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ORIGINAL ARTICLE

Retrospective Study

Apolipoprotein E variants correlate with the clinical presentation of paediatric inflammatory bowel disease: A cross-sectional study

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Abstract

BACKGROUND

It has been suggested that apolipoprotein E (*APOE*) polymorphisms are associated with the risk of developing inflammatory bowel disease (IBD) and the early age of disease onset. However, there are no reports regarding the relationship with clinical characteristics and disease severity.

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AIM

To summarise that APOE polymorphisms are associated with the risk of developing IBD and the early age of disease onset.

METHODS

In total, 406 patients aged 3-18 with IBD (192 had ulcerative colitis and 214 had Crohn's disease) were genotyped using the TaqMan hydrolysis probe assay. Clinical expression was described at diagnosis and the worst flare by disease activity scales, albumin and C-reactive protein levels, localisation and behaviour (Paris classification). Systemic steroid intake with the total number of courses, immunosuppressive, biological, and surgical treatment with the time and age of the first intervention were determined. The total number of exacerbation-caused hospitalisations, the number of days spent in hospital due to exacerbation, the number of relapses, and severe relapses were also estimated.

RESULTS

Ulcerative colitis patients with the *APOEε4* allele had lower C-reactive protein values at diagnosis (P = 0.0435) and the worst flare (P = 0.0013) compared to patients with the *APOEε2* allele and genotype *APOEε3/ε3*. Crohn's disease patients with the *APOEε2* allele scored lower on the Pediatric Crohn's Disease Activity Index at diagnosis (P = 0.0204). IBD patients with *APOEε2* allele spent fewer days in the hospital due to relapse (P = 0.0440).

CONCLUSION

APOE polymorphisms are associated with the risk of developing IBD and the clinical expression of IBD. However, the clinical relevance of the differences identified is rather modest.

Key Words: Apolipoprotein E polymorphism; Crohn's disease; Ulcerative colitis; Immunosuppression; Surgery; Disease severity

Core Tip: Apolipoprotein E polymorphisms are associated with the risk of developing inflammatory bowel disease and seem to be associated with the disease expression and treatment. However, the clinical relevance of the differences is relatively modest.

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INTRODUCTION

Heritability and disease risk can only be partly explained by genetic factors alone[1-4]. Inflammatory bowel disease (IBD) has a strong genetic makeup. To date, 240 risk gene loci have been associated with the disease[1]. Several genetic variations are linked to specific IBD phenotypes. For instance, *NOD2*, *IRGM*, *ATG16L1*, and *NCF4/NCF2* are related to segmental, structuring, or early-onset disease[5-10]. Genetic testing for these and other variants may prove useful in predicting the disease course for future clinical use.

One of the well-known genetic determinants of some diseases other than IBD is apolipoprotein E (*APOE*), most commonly known for its role in Alzheimer's disease[11]. Although first recognised for its role in lipoprotein metabolism, APOE is involved in several biological processes not directly related to lipid transport function[12]. Importantly, APOE is a key player in immunoregulation[13-15] and

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associated with autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, and psoriasis[16-18]. It has been reported that APOE has several immune-related functions such as suppressing T-cell proliferation[19-21], possibly by downregulating DNA synthesis and reducing phospholipid turnover in T cells[22-24], neutrophil activation[25], and modulation of macrophage assisted[26-28] antigen presentation[14,15].

APOE is a polymorphic protein present in three major isoforms that differ only by two single amino acid substitutions, APOEε4 (arg112, arg158), APOEε3 (cys112, arg158), and APOEε2 (cys112, cys158). The amino acid replacement causes profound functional changes at the cellular and molecular level as well as in the immune system. APOE suppresses the production of proinflammatory cytokines such as tumour necrosis factor-α in microglia in an isoform-dependent manner (ε2 > ε3 > ε4)[29]. In turn, inflammatory cytokines can promote APOE synthesis and release or downregulate the production of APOE in different tissues[30,31]. However, interactions between APOE and cytokines are occasionally conflicting, highlighting the complex roles of APOE and cytokines in various disorders[15].

In IBD, inflammation alters lipid, apolipoprotein, and lipoprotein profiles in subjects with active disease[32,33] and patients with limited response to infliximab[34]. A previous study from Saudi Arabia showed that the genetic distribution of *APOE* polymorphisms in IBD seems to be altered compared to healthy subjects[35]. The study also suggested that the *ε4* allele increased the risk of IBD and was associated with an early onset of the disease. Similarly, *APOEε4* has been associated with severity in another immunologic disorder: rheumatoid arthritis[16]. For these reasons, this study aimed to investigate the relationship between *APOE* variants with disease severity in IBD.

MATERIALS AND METHODS

Patients

Patients recruited to the study belonged to the Polish Paediatric Crohn's and Colitis cohort and involved 406 paediatric IBD patients: 214 with Crohn's disease (CD; 86 females, 128 males) and 192 with ulcerative colitis (UC; 87 females, 105 males) (Table 1). Patients were recruited in the course of hospital treatment or during scheduled visits at outpatient clinics (Department of Pediatric Gastroenterology and Metabolic Diseases, Poznań University of Medical Sciences; The Department of Gastroenterology, Hepatology, Feeding Disorders and Paediatrics; The Children's Memorial Health Institute, Warsaw; Department of Pediatric Gastroenterology and Nutrition, Medical University of Warsaw; Department and Clinic of Pediatrics, Gastroenterology and Nutrition, Wroclaw Medical University; Department of Pediatrics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice; Department of Pediatrics, Faculty of Medical Sciences, Medical University of Silesia in Katowice and Department of Pediatric Endoscopy and Gastrointestinal Function Testing, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland). The diagnosis of IBD was confirmed by experienced gastroenterologists using standard diagnostic criteria[36,37]. The inclusion criteria were a diagnosis of CD or UC and aged 3-18. Patients in life-threatening, severe general condition were excluded from the study. The study obtained the approval of the Bioethical Committee at Poznań University of Medical Sciences (960/15 with the associated amendments).

