen J, Pasternack A, Hurme M. Presence of apolipoprotein E epsilon4 allele predisposes to early onset of primary Sjogren's syndrome. *Rheumatology* (Oxford) 2004; **43**: 1484-1487 [PMID: 15328426 DOI: 10.1093/rheumatology/keh383]31 **Mooyaart AL**, Valk EJ, van Es LA, Bruijn JA, de Heer E, Freedman BI, Dekkers OM, Baelde HJ. Genetic associations in diabetic nephropathy: a meta-analysis. *Diabetologia* 2011; **54**: 544-553 [PMID: 21127830 DOI: 10.1007/s00125-010-1996-1]32 **Maehlen MT**, Provan SA, de Rooy DP, van der Helm-van Mil AH, Krabben A, Saxne T, Lindqvist E, Semb AG, Uhlig T, van der Heijde D, Mero IL, Olsen IC, Kvien TK, Lie BA. Associations between APOE genotypes and disease susceptibility, joint damage and lipid levels in patients with rheumatoid arthritis. *PLoS One* 2013; **8**: e60970 [PMID: 23613766]33 **Al Harthi F**, Huraib GB, Zouman A, Arfin M, Tariq M, Al-Asmari A. Apolipoprotein E gene polymorphism and serum lipid profile in Saudi patients with psoriasis. *Dis Markers* 2014; **2014**: 239645 [PMID: 24782577]34 **Li K**, Wang B, Sui H, Liu S, Yao S, Guo L, Mao D. Polymorphisms of the macrophage inflammatory protein 1 alpha and ApoE genes are associated with ulcerative colitis. *Int J Colorectal Dis* 2009; **24**: 13-17 [PMID: 18762952]35 **Liang WD**, Yang JF, Yan J, Jin J, Li KS, Li JS, Bi YT. [Association of combined polymorphisms in MIP-1α and ApoE genes with the susceptibility of inflammatory bowel disease]. *Zhonghua Yi Xue Za Zhi* 2011; **91**: 1250-1253 [PMID: 21756796]36 **Lennard-Jones JE**. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989; **170**: 2-6; discussion 16-9 [PMID: 2617184]37 **Silverberg MS**, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, Caprilli R, Colombel JF, Gasche C, Geboes K, Jewell DP, Karban A, Loftus EV, Peña AS, Riddell RH, Sachar DB, Schreiber S, Steinhart AH, Targan SR, Vermeire S, Warren BF. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** Suppl A: 5A-36A [PMID: 16151544]38 **Al- Dabbagh NM**, Al-Saleh S, Al-Dohayan N, Al-Asmari AK, Arfin M, Tariq M. **The role of Apolipoprotein E gene polymorphisms in Primary Glaucoma and Pseudoexfoliation Syndrome. In:** Rumelt S.Glaucoma - Basic and Clinical Aspects.: *In Tech* 2013; 130-156 [DOI: 10.5772/54614]39 **Schallreuter KU**, Levenig C, Kühnl P, Löliger C, Hohl-Tehari M, Berger J. Histocompatibility antigens in vitiligo: Hamburg study on 102 patients from northern Germany. *Dermatology* 1993; **187**: 186-192 [PMID: 8219421]40 **Svejgaard A**, Platz P, Ryder LP. HLA and disease 1982--a survey. *Immunol Rev* 1983; **70**: 193-218 [PMID: 6339368]41 **Halford J**, Mazeika G, Slifer S, Speer M, Saunders AM, Strittmatter WJ, Morgenlander JC. APOE2 allele increased in tardive dyskinesia. *Mov Disord* 2006; **21**: 540-542 [PMID:16261623 DOI: 10.1002/mds.20768]42**Agouridis AP**, Elisaf M, Milionis HJ. An overview of lipid abnormalities in patients with inflammatory bowel disease. *Ann Gastroenterol* 2011; **24**: 181-187 [PMID: 24713706]43 **Koutroubakis IE**, Malliaraki N, Vardas E, Ganotakis E, Margioris AN, Manousos ON, Kouroumalis EA. Increased levels of lipoprotein (a) in Crohn's disease: a relation to thrombosis? *Eur J Gastroenterol Hepatol* 2001; **13**: 1415-1419 [PMID: 11742189]44 **Ripollés Piquer B**, Nazih H, Bourreille A, Segain JP, Huvelin JM, Galmiche JP, Bard JM. Altered lipid, apolipoprotein, and lipoprotein profiles in inflammatory bowel disease: consequences on the cholesterol efflux capacity of serum using Fu5AH