

Case Control Study

Genetic association of apolipoprotein E polymorphisms with inflammatory bowel disease

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 Al-Robayan, Reem Al-Amro, Ahmd Saad Al-Malki, Department of Gastroenterology, Prince Sultan Military Medical City, Riyadh 11159, Saudi Arabia
Misbahul Arfin, Abdulrahman K Al-Asmari, Research Center, Prince Sultan Military Medical City, Riyadh 11159, Saudi Arabia
Author contributions: Al-Meghaiseeb ES, Al-Robayan A, Al-Otaibi MM, Al-Amro R and Al-Malki AS performed clinical examinations; Al-Meghaiseeb ES and Al-Robayan A collected demographic data; Al-Otaibi MM, Al-Amro R and Al-Malki AS searched the literature; Arfin M analyzed genotyping results and drafted the manuscript; and Al-Asmari AK designed the study, supervised and edited the manuscript.

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Correspondence to: Abdulrahman K Al-Asmari, Senior Consultant and Director of Research Center, 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

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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 with ulcerative colitis ($n = 84$) or Crohn's disease ($n = 94$) and matched controls ($n = 200$) using polymerase chain reaction and reverse-hybridization techniques.

RESULTS: The frequencies of the APOE $\epsilon 2$ allele and $\epsilon 2/\epsilon 3$ and $\epsilon 2/\epsilon 4$ genotypes were significantly higher in IBD patients than in controls ($P < 0.05$), suggesting that the $\epsilon 2$ allele and its heterozygous genotypes may increase the susceptibility to IBD. On the contrary, the frequencies of the $\epsilon 3$ allele and $\epsilon 3/\epsilon 3$ genotype were lower in IBD patients as compared to controls, suggesting a protective effect of APOE $\epsilon 3$ for IBD. The prevalence of the $\epsilon 4$ allele was also higher in the patient group compared to controls, suggesting that the $\epsilon 4$ allele may also increase the risk of IBD. Our results also indicated that the APOE $\epsilon 4$ allele was associated with an early age of IBD onset. 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: APOE polymorphism is associated with risk of developing IBD and early age of onset in Saudi patients, though further studies with a large-size population are warranted.

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

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Abstract

AIM: To study the association of apolipoprotein E (APOE) polymorphisms with the susceptibility of

Core tip: This study shows apolipoprotein E (APOE) polymorphism is associated with risk of developing inflammatory bowel disease (IBD) in Saudi patients.

Allele $\epsilon 2$ and its heterozygous genotypes increase the susceptibility to IBD, whereas the $\epsilon 3$ allele and $\epsilon 3/\epsilon 3$ genotype are protective for IBD. The APOE $\epsilon 4$ 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).

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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 increasing incidence and prevalence 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 the 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 are thought to play a key pathogenic role in the etiology of IBD, however the precise environmental factors influencing 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 epidemiologic 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 alleles ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$) differing from one another by the presence of either a 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 ($\epsilon 2/\epsilon 2$, $\epsilon 3/\epsilon 3$, $\epsilon 2/\epsilon 3$, $\epsilon 3/\epsilon 4$, $\epsilon 2/\epsilon 4$, and $\epsilon 4/\epsilon 4$) are formed^[26,27]. Although the frequency of these alleles/genotypes varies significantly among different ethnic populations, APOE $\epsilon 3/\epsilon 3$ is the most common genotype and $\epsilon 3$ the most predominant allele in majority of the 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 patients^[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 the Gastroenterology Clinic and 200 age- and sex-matched healthy donors visiting the 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 ($n = 20$) and sporadic ($n = 158$) forms. They were grouped into patients with CD ($n = 94$, including 56 men and 38 women) with a mean age of 32 years (range: 17-65 years), and patients with UC ($n = 84$, including 34 men and 50 women) with mean age of 34 years (range: 22-68 years). Two hundred healthy Saudis (120 men and 80 women) 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, radiologic, and histologic criteria as describe by Lennard-Jones^[36]. Patient 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 the Montreal classification^[37]. This study was approved by the ethical committee of PSMC 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 QIAamp DNA mini kit (Qiagen, Venlo, Limburg, the Netherlands). APOE genotyping was performed using an APOE StripAssay

Table 1 Apolipoprotein E allele frequencies *n* (%)

Allele	IBD (<i>n</i> = 356)	Control (<i>n</i> = 400)	<i>P</i> value	RR	EF/PF
ε3	293 (82.30)	383 (95.75)	< 0.01	0.206	0.549
ε4	36 (10.11)	17 (4.25)	< 0.01	2.531	0.411
ε2	27 (7.59)	0 (0)	< 0.01	-	-

EF: Etiologic fraction; IBD: Inflammatory bowel disease; PF: Preventive fraction; RR: Relative risk; *n*: Number of alleles.