Disease severity evaluation

Disease activity was assessed using appropriate scales at diagnosis and the worst flare [Pediatric Ulcerative Colitis Activity Index and Pediatric Crohn's Disease Activity Index (PCDAI)][38], which was defined by the highest Pediatric Ulcerative Colitis Activity Index and PCDAI scales in their medical history. Albumin (g/dL) and C-reactive protein (CRP; mg/L) concentrations at diagnosis and the worst flare were obtained from medical records (CRP reference range 0-5 mg/L). The treatment domain included data regarding systemic steroid intake with the total number of courses, immunosuppressive treatment with the time and age of the first intake, biological therapy with time and age of first admission, and operative treatment with time and age of first surgery. The localisation and behaviour of the disease were defined by the Paris Classification at the diagnosis and worst flare[39]. Most CD patients presented with an ileocolonic location and nonstricturing behaviour of the disease (Supplementary Table 1), while most UC patients presented with pancolitis and were never severe (S0: > 65 on the Pediatric Ulcerative Colitis Activity Index scale;

Table 1 Demographic and clinical expression of Crohn's disease and ulcerative colitis

Variables median (IQR) or *n* (%)	*n*	Crohn's disease	Ulcerative colitis	*P* value
Age in yr				
At inclusion	397	15.18 (13.32-17.05)	15.11 (11.70-16.75)	0.044
At diagnosis	404	12.58 (10.02-14.32)	12.14 (7.89-14.94)	0.365
At worst flare	355	13.63 (11.54-15.85)	13.76 (10.13-15.84)	0.244
Duration of the disease (yr)	390	2.23 (0.82-4.25)	1.88 (0.36-3.77)	0.239
Female	173	86 (40.2)	87 (45.3)	0.297
Nutritional status				
Weight at diagnosis in kg	387	38.0 (27.0-49.8)	40.0 (27.8-53.9)	0.490
Weight at diagnosis, z score	383	-0.82 [(-1.39)-(-0.04)]	-0.51 [(-1.12)-0.22]	0.003
Height at diagnosis in cm	382	151.0 (137.0-164.5)	152.0 (130.5-168.3)	0.718
Height at diagnosis, z score	378	-0.37 [(-1.29)-0.47]	0.06 [(-0.67)-0.81]	0.001
Body mass index at diagnosis in kg/m^2	382	16.6 (14.5-18.4)	17.4 (15.5-19.3)	0.019
Body mass index at diagnosis, z score	378	-0.79 [(-1.47)-(-0.04)]	-0.49 [(-1.00)-0.16]	0.006
Albumin level at diagnosis in g/dL	345	3.90 (3.51-4.25)	4.10 (3.70-4.40)	< 0.003
Parameter of inflammation				
CRP at diagnosis in mg/L[1]	386	12.94 (2.10-29.25)	2.24 (0.50-10.80)	< 0.001
CRP at worst flare in mg/L	347	13.95 (3.03-32.43)	2.70 (0.63-13.44)	< 0.001
Disease activity scales				
PCDAI/PUCAI at diagnosis	190/166	32 (23-48)	45 (28-60)	
PCDAI/PUCAI at worst flare	170/155	40 (30-53)	50 (35-65)	
Treatment				
Systemic steroids[2]	406	115 (53.7)	138 (71.9)	< 0.001
Immunosuppressive treatment[3]	405	168 (78.5)	112 (58.6)	< 0.001
Biological therapy[4]	406	107 (50.0)	49 (25.5)	< 0.001
Operative treatment[5]	406	29 (13.6)	4 (2.1)	< 0.001

[1]C-reactive protein reference range 0-5 mg/L.
[2]Systemic steroid therapy included: methylprednisolone, prednisone, hydrocortisone.
[3]Immunosuppressive and anti-inflammatory agents included: Azathioprine, methotrexate, mercaptopurine, cyclosporine, mycophenolate mofetil, tacrolimus, sulfasalazine.
[4]Biological agents included: infliximab, adalimumab, golimumab, vedolizumab.
[5]Only surgery related to inflammatory bowel disease-specific problems (*e.g.*, colectomy, resection, fistula, perforation, abscess) was included. CRP: C-reactive protein; IBD: Inflammatory bowel disease; IQR: Interquartile range; PCDAI: Pediatric Crohn's Disease Activity Index; PUCAI: Pediatric Ulcerative Colitis Activity Index.

Supplementary Table 2). Based on medical records, the total number of exacerbation hospitalisations, the number of days spent in hospital due to exacerbation, the number of relapses, and severe relapses from diagnosis were estimated and calculated per year of the disease duration. The associated extraintestinal symptoms and concomitant diseases were collected from the medical history.