cell system. *Metabolism* 2006; **55**: 980-988 [PMID: 16784973 DOI:10.1016/ j.metabol.2006.03.006]45 **Miyauchi H**. [Immunohistochemical study for the localization of apolipoprotein AI, B100, and E in normal and psoriatic skin]. *Igaku Kenkyu* 1991; **61**: 79-86 [PMID: 1823509]46 **Furumoto H**, Nakamura K, Imamura T, Hamamoto Y, Shimizu T, Muto M, Asagami C. Association of apolipoprotein allele epsilon 2 with psoriasis vulgaris in Japanese population. *Arch Dermatol Res* 1997; **289**: 497-500 [PMID: 9341968]47 **Couderc R**, Mahieux F, Bailleul S, Fenelon G, Mary R, Fermanian J. Prevalence of apolipoprotein E phenotypes in ischemic cerebrovascular disease. A case-control study. *Stroke* 1993; **24**: 661-664 [PMID: 8488520 DOI: 10.1161/01.STR. 24.5.661]48 **Hsia SH**, Connelly PW, Hegele RA. Restriction isotyping of apolipoprotein E R145C in type III hyperlipoproteinemia. *J Investig Med* 1995; **43**: 187-194 [PMID: 7735921]49 **Danesh J**, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004; **350**: 1387-1397 [PMID: 15070788 DOI: 10.1056/NEJMoa032804]50 **Papa A**, Santoliquido A, Danese S, Covino M, Di Campli C, Urgesi R, Grillo A, Guglielmo S, Tondi P, Guidi L, De Vitis I, Fedeli G, Gasbarrini G, Gasbarrini A. Increased carotid intima-media thickness in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2005; **22**: 839-846 [PMID: 16225493 DOI: 10.1111/j.1365-2036.2005.02657.x]51 **Danese S**, Sgambato A, Papa A, Scaldaferri F, Pola R, Sans M, Lovecchio M, Gasbarrini G, Cittadini A, Gasbarrini A. Homocysteine triggers mucosal microvascular activation in inflammatory bowel disease. *Am J Gastroenterol* 2005; **100**: 886-895 [PMID: 15784037]52 **Bregenzer N**, Hartmann A, Strauch U, Schölmerich J, Andus T, Bollheimer LC. Increased insulin resistance and beta cell activity in patients with Crohn's disease. *Inflamm Bowel Dis* 2006; **12**: 53-56 [PMID: 16374259]53 **Dagli N**, Poyrazoglu OK, Dagli AF, Sahbaz F, Karaca I, Kobat MA, Bahcecioglu IH. Is inflammatory bowel disease a risk factor for early atherosclerosis? *Angiology* 2010; **61**: 198-204 [PMID: 19398421 DOI: 10.1177/0003319709333869]54 **Rungoe C**, Basit S, Ranthe MF, Wohlfahrt J, Langholz E, Jess T. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. *Gut* 2013; **62**: 689-694 [PMID: 22961677 DOI: 10.1136/gutjnl-2012-303285]55 **Visschers RG**, Olde Damink SW, Schreurs M, Winkens B, Soeters PB, van Gemert WG. Development of hypertriglyceridemia in patients with enterocutaneous fistulas. *Clin Nutr* 2009; **28**: 313-317 [PMID: 19327876 DOI: 10.1016/j.clnu.2009.03.001]56 **Crook MA**, Velauthar U, Moran L, Griffiths W. Hypocholesterolaemia in a hospital population. *Ann Clin Biochem* 1999; **36** (Pt 5): 613-616 [PMID: 10505211]57 **Shiraki M**, Shiraki Y, Aoki C, Hosoi T, Inoue S, Kaneki M, Ouchi Y. Association of bone mineral density with apolipoprotein E phenotype. *J Bone Miner Res* 1997; **12**: 1438-1445 [PMID: 9286760 DOI: 10.1359/jbmr.1997.12.9.1438]58 **Wong SY**, Lau EM, Li M, Chung T, Sham A, Woo J. The prevalence of Apo E4 genotype and its relationship to bone mineral density in Hong Kong Chinese. *J Bone Miner Metab* 2005; **23**: 261-265 [PMID: 15838630]59 **Ulivieri FM**, Lisciandrano D, Ranzi T, Taioli E, Cermesoni L, Piodi LP, Nava MC, Vezzoli M, Bianchi PA. Bone mineral density and body composition in patients with ulcerative colitis. *Am J Gastroenterol* 2000; **95**: 1491-1494 [PMID: 10894585]60 **Lynch JR**, Tang W, Wang H, Vitek MP, Bennett