Table 2 Apolipoprotein E genotype frequencies *n* (%)

Genotype	IBD (<i>n</i> = 178)	Control (<i>n</i> = 200)	<i>P</i> value	RR	EF/PF
ε3/ε3	118 (66.29)	183 (91.5)	< 0.01	0.183	0.637
ε3/ε4	25 (14.05)	17 (8.5)	0.10	1.759	0.256
ε2/ε3	24 (13.48)	0 (0)	< 0.01	-	-
ε2/ε4	11 (6.18)	0 (0)	< 0.01	-	-
ε2/ε2	0 (0)	0 (0)	-	-	-
ε4/ε4	0 (0)	0 (0)	-	-	-

EF: Etiologic fraction; IBD: Inflammatory bowel disease; PF: Preventive fraction; RR: Relative risk; *n*: Number of alleles.

kit based on a PCR and reverse-hybridization technique (ViennaLab Diagnostics GmbH, Vienna, Austria). To cross-check the results, the APOE genotyping was also performed by PCR and restriction fragment length polymorphism technique as previously described^[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, and visualized by ethidium bromide fluorescence. Fragments with the expected size were cut from the gel, purified using a GFX PCR DNA Gel band purification kit (GE Healthcare, Little Chalfont, Buckinghamshire, UK). Purified DNA was digested with *HhaI* enzyme and 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 a *P* < 0.05 was 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 genotypes that were increased or decreased in IBD patients as compared to normal Saudis. RR was calculated using the following formula:

$$RR = (a \times d) / (b \times c)$$

Where *a* is number of patients expressing the allele or genotype; *b* is the number of patients without allele or genotype expression; *c* is number of controls expressing the allele or genotype; and *d* is the 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 Svegaard *et al.*^[40]:

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

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]:

$$PF = (1-RR)/[RR(1-f)] + f, \text{ where } f = a/(a+b)$$

Values of < 1.0 indicate the protective effect of an allele/genotype against the manifestation of disease.

RESULTS

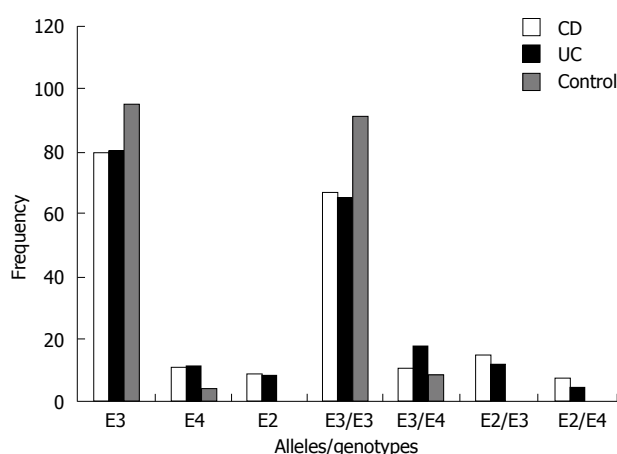
The results of APOE genotyping in the IBD patients and the healthy controls are summarized in Tables 1, 2, 3 4 and 5. In both the IBD patient and control groups the genotype distributions were in Hardy-Weinberg equilibrium. The ε2 allele was present in 7.59% of IBD patients, while altogether absent in controls (*P* < 0.01) (Table 1). The frequency of allele ε4 was also significantly higher in patients compared with controls (*P* < 0.01), whereas the frequency of the ε3 allele was significantly lower (*P* < 0.01).