Genotyping

DNA was isolated from whole blood using the Blood Mini (A and A Biotechnology). A hydrolysis probe assay (TaqMan assay) was used with the following probes, C_904973_10 and C_3084793_20, to genotype patients (Life Technologies Corp. Carlsbad. California, United States). The genotyping was performed on the CFX-96 thermocycler system with allele discrimination plots provided by CFX Manager Software (Bio-Rad, Hercules, CA, United States).

Statistical analysis

Differences in categorical variables were compared with two-tailed Fisher's exact test. Differences in continuous variables were evaluated by the Mann Whitney *U* test and Kruskal-Wallis test. Post hoc comparisons were performed with Dunn's test, and the significance level for the time-to-treatment analysis was evaluated by Gehan's test. The explanatory factor analysis was used to analyse the underlying factors in the questionnaire. The significance level was set at $P < 0.05$, and statistical analyses were performed using Statistica 13.1 software (StatSoft Inc, Tulsa, OK, United States), JASP 0.10.2 (University of Amsterdam, Amsterdam, the Netherlands), and G*Power (Dusseldorf University, Germany). Comparisons between groups with less than ten patients were not included.

RESULTS

Genotyping

The most prevalent genotype in UC and CD was *APOEε3/ε3* (Table 2). No differences in the distribution of alleles and genotypes between UC and CD were documented.

The distribution of the *APOE* genotypes was compared to previous studies in the Polish population (Supplementary Table 3). Pooling available data[40-42] to obtain a similar sample size (n = 425) showed a significantly lower frequency of *APOEε3/ε3* genotype in IBD patients compared to controls (62.3% *vs* 71.5%; P = 0.0051; odds ratio = 0.66; 95% confidence interval: 0.49-0.88) and simultaneously higher frequency of *APOEε3/ε4* genotype (21.7% *vs* 15.1%; P = 0.0153; odds ratio = 1.56; 95% confidence interval: 1.09-2.23) with no difference in other genotypes or for the *APOEε3* allele (P = 0.8625). However, in the study of Bojar *et al*[43] (postmenopausal women; n = 402), the distribution of *APOEε3/ε3* genotype was similar to the present study (62.9% *vs* 62.3%; P = 0.8555; odds ratio = 0.97; 95% confidence interval: 0.73-1.30).

UC patients with *APOEε3ε3* had higher CRP values, and the *APOEε2/ε3* genotype were predisposed to left-sided colitis (E2) at diagnosis (Table 3). Concomitant diseases in CD patients occurred at different frequencies in major *APOE* genotypes, and children with *APOEε2ε3* genotype had significantly lower PCDAI scores at diagnosis than patients with the remaining genotypes (Table 4). UC patients with *t*he *APOEε4* allele had significantly lower CRP levels than the patients with *APOEε3ε3* genotype and *APOEε2*-positive, both at diagnosis and at the worst flare (Table 5). There were also differences in age at first biological treatment. Additionally, *APOEε2*-positive patients with IBD spent significantly fewer days in the hospital due to relapse per year of disease duration than *APOEε4*-positive patients and with the *APOEε3/ε3* genotype (Table 5). Patients with CD and *APOEε3ε3* genotype had lower values of standardised body height at diagnosis (Table 5). No difference was observed in the frequency of systemic steroids, immunosuppressive, and biological treatment between *APOE* genotypes in UC and CD patients. Supplementary Table 4 shows the results for the whole group of IBD patients.

DISCUSSION

The present study investigated the relationship between *APOE* genotype and disease severity in IBD, suggesting that the *APOE* genotype might be associated with some indices of disease course such as CRP and albumin levels at the worst flare, age at surgery and numbers of hospitalisation days. UC patients with the *APOEε4* allele had the lowest values of CRP, both at diagnosis and the worst flare. The median age at first biological therapy in UC was lowest in patients with the *APOEε4* allele, whereas left-side colitis was more frequent among patients with the *APOEε2* allele. In CD patients, the *APOEε4* allele was associated with higher albumin at worst flare and higher standardised body height at diagnosis. Moreover, patients with the *APOEε2* allele scored lower on the PCDAI. This study is the largest to show the genetic distribution of *APOE* polymorphisms in IBD to date.

APOE is known to be associated with inflammation indicators[13]. The findings of the present study confirm this relationship as the CRP levels differed between *APOE* genotypes. Patients with the *APOEε4* allele and *APOEε3ε4* genotype had lower CRP values at diagnosis and the worst flare, while patients with the *APOEε3ε3* genotype had higher levels of CRP at the worst flare. These results are similar to those obtained in healthy adults, which showed that subjects with *APOEε3ε3* had the highest plasma

Table 2 Apolipoprotein E genotype and allele distribution compared between ulcerative colitis and Crohn's disease

Genotype/allele	UC, *n* = 192	CD, *n* = 214	*P* value, two-tailed Fisher exact	Odds ratio (95%CI)
ε3/ε3	118	135	0.7590	0.93 (0.62-1.40)
ε3/ε4	47	41	0.2278	1.37 (0.85-2.20)
ε2/ε3	18	35	0.0397	0.53 (0.29-0.97)
ε3+	183	211	0.0757	0.29 (0.08-1.08)
ε4+	54	43	0.0629	1.56 (0.98-2.46)
ε2+	24	37	0.2108	0.68 (0.39-1.19)

CD: Crohn's disease; CI: Confidence interval; UC: Ulcerative colitis.

levels of CRP and individuals with *APOEε4ε4* and *APOEε2ε4* had the lowest levels[13]. A similar pattern has also been observed in other diseases such as coronary artery disease[43-46]. März *et al*[47] proved that in coronary artery disease, both white cell count and fibrinogen were not related to the *APOE* genotype, suggesting that the underlying mechanism is not associated with inflammation[46] but rather to the mevalonate/cholesterol synthetic pathway, which may be downregulated in patients with *APOEε4* in response to altered lipoprotein metabolism and hepatic uptake[46]. In another study, the *APOEε4* allele was also associated with lower CRP but not white blood cell count[47]. Further mechanistic studies are needed to explain the link.