ER, Sullivan PM, Warner DS, Laskowitz DT. APOE genotype and an ApoE-mimetic peptide modify the systemic and central nervous system inflammatory response. *J Biol Chem* 2003; **278**: 48529-48533 [PMID: 14507923 DOI: 10.1074/jbc.M306923200]61 **Jofre-Monseny L**, Minihane AM, Rimbach G. Impact of apoE genotype on oxidative stress, inflammation and disease risk. Mol Nutr Food Res 2008; 52: 131-145 [DOI: 10.1002/mnfr.20070032\*2]62 **Vitek MP**, Brown CM, Colton CA. APOE genotype-specific differences in the innate immune response. *Neurobiol Aging* 2009; **30**: 1350-1360 [PMID: 18155324 DOI: 10.1016/j.neurobiolaging.2007.11.014]63 **Ophir G**, Amariglio N, Jacob-Hirsch J, Elkon R, Rechavi G, Michaelson DM. Apolipoprotein E4 enhances brain inflammation by modulation of the NF-kappaB signaling cascade. *Neurobiol Dis* 2005; **20**: 709-718 [PMID: 15979312 DOI: org/10.1016/j.nbd.2005.05.002]64 **Jofre-Monseny L**, Loboda A, Wagner AE, Huebbe P, Boesch-Saadatmandi C, Jozkowicz A, Minihane AM, Dulak J, Rimbach G. Effects of apoE genotype on macrophage inflammation and heme oxygenase-1 expression. *Biochem Biophys Res Commun* 2007; **357**: 319-324 [PMID: 17416347 DOI: 10.1016/j.bbrc.2007.03.150]65 **Kwon OD**, Khaleeq A, Chan W, Pavlik VN, Doody RS. Apolipoprotein E polymorphism and age at onset of Alzheimer's disease in a quadric ethnic sample. *Dement Geriatr Cogn Disord* 2010; **30**: 486-491 [PMID: 21252542 DOI: 10.1159/000322368]66 **Peng H**, Wang C, Chen Z, Sun Z, Jiao B, Li K, Huang F, Hou X, Wang J, Shen L, Xia K, Tang B, Jiang H. The APOE ε2 allele may decrease the age at onset in patients with spinocerebellar ataxia type 3 or Machado-Joseph disease from the Chinese Han population. *Neurobiol Aging* 2014; **35**: 2179.e15-2179.e18 [PMID: 24746364 DOI: 10.1016/j.neurobiolaging]67 **Harwood DG**, Barker WW, Ownby RL, St George-Hyslop P, Mullan M, Duara R. Apolipoprotein E polymorphism and age of onset for Alzheimer's disease in a bi-ethnic sample. *Int Psychogeriatr* 2004; **16**: 317-326 [PMID: 15559755]68 **Kampman O**, Anttila S, Illi A, Mattila KM, Rontu R, Leinonen E, Lehtimäki T. Apolipoprotein E polymorphism is associated with age of onset in schizophrenia. *J Hum Genet* 2004; **49**: 355-359 [PMID: 15221639 DOI: 10.1007/s10038-004-0157-0]69 **Grant WB**. A multicountry ecological study of risk-modifying factors for prostate cancer: apolipoprotein E epsilon4 as a risk factor and cereals as a risk reduction factor. *Anticancer Res* 2010; **30**: 189-199 [PMID: 20150635]70 **Kelly ME**, Clay MA, Mistry MJ, Hsieh-Li HM, Harmony JA. Apolipoprotein E inhibition of proliferation of mitogen-activated T lymphocytes: production of interleukin 2 with reduced biological activity. *Cell Immunol* 1994; **159**: 124-139 [PMID: 7994749]71 **Koga T**, Duan H, Urabe K, Furue M. In situ localization of CD83-positive dendritic cells in psoriatic lesions. *Dermatology* 2002; **204**: 100-103 [PMID: 11937733]72 **Oestreicher JL**, Walters IB, Kikuchi T, Gilleaudeau P, Surette J, Schwertschlag U, Dorner AJ, Krueger JG, Trepicchio WL. Molecular classification of psoriasis disease-associated genes through pharmacogenomic expression profiling. *Pharmacogenomics J* 2001; **1**: 272-287 [PMID: 11911124]73 **Chasman DI**, Kozlowski P, Zee RY, Kwiatkowski DJ, Ridker PM. Qualitative and quantitative effects of APOE genetic variation on plasma C-reactive protein, LDL-cholesterol, and apoE protein. *Genes Immun* 2006; **7**: 211-219 [PMID: 16511556 DOI:10.1038/sj. gene] |