The frequency of various genotypes of APOE also showed variations in patient and control groups. The prevalences of genotypes ε2/ε3, and ε2/ε4 were 13.48, and 6.18% in patients, while totally absent in the control group (*P* < 0.01) (Table 2). The difference in the frequencies of the ε3/ε4 genotype was not statistically significant between the patient and control groups, albeit that there is a trend towards a higher frequency in IBD patients. The frequency of the ε3/ε3 genotype was significantly higher in controls than that in IBD patients (*P* < 0.01). The genotypes ε2/ε2 and ε4/ε4 were absent in both patients and controls.

The frequencies of alleles and genotypes of APOE

Table 3 Gender comparison of apolipoprotein E genotypes and alleles *n* (%)

Genotype/allele	Male (<i>n</i> = 90)	Female (<i>n</i> = 88)	<i>P</i> value
ε3/ε3	66 (73.33)	52 (59.09)	< 0.05 ¹
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

¹Statistically significant.**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.**

polymorphism were not significantly different in male and female patients, except for the ε3 allele and homozygous ε3/ε3 genotype, which were present in significantly higher frequencies in female than male patients ($P < 0.05$) (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, an almost similar pattern was noticed for both UC and CD, except that the frequency of genotype ε3/ε4 was significantly higher in UC patients ($P = 0.03$), but not in CD patients ($P = 0.66$), as compared to controls. However, the RR values calculated for the ε3/ε4 genotype in UC and CD (RR = 2.34 and 1.28, respectively) indicated a 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 (Table 5). The APOE ε4 allele was significantly associated with an early age of onset in IBD ($P \leq 0.05$). 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.

Table 4 Apolipoprotein E genotypes and alleles in Crohn's disease and ulcerative colitis *n* (%)

Genotype/allele	CD (<i>n</i> = 94)	UC (<i>n</i> = 84)
ε3/ε3	63 (67.02 ¹)	55 (65.48 ¹)
ε3/ε4	10 (10.64 ²)	15 (17.86 ^{1,3})
ε2/ε3	14 (14.89 ¹)	10 (11.90 ¹)
ε2/ε4	7 (7.45 ¹)	4 (4.76 ¹)
ε3	150 (79.79 ¹)	135 (80.36 ¹)
ε4	21 (11.17 ¹)	19 (11.31 ¹)
ε2	17 (9.04 ¹)	14 (8.33 ¹)

¹ $P < 0.05$ vs controls; ²Relative risk = 2.34, ³Relative risk = 1.28. CD: Crohn's disease; UC: Ulcerative colitis.**Table 5 Apolipoprotein E genotypes and alleles in familial and sporadic inflammatory bowel disease *n* (%)**

Genotype/allele	Familial (<i>n</i> = 20)	Sporadic (<i>n</i> = 158)	<i>P</i> value
ε3/ε3	14 (70.00)	104 (65.82)	0.80
ε3/ε4	4 (20.00)	21 (13.30)	0.49
ε2/ε3	2 (10.00)	22 (13.92)	1.00
ε2/ε4	0 (0)	11 (6.96)	0.61
ε3	34 (85.00)	251 (79.43)	0.52
ε4	4 (10.00)	32 (10.13)	1.00
ε2	2 (5.00)	33 (10.44)	0.40

DISCUSSION

Our results showed a higher frequency of the APOE ε2 allele and predominance of ε2/ε3 and ε2/ε4 genotypes in IBD patients in comparison with matched controls, 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 and 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 it 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, and 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 compared to ε3 and ε4 carriers, due to low receptor binding affinity of ε2. Individuals 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 the pathogenesis of diseases *via* the sequestration of lipids contributing to the epidermal barrier function^[46].

We also observed a significantly higher frequency of the $\epsilon 2/\epsilon 3$ genotype in Saudi IBD patients as compared to matched controls. This genotype has been associated with significant imbalance in lipids and lipoprotein metabolism, as well as with ischemic cerebrovascular diseases^[47,48]. Parameters associated with atherosclerosis, such as inflammation, carotid intima media thickness, 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 ischemic heart diseases, including atherosclerosis^[49,53,54]. Furthermore, it has been reported that IBD is an independent predictor of hypertriglyceridemia^[55] and hypocholesterolemia^[56].