Our study is the first to report that in CD patients, the *APOEε4* allele is associated with higher median levels of albumins at the worst flare. Albumin level is negatively correlated with the extent of the inflammatory response, which is caused by a hypercatabolic state and a decrease of albumin synthesis in the liver[48]. Tumour necrosis factor-α inhibits albumin expression causing hypoalbuminemia[48] , a state associated with IBD activity, unresponsiveness to treatment, and increased risk of colectomy in UC. Patients with hypoalbuminemia had a higher likelihood of having more than two courses of corticosteroids, thiopurine, or anti-tumour necrosis factor treatment[49]. In CD, albumin levels were reported as a marker of postoperative complications[50] and active clinical disease[51]. Low albumin level together with high CRP may correlate with an increased inflammatory response[52]. In the study of Sayar *et al*[53], the area under the curve values for severe UC were 0.883 for albumin levels (cut-off 3.6 g/dL) and 0.941 for CRP/albumin ratio (cut-off 0.6)[52]. Given these data, the results of our study may suggest that the *APOEε4* allele is associated with a milder disease course of CD. The association of the *APOEε2* allele with lower PCDAI scores and fewer days of hospitalisation due to relapse might suggest a protective role of this allele on disease severity. However, this relationship is more complicated as we found that the *APOEε2* allele is also associated with a younger age at first surgery. This finding should be verified, preferably in a group of adult patients with a longer disease course and higher surgery rates.

The biology of APOE in IBD has not been fully elucidated, but recent studies have shown that the *APOE* transcript is overexpressed in paediatric IBD patients[53]. Studies in colonic epithelial cells in a mouse model showed that the apoE-mimetic peptide (COG112) inhibited the inflammatory response to *Citrobacter rodentium*[54], a bacterium known to cause colitis in mice[55]. The authors suggested this occurred by preventing the activation of nuclear factor κB[54]. Therefore, further mechanistic studies of APOE action are warranted.

A previous study on *APOE* in IBD in a group with a different genetic background (Saudi Arabia) did not focus on disease severity. Therefore, any comparisons are difficult[35]. In that study, the *APOEε4* allele was associated with the risk of developing IBD and early onset, whereas our study did not identify significant differences between *APOE* genotypes and age at diagnosis. The frequencies of *APOEε3ε3* genotype were lower in IBD patients in comparison to controls, which is consistent with the above-mentioned report[35].

The present study involved a large multicentre paediatric cohort, including a comprehensive clinical description, which allowed a detailed genotype-phenotype analysis. However, defining the global severity of the disease course remains challenging, especially in diseases with such a differentiated clinical presentation. The major limitation of this study is related to the retrospective character of the data collection regarding diagnosis and the worst flare. Need for surgery, which is one of

Table 3 Clinical characteristics in patients with ulcerative colitis depending on major apolipoprotein E genotypes