**P-Reviewers:** Il Kim T, Kochhar R, Sperti C **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Table 1 Apolipoprotein E alleles frequencies in inflammatory bowel disease patients and matched controls**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Allele** | **IBD (*n* = 356)** | **Control (*n* = 400)** | ***P* value** | **RR** | **EF2/PF** |
| **N** | **Frequency %** | **N** | **Frequency %** |
| ε3 | 293 | 82.30 | 383 | 95.75 | 0.00011 | 0.206 | 0.549 |
| ε4 | 36 | 10.11 | 17 | 4.25 | 0.0021 | 2.531 | 0.411**2** |
| ε2 | 27 | 7.59 | 0 | 0 | 0.00011 | - | - |

1Statistically significant, 2Number of alleles. IBD: Inflammatory bowel disease; RR: Relative risk; EF: Etiological fraction; PF: Preventive fraction.

**Table 2 Apolipoprotein E genotypes frequencies in inflammatory bowel disease patients and matched controls**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Genotype** | **IBD (*n* = 178)** | **Control (*n* =200)** | ***P v*alue** | **RR** | **EF1/PF** |
| **N** | **Frequency %** | **N** | **Frequency %** |
| ε3/ε3 | 118 | 66.29 | 183 | 91.5 | 0.00011 |  0.183 | 0.637 |
| ε3/ε4 | 25 | 14.05 | 17 | 8.5 | 0.101 | 1.759 | 0.256**†** |
| ε2/ε3 | 24 | 13.48 | 0 | 0 | 0.00011 | - | - |
| ε2/ε4 | 11 | 6.18 | 0 | 0 | 0.0011 | - | - |
| ε2/ε2 | 0 | 0 | 0 | 0 | - | - | - |
| ε4/ε4 | 0 | 0 | 0 | 0 | **-** | - | - |

1Statistically significant; RR: Relative risk; N: Number of subjects; EF: Etiological fraction; IBD: Inflammatory bowel disease; PF: Preventive fraction.

**Table 3 Comparison of apolipoprotein E genotypes and alleles in male and female inflammatory bowel disease patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Genotype/Allele** |  **Male (*n* = 90)** |  **Female (*n* = 88)** | ***P* value** |
| **N** | **Frequency %** | **N** | **Frequency %** |
| ε3/ε3 | 66 | 73.33 | 52 | 59.09 | 0.051 |
| ε3/ε4 | 11 | 12.22 | 14 | 15.91 | 0.52 |
| ε2/ε3 | 9 | 10.00 | 15 | 17.05 | 0.19 |
| ε2/ε4 | 4 | 4.45 | 7 | 7.95 | 0.36 |
| ε3 | 152 | 84.45 | 133 | 75.57 | 0.04 1 |
| ε4 | 13 | 7.22 | 21 | 11.93 | 0.15 |
| ε2 | 15 | 8.33 | 22 | 12.50 | 0.22 |

N: Number of subjects; 1Statistically significant.

**Table 4 Comparison of apolipoprotein E genotypes and alleles in Crohn's disease and ulcerative colitis patients and controls**

|  |  |  |  |
| --- | --- | --- | --- |
| **Genotype/Allele** |  **CD (*n* = 94 )** |  **UC (*n* = 84)** |  **Control (*n* = 200)** |
| **N** | **Frequency %** | **N** | **Frequency %** | **N** | **Frequency %** |
| ε3/ε3 | 63 | 67.02a | 55 | 65.48a | 183 | 91.5 |
| ε3/ε4 | 10 | 10.64**2** | 15 | 17.86a **1** | 17 | 8.5 |
| ε2/ε3 | 14 | 14.89a | 10 | 11.90a | 0 | 0 |
| ε2/ε4 | 7 | 7.45a | 4 | 4.76a | 0 | 0 |
| ε3 | 150 | 79.79a | 135 | 80.36a | 383 | 95.75 |
| ε4 | 21 | 11.17a  | 19 | 11.31a | 17 | 4.25 |
| ε2 | 17 | 9.04 a | 14 | 8.33a | 0 | 0 |

 N: Number of subjects; a*P* < 0.05*vs* the frequency in controls; **1**Relative risk= 2.34, **2**Relative risk = 1.28. CD: Crohn's disease; UC: Ulcerative colitis.

**Table 5 Comparison of apolipoprotein E genotypes and alleles in familial and sporadic inflammatory bowel disease patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Genotype/****Allele** | **Familial (*n* = 20)** | **Sporadic (*n* = 158)** | ***P* value** |
| **N** | **Frequency %** | **N** | **Frequency %** |
| ε3/ε3 | 14 | 70 | 104 | 65.82 | 0.80 |
| ε3/ε4 | 4 | 20 | 21 | 13.30 | 0.49 |
| ε2/ε3 | 2 | 10 | 22 | 13.92 | 1.00 |
| ε2/ε4 | 0 | 0 | 11 | 06.96 | 0.61 |
| ε3 | 34 | 85 | 251 | 79.43 | 0.52 |
| ε4 | 4 | 10 | 32 | 10.13 | 1.00 |
| ε2 | 2 | 5 | 33 | 10.44 | 0.40 |

N: Number of subjects; EF: Etiological fraction; PF: Preventive fraction.

**Figure 1 Comparison of apolipoprotein E genotypes and alleles in Crohn's disease and ulcerative colitis patients and controls**. CD: Crohn's disease; UC: Ulcerative colitis.