Results of this study showed a higher frequency of the $\epsilon 4$ allele in patients group compared to controls, suggesting that it also may increase the risk of IBD. Similarly, a higher frequency of the $\epsilon 4$ allele has been reported in Chinese UC patients^[34]. These authors therefore suggested that APOE $\epsilon 4$ confers greater risk for the development of UC in Chinese. Our results indicate that allele $\epsilon 4$ increases the risk for both UC and CD in Saudi patients. The $\epsilon 4$ allele of the APOE gene is an established risk factor for low bone mineral density^[57,58], and the high frequency of APOE $\epsilon 4$ in UC and CD patients may be responsible for low bone mineral density 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 with both CD and UC.

APOE is multifunctional in nature, and the presence of APOE $\epsilon 4$ has been associated with an enhanced inflammatory immune response^[60-62]. Though the exact mechanisms by which APOE $\epsilon 4$ regulates the innate immune response is far from clear. Significantly higher levels of the pro-inflammatory cytokines tumor necrosis factor- α and interleukin-6 have been reported in animals expressing the $\epsilon 4$ allele compared to those with the $\epsilon 3$ allele^[60]. Increased oxidative stress in the APOE $\epsilon 4$ cells has been suggested to contribute to higher cytokine production by enhancing the activation of nuclear factor- κB ^[63]. Moreover, increased expression of interleukin-1 β , macrophage inflammatory protein (MIP)-1 α , and tumor necrosis factor- α , as well as the transactivation of nuclear factor- κB , have been observed in APOE $\epsilon 4$ macrophages^[64]. Recently Li *et al*^[34] postulated that the epistatic interaction of MIP-1 α and APOE polymorphism may contribute to individual variation in MIP-1 α levels in mucosa of UC patients.

Our results also indicate that the APOE $\epsilon 4$ allele is associated with early age at onset of IBD. Polymorphism in the APOE gene has been defined as a modifying factor for age at onset in neurodegenerative and autoimmune

diseases^[30,65,66]. Our results are also in accordance with various reports showing an association of the $\epsilon 4$ allele with early onset of some autoimmune and neurodegenerative diseases^[30,64,67,68]. The APOE $\epsilon 4$ allele is believed to be responsible for reducing high-density lipoprotein and increasing low-density lipoprotein in high-fat intake individuals^[69], which are critical risk factors for occlusive lipid disorders. The implication of APOE $\epsilon 4$ in lipid metabolism and development of immunologic responses to lipid antigens may contribute to IBD in Saudis with high-fat intake as reported earlier for psoriasis^[70-72]. APOE $\epsilon 4$ has also been linked to lower C-reactive protein, and it has been suggested that this effect is a consequence of intrinsic functional differences among the $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ APOE proteins in plasma^[73]. Our results also show 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. The $\epsilon 2$ allele is associated with increased susceptibility for IBD, whereas the $\epsilon 3$ allele may be protective for IBD in Saudis. In addition, the $\epsilon 4$ allele 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 a larger population. Similar studies on different ethnic populations will be helpful in defining the role of APOE as a putative pharmacologic target for IBD.

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COMMENTS

Background

Inflammatory bowel diseases (IBD), including ulcerative colitis, and Crohn's disease, 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. Apolipoprotein E (APOE) plays a pivotal role in immunogenic response by interacting with several cytokines and regulating macrophage functions. Therefore, 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 ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$) differing from one another by the presence of either a C or T nucleotide at codons 112 and 158. Alleles $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ 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 varies 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

There are increasing prevalences of obesity and lipid disorders in the Saudi population due to sedentary lifestyle, lack of exercise, and unique dietary habits of rich fat, sugar and red meat. Being a closed society with high rate of consanguinity, it is ideal for genetic association studies. However, the genetic studies on IBD/other autoimmune disorders in KSA and other Arab countries are scarce and inconclusive. This is the first report from a Saudi population

showing the role of APOE polymorphism in the etiology of ulcerative colitis and Crohn's disease.

Applications

The study results suggest that APOE polymorphism is associated with risk of developing IBD in Saudi patients. The $\epsilon 2$ allele and its heterozygous genotypes increase the susceptibility to IBD, whereas the $\epsilon 3$ allele and $\epsilon 3/\epsilon 3$ genotype are protective. The APOE $\epsilon 4$ 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 pharmacologic target for IBD. Understanding this relationship may be potentially useful for predicting the vulnerability of individuals/populations to various autoimmune diseases.

Peer review

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

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