Variables median (IQR) or *n* (%)	*n*	ε2/ε3	ε3/ε3	ε3/ε4	*P* value
Age in yr					
At inclusion	184	15.7 (12.5-16.9)	15.3 (11.9-16.9)	14.3 (11.5-16.3)	0.2464
At diagnosis	191	11.4 (7.9-14.6)	12.4 (7.9-15.0)	12.4 (8.2-14.9)	0.9070
At worst flare	171	14.6 (9.9-16.4)	13.7 (10.4-16.0)	13.7 (10.0-15.7)	0.7255
Duration of the disease in yr	179	3.0 (1.4-6.2)	1.9 (0.4-3.5)	1.2 (0.0-3.5)	0.0868
Nutritional status					
Weight at diagnosis in kg	180	40.0 (28.8-59.5)	39.0 (27.8-54.0)	43.8 (29.5-53.4)	0.9704
Weight at diagnosis, z score	179	-0.20 [(-0.86)-0.43]	-0.5 [(-1.1)-0.1]	-0.24 [(-0.95)-0.63]	0.3037
Height at diagnosis in cm	175	146.5 (129.0-169.0)	153.0 (131.0-168.5)	156.0 (131.5-169.0)	0.9175
Height at diagnosis, z score	174	0.12 [(-0.62)-0.75]	0.09 [(-0.69)-0.79]	0.22 [(-0.44)-1.06]	0.5823
Body mass index at diagnosis in kg/m^2	175	17.61 (16.02-19.74)	17.0 (15.4-19.1)	17.9 (15.4-20.3)	0.5121
Body mass index at diagnosis, z score	174	-0.11 [(-0.70)-0.29)]	-0.56 [(-0.99)-0.11]	-0.30 [(-1.12)-0.56]	0.2293
Weight at worst flare in kg	164	46.1 (31.6-62.0)	46.2 (31.9-55.6)	50.0 (28.0-61.0)	0.9600
Weight at worst flare, z score	161	-0.33 [(-1.00)-0.56]	-0.58 [(-0.95)-0.16]	-0.52 [(-0.90)-0.40]	0.6559
Height at worst flare in cm	162	162.5 (138.5-173.5)	159.0 (140.9-171.0)	160.0 (135.0-172.0)	0.9688
Height at worst flare, z score	161	0.11 [(-0.72)-1.16]	-0.09 [(-0.62)-0.78]	0.06 [(-0.62)-0.89]	0.8376
Body mass index at worst flare in kg/m^2	160	18.20 (16.47-19.74)	17.36 (15.75-19.71)	17.93 (15.89-20.96)	0.6013
Body mass index at worst flare, z score	159	-0.22 [(-1.16)-0.14]	-0.68 [(-1.10)-0.16]	-0.43 [(-1.12)-0.63]	0.6789
Albumin level					
At diagnosis in g/dL	159	4.2 (4.0-4.6)	4.1 (3.7-4.4)	4.1 (3.6-4.4)	0.2569
At worst flare in g/ dL	148	4.3 (4.0-4.7)	4.1 (3.6-4.4)	4.2 (4.0-4.4)	0.3488
Parameter of inflammation					
CRP at diagnosis in mg/L	178	3.8 (0.7-6.6)	2.5 (0.7-12.2)	1.1 (0.2-8.0)	0.0515
CRP at worst flare in mg/L	162	2.1 (1.1-23.3)	3.7 (1.1-19.0)	0.8 (0.3-2.9)	0.0012
Disease activity scales					
PUCAI at diagnosis	166	40 (18-55)	45 (30-60)	50 (25-60)	0.5144
PUCAI at worst flare	155	48 (20-65)	55 (40-65)	50 (30-65)	0.3766
Disease localisation and behaviour					
E1 at diagnosis	19/192	3 (16.7)	10 (8.5)	6 (12.8)	0.4694
E2 at diagnosis	33/192	8 (44.4)	16 (13.6)	9 (19.1)	0.0063
E3 at diagnosis	28/192	1 (5.6)	18 (15.3)	9 (19.1)	0.3953
E4 at diagnosis	83/192	5 (27.8)	60 (50.8)	18 (38.3)	0.0990
S0 at diagnosis	110/192	13 (72.2)	69 (58.5)	28 (59.6)	0.5383
S1 at diagnosis	37/192	3 (16.7)	23 (19.5)	11 (23.4)	0.7885
E1 at worst flare	9/192	1 (5.6)	4 (3.4)	4 (8.5)	0.3863
E2 at worst flare	27/192	3 (16.7)	18 (15.3)	6 (12.8)	0.8943
E3 at worst flare	23/192	3 (16.7)	16 (13.6)	4 (8.5)	0.5814
E4 at worst flare	75/192	7 (38.9)	50 (42.4)	18 (38.3)	0.8750
S0 at worst flare	83/192	9 (50.0)	52 (44.1)	22 (46.8)	0.8713
S1 at worst flare	49/192	5 (27.8)	34 (28.8)	10 (21.3)	0.6114
Treatment					

Systemic steroids[1]	192	11 (61.1)	92 (78.0)	29 (61.7)	0.0599
Number of courses of steroid treatment	190	1 (0-2)	1 (1-2)	1 (0-2)	0.0672
Immunosuppressive treatment[2]	191	9 (50.0)	74 (63.2)	25 (53.2)	0.3451
Number of immunosuppressants	191	1 (0-1)	1 (0-1)	1 (0-1)	0.2572
Time-to-first dose of immunosuppressive treatment in mo	109	3.0 (2.0-17.0)	4.0 (0.0-10.0)	2.8 (0.0-8.0)	0.4356
Age at first intake of immunosuppressive treatment in yr	109	14.7 (10.4-16.1)	12.3 (7.8-14.1)	11.0 (7.3-15.5)	0.2381
Biological therapy[3]	192	4 (22.2)	29 (24.8)	13 (27.7)	0.8781
Total number of biologics	192	0 (0-0)	0 (0-0)	0 (0-1)	0.8164
Time-to-first dose of biological treatment in mo	48	19.9 (12.8-50.3)	16.4 (9.1-28.1)	10.8 (4.0-27.7)	0.3152
Age at first biological treatment	49	15.7 (14.7-15.9)	11.5 (7.9-14.6)	10.7 (4.5-15.5)	0.0852
Operative treatment[4]	192	0 (0.0)	3 (2.5)	1 (2.1)	0.7893
Age at first surgery in yr	6	7.7 (5.9-9.6)	14.8 (6.8-17.1)	13.0 (10.4-15.6)	0.2969
Time-to-first surgery in mo	4		16.7 (5.0-28.7)	19.1 (0.9-37.4)	1.0000
Hospitalisations, if duration ≥ 1 yr					
Hospitalisations for relapse, per 1 yr of the disease	98	0.3 (0.3-0.8)	0.6 (0.3-1.6)	0.9 (0.5-1.3)	0.2518
Days of hospitalisation for relapse, per 1 yr of the disease	98	2.5 (0.6-4.5)	4.8 (1.8-9.3)	7.3 (3.8-8.7)	0.1362
Relapses from diagnosis, per 1 yr of the disease	98	0.3 (0.1-0.8)	0.6 (0.3-1.2)	0.8 (0.3-1.3)	0.3491
Severe relapses from diagnosis, per 1 yr of the disease	100	0.0 (0.0-0.3)	0.1 (0.0-0.6)	0.2 (0.0-0.4)	0.7150
Concomitant diseases[5]	192	9 (50.0)	41 (34.7)	15 (31.9)	0.3781
Extraintestinal manifestations	192	3 (16.7)	23 (19.5)	10 (21.3)	0.9131

[1]Systemic steroid therapy included: methylprednisolone, prednisone, hydrocortisone.
[2]Immunosuppressive and anti-inflammatory agents included: azathioprine, methotrexate, mercaptopurine, cyclosporine, mycophenolate mofetil, tacrolimus, sulfasalazine.
[3]Biological agents included: Infliximab, adalimumab, golimumab, vedolizumab.
[4]Only surgery related to inflammatory bowel disease-specific problems (*e.g.*, colectomy, resection, fistula, perforation, abscess) was included.
[5]*e.g.*, celiac disease, bronchial asthma, obesity, gastroesophageal reflux disease, epilepsy, hypothyroidism. CRP: C-reactive protein; IBD: Inflammatory bowel disease; IQR: Interquartile range; PUCAI: Pediatric Ulcerative Colitis Activity Index.

the most crucial measures of disease course, would require longer follow-up in order to describe disease severity. Although we did not include a control group, *APOE* polymorphisms in healthy subjects have been studied in the Polish population[40-42,56], which allowed us to estimate whether there was any frequency distribution difference.

CONCLUSION

APOE polymorphisms are associated with the risk of developing IBD and seem to be associated with the clinical expression of the disease and applied treatment (with inflammatory markers and nutritional status, disease activity and localisation, hospitalisations). However, the clinical relevance of the differences identified is relatively modest.

Table 4 Clinical characteristics in patients with Crohn's disease depending on major apolipoprotein E genotypes

Variables median (IQR) or *n* (%)	*n*	ε2/ε3	ε3/ε3	ε3/ε4	*P* value
Age in yr					
At inclusion	213	15.5 (13.2-16.8)	15.2 (13.3-17.2)	15.2 (13.4-16.2)	0.8055
At diagnosis	213	11.8 (10.1-14.6)	12.7 (9.9-14.5)	12.6 (10.0-13.9)	0.8796
At worst flare	184	13.3 (11.6-15.2)	13.6 (11.3-15.8)	14.3 (12.8-15.9)	0.5121
Duration of the disease in yr	211	2.8 (0.6-5.4)	2.0 (0.8-4.0)	2.3 (0.8-4.1)	0.7843
Nutritional status					
Weight at diagnosis in kg	207	38.3 (27.6-48.0)	37.3 (25.3-49.5)	38.4 (28.3-57.6)	0.5360
Weight at diagnosis, z score	204	-0.53 [(-1.02)-(-0.02)]	-0.91 [(-1.46)-(-0.12)]	-0.73 [(-1.34)-0.38]	0.2062
Height at diagnosis in cm	207	148.3 (141.0-164.0)	151.5 (134.0-164.0)	151.3 (141.0-170.0)	0.6757
Height at diagnosis, z score	204	-0.17 [(-0.85)-0.51]	-0.47 [(-1.43)-0.32]	0.05 [(-1.10)-0.96]	0.0617
Body mass index at diagnosis in kg/m^2	207	16.73 (14.28-18.42)	16.59 (14.41-18.22)	16.40 (14.78-20.78)	0.8397
Body mass index at diagnosis, z score	204	-0.72 [(-1.33)-(-0.16)]	-0.79 [(-1.53)-(-0.08)]	-0.88 [(-1.29)-0.49]	0.7878
Weight at worst flare in kg	181	41.8 (34.8-50.3)	41.9 (29.6-52.6)	46.8 (36.2-58.9)	0.2294
Weight at worst flare, z score	178	-0.67 [(-1.16)-0.10]	-1.14 [(-1.64)-(-0.25)]	-0.60 [(-1.22)-0.02]	0.0756
Height at worst flare in cm	183	153.0 (148.5-166.0)	158.0 (141.5-167.0)	162.0 (148.5-171.5)	0.3088
Height at worst flare, z score	180	-0.15 [(-1.09)-0.61]	-0.52 [(-1.41)-0.21]	-0.24 [(-1.10)-0.43]	0.1234
Body mass index at worst flare in kg/m^2	181	17.29 (15.53-18.60)	16.89 (14.87-19.03)	17.09 (15.56-21.74)	0.4172
Body mass index at worst flare, z score	178	-0.87 [(-1.38)-0.01]	-1.03 [(-1.55)-(-0.19)]	-0.53 [(-1.46)-0.49]	0.3913
Albumin level					
At diagnosis in g/dL	186	3.9 (3.7-4.3)	3.8 (3.4-4.2)	3.9 (3.4-4.3)	0.5796
At worst flare in g/dL	179	3.9 (3.8-4.3)	3.9 (3.4-4.1)	3.9 (3.6-4.3)	0.0611
Parameter of inflammation					
CRP at diagnosis in mg/L	208	13.8 (0.8-40.0)	13.0 (2.1-29.6)	12.0 (3.4-24.9)	0.8818
CRP at worst flare in mg/L	185	18.3 (1.7-31.5)	14.0 (3.3-38.5)	13.6 (3.2-26.8)	0.7672
Disease activity scales					
PCDAI at diagnosis	190	25 (20-35)	35 (25-50)	30 (25-43)	0.0282
PCDAI at worst flare	170	35 (23-50)	45 (30-53)	38 (30-53)	0.1898
Disease localisation and behaviour					
L1 at diagnosis	53/213	9 (25.7)	35 (26.1)	8 (19.5)	0.6852
L2 at diagnosis	40/213	9 (25.7)	19 (14.2)	11 (26.8)	0.0935
L3 at diagnosis	99/213	13 (37.1)	67 (50.0)	16 (39.0)	0.2507
L4a at diagnosis	23/213	4 (11.4)	14 (10.4)	4 (9.8)	0.9721
L4b at diagnosis	8/213	1 (2.9)	7 (5.2)	0 (0.0)	0.2950
B1 at diagnosis	146/213	24 (68.6)	89 (66.4)	33 (80.5)	0.2287
B2 at diagnosis	15/213	3 (8.6)	11 (8.2)	1 (2.4)	0.4263
B3 at diagnosis	19/213	3 (8.6)	15 (11.2)	1 (2.4)	0.2304
B2B3 at diagnosis	4/213	1 (2.9)	3 (2.2)	0 (0.0)	0.5927
G0 at diagnosis	145/213	24 (68.6)	92 (68.7)	29 (70.7)	0.9667
G1 at diagnosis	33/213	3 (8.6)	24 (17.9)	6 (14.6)	0.3921
P at diagnosis	19/213	0 (0.0)	16 (11.9)	3 (7.3)	0.0824
L1 at worst flare	40/213	5 (14.3)	26 (19.4)	9 (22.0)	0.6873

L2 at worst flare	27/213	7 (20.0)	14 (10.4)	6 (14.6)	0.3007
L3 at worst flare	92/213	10 (28.6)	66 (49.3)	16 (39.0)	0.0708
L4a at worst flare	18/213	3 (8.6)	12 (9.0)	3 (7.3)	0.9477
L4b at worst flare	9/213	1 (2.9)	5 (3.7)	3 (7.3)	0.5507
B1 at worst flare	114/213	17 (48.6)	74 (55.2)	23 (56.1)	0.7549
B2 at worst flare	19/213	2 (5.7)	12 (9.0)	5 (12.2)	0.6165
B3 at worst flare	21/213	1 (2.9)	16 (11.9)	4 (9.8)	0.2798
B2B3 at worst flare	5/213	1 (2.9)	4 (9.8)	0 (0.0)	0.5367
G0 at worst flare	121/213	18 (51.4)	79 (59.0)	24 (58.5)	0.7184
G1 at worst flare	34/213	2 (5.7)	24 (17.9)	8 (19.5)	0.1776
P at worst flare	20/213	0 (0.0)	17 (12.7)	3 (7.3)	0.0649
Treatment					
Systemic steroids[1]	214	19 (34.3)	73 (54.1)	21 (51.2)	0.9455
Number of courses of steroid treatment	212	1 (0-2)	1 (0-2)	1 (0-1)	0.5535
Immunosuppressive treatment[2]	214	25 (71.4)	110 (81.5)	31 (75.6)	0.3756
Number of immunosuppressants	214	1 (0-1)	1 (1-1)	1 (1-1)	0.2632
Time-to-first dose of immunosuppressive treatment in mo	166	1.3 (0.0-13.0)	2.0 (0.0-7.0)	1.0 (0.0-9.6)	0.8866
Age at first intake of immunosuppressive treatment in yr	166	12.9 (10.3-13.9)	13.0 (10.7-14.9)	12.7 (9.6-14.3)	0.6668
Biological therapy[3]	214	15 (42.9)	73 (54.1)	18 (43.9)	0.3303
Total number of biologics	214	0 (0-1)	1 (0-1)	0 (0-1)	0.2243
Time-to-first dose of biological treatment in mo	102	17.8 (6.3-44.0)	12.6 (5.6-25.9)	13.3 (6.1-26.7)	0.6313
Age at first biological treatment	102	13.8 (12.7-14.8)	13.6 (11.3-15.3)	14.0 (10.7-15.6)	0.8880
Operative treatment[4]	214	2 (5.7)	19 (14.1)	8 (19.5)	0.2158
Age at first surgery in yr	30	11.3 (9.4-13.1)	14.5 (12.5-16.5)	14.9 (14.0-15.7)	0.1698
Time-to-first surgery in mo	26	12.0	19.4 (0.0-41.1)	25.1 (7.9-43.5)	0.7807
Hospitalisations, if duration ≥ 1 yr					
Hospitalisations for relapse, per 1 yr of the disease	133	0.4 (0.2-0.7)	0.5 (0.3-0.8)	0.4 (0.2-1.3)	0.6615
Days of hospitalisation for relapse, per 1 yr of the disease	132	2.7 (0.7-5.6)	4.7 (1.6-7.5)	4.0 (1.1-7.6)	0.4001
Relapses from diagnosis, per 1 yr of the disease	132	0.4 (0.2-0.9)	0.5 (0.2-0.9)	0.4 (0.2-1.4)	0.8664
Severe relapses from diagnosis, per 1 yr of the disease	129	0.0 (0.0-0.3)	0.2 (0.0-0.5)	0.2 (0.0-0.5)	0.1996
Concomitant diseases[5]	214	16 (45.7)	40 (29.6)	8 (19.5)	0.0446
Extraintestinal manifestations	214	7 (20.0)	34 (25.2)	11 (26.8)	0.7660

[1]Systemic steroid therapy included: methylprednisolone, prednisone, hydrocortisone.
[2]Immunosuppressive and anti-inflammatory agents included: azathioprine, methotrexate, mercaptopurine, cyclosporine, mycophenolate mofetil, tacrolimus, sulfasalazine.
[3]Biological agents included: infliximab, adalimumab, golimumab, vedolizumab.
[4]Only surgery related to inflammatory bowel disease-specific problems (*e.g.* colectomy, resection, fistula, perforation, abscess) was included.
[5]*e.g.*, celiac disease, bronchial asthma, obesity, gastroesophageal reflux disease, epilepsy, hypothyroidism. CRP: C-reactive protein; IQR: Interquartile range; PCDAI: Pediatric Crohn's Disease Activity Index.

Table 5 Summary of relevant findings depending on apolipoprotein E genotypes and alleles

Variables median (IQR) or *n* (%)	*n*	*ε3/ε3*	*APOEε2*-positive	*APOEε4*-positive	*P* value
IBD					
Albumin level at worst flare in g/dL	327	3.9 (3.4-4.3)	4.0 (3.9-4.5)	4.1 (3.8-4.4)	0.0176[a]
CRP at worst flare in mg/L	347	7.7 (1.9-31.3)	4.3 (1.1-28.3)	3.2 (0.5-16.7)	0.0146[b]
Age at first surgery in yr	36	14.5 (11.7-16.7)	9.5 (7.7-11.4)	14.9 (14.0-15.6)	0.0378
Days of hospitalisation for relapse, per 1 yr of the disease	230	4.7 (1.6-8.3)	2.2 (0.7-4.8)	6.1 (1.7-8.7)	0.0440[c]
CD					
Albumin level at worst flare in g/dL	327	3.9 (3.4-4.1)	3.9 (3.8-4.4)	4.4 (3.6-4.3)	0.0363
PCDAI at diagnosis	190	35 (25-50)	25 (20-35)	30 (25-45)	0.0204[c]
Height at diagnosis, z score	378	-0.47 [(-1.43)-0.32]	-0.16 [(-0.85)-0.61]	0.00 [(-1.10)-0.96]	0.0482
UC					
CRP at diagnosis in mg/L	386	2.5 (0.7-12.2)	3.8 (0.8-7.3)	1.1 (0.2-8.2)	0.0435
CRP at worst flare in mg/L	347	3.7 (1.1-19.0)	2.1 (1.8-7.3)	0.9 (0.3-3.6)	0.0013
Age at first biological treatment	151	11.5 (7.9-14.6)	15.7 (15.3-15.7)	10.7 (4.8-15.5)	0.0432
E2 at diagnosis	192	16 (13.6)	8 (40.0)	9 (18.0)	0.0160

[a]Post hoc APOEε3ε3 *vs* APOEε2-positive $P = 0.0383$ (Bonferroni and Holm); APOEε3ε3 *vs* APOEε4-positive $P = 0.0417$ (Bonferroni) and $P = 0.0383$ (Holm).
[b]Post hoc APOEε3ε3 *vs* APOEε4-positive $P = 0.0056$ (Bonferroni and Holm).
[c]APOEε3ε3 *vs* APOEε2-positive $P = 0.0534$ (Bonferroni) and $P = 0.0356$ (Holm), APOEε2-positive *vs* APOEε4-positive $P = 0.0216$ (Bonferroni and Holm).
CD: Crohn's disease; CRP: C-reactive protein; IBD: Inflammatory bowel disease; PCDAI: Pediatric Crohn's Disease Activity Index; UC: Ulcerative colitis.

ARTICLE HIGHLIGHTS

Research background

Apolipoprotein E (*APOE*) polymorphisms were previously reported to be linked with the risk of developing inflammatory bowel diseases (IBD).

Research motivation

No data on the relationship between *APOE* polymorphisms and disease severity are available.

Research objectives

This study aimed to investigate the link between *APOE* variants and disease severity in IBD.

Research methods

The TaqMan hydrolysis probe assay was used to genotype 406 patients with IBD (192 had ulcerative colitis and 214 had Crohn's disease). Clinical expression involved disease activity scales, albumin and C-reactive protein levels, disease localisation and behaviour, and treatment with the time and age of the first intervention. The number of hospitalisations and days spent in hospital due to exacerbation as well as the number of relapses and severe relapses were also estimated.

Research results

Ulcerative colitis patients with the *APOEε4* allele had the lowest C-reactive protein values both at diagnosis ($P = 0.0435$) and the worst flare ($P = 0.0013$) compared to patients with the *APOEε2* allele and genotype *APOEε3/ε3*. Crohn's disease patients with the *APOEε2* allele scored lower on the Pediatric Crohn's Disease Activity Index at diagnosis ($P = 0.0204$). All IBD patients with the *APOEε2* allele spent fewer days in the hospital due to relapse ($P = 0.0440$).

Research conclusions

The *APOE* genotype seems to be associated with some indices of disease course such

as inflammatory markers, disease activity, and applied treatment. However, the clinical significance of the differences identified remains modest.

Research perspectives

Further mechanistic studies of APOE action in IBD are warranted.

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