

NOD2, IL23R and ATG16L1 polymorphisms in Lithuanian patients with inflammatory bowel disease

Jurgita Sventoraityte, Aida Zvirbliene, Andre Franke, Ruta Kwiatkowski, Gediminas Kiudelis, Limas Kupcinskas, Stefan Schreiber

Abstract

AIM: To investigate the frequency of NOD2, IL23R and ATG16L1 genetic variants in a case-control panel for inflammatory bowel disease (IBD) from Lithuania.

METHODS: One hundred and eighty unrelated IBD patients [57 Crohn’s disease (CD) and 123 ulcerative colitis (UC)] and 186 healthy controls were genotyped for the following known genetic susceptibility variants: NOD2 - Arg702Trp (rs2066844), Gly908Arg (rs2066845) and Leu1007insC (rs2066847), as well as IL23R - Arg381Gln (rs11209026) and ATG16L1 - Thr300Ala (rs2241880).

RESULTS: The effect that carrihership of at least one NOD2 risk allele predisposes to CD was replicated in the Lithuanian population (41.1% CD vs 16.9% controls, \( P = 2 \times 10^{-4}, \text{OR} = 3.48, \text{95\% CI:} 1.81-6.72 \)). In the allelic single marker analysis, Leu1007insC was strongly associated with CD (21.4% CD vs 4.7% controls, \( P = 3.687 \times 10^{-8}, \text{OR} = 5.54, \text{95\% CI:} 2.85-10.75 \)). Neither the other two NOD2 variants, nor the known variants in IL23R and ATG16L1 were found to be risk factors for CD, UC or IBD. However, our relatively small study population was underpowered to demonstrate such weak to moderate disease associations.

CONCLUSION: The results support a strong association between CD susceptibility and the Leu1007insC variant in NOD2 in the Lithuanian study population.

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Key words: NOD2; IL23R; ATG16L1; Single nucleotide polymorphisms; Crohn’s disease; Ulcerative colitis; Lithuania

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clinically defined conditions, ulcerative colitis (UC) and Crohn’s disease (CD) that represent major burdens of morbidity in Western countries, with prevalence rates in North America and Europe ranging from 21 to 246 per 100 000 inhabitants for UC and 8 to 214 per 100 000 inhabitants for CD. Although the exact aetiology of IBD remains unclear, accumulating data suggests that IBD occurs from the combined effects of genetic predisposition and environmental factors.

Linkage, candidate gene, targeted association mapping and genome-wide association studies have identified many common variants associated with IBD and have rapidly expanded our fundamental knowledge of complex disease biology. The first and most consistently replicated genetic susceptibility variants, were found in the NOD2 gene, attributed to the recognition of bacterial products, along with several other genetic loci coding for cytokines involved in acquired immune responses (IL23R) and genes related to the autophagy pathway (ATG16L1).

Given the heterogeneity in allele frequencies reported for the genetic factors involved in the pathogenesis of IBD in different European populations, we aimed to perform the first genetic study of IBD in a low-incidence population of North-Eastern Europe – Lithuania. We examined the frequencies of the previously described variants in the NOD2, IL23R and ATG16L1 genes in a Lithuanian IBD study population.

MATERIALS AND METHODS

Patients

The study included 57 unrelated patients with CD, 123 with UC and 186 healthy, age- and gender-matched controls. All study participants were of Caucasian ethnicity. The recruitment of the study individuals was performed at the Department of Gastroenterology, Kaunas University of Medicine Hospital during the period from 2003 to 2006. Written informed consent from all participants and approval of the Kaunas Regional Biomedical Research Ethics Committee (Protocol No. 84/2003) was obtained. The diagnosis of either CD or UC was based on standard clinical, endoscopic, radiological and histological criteria. Patients’ demographic and phenotypic details are summarized in Table 1. The clinical characteristics provided in the table are given according to the Montreal classification.

Genotyping

Genomic DNA was isolated from EDTA peripheral blood using the Invisorb Blood Giga Kit fromInvitek (Berlin, Germany). The three NOD2 variants - Arg702Trp (rs2066844), Gly908Arg (rs2066845) and Leu1007insC (rs2066847), and the IL23R variant Arg381Gln (rs11209026) were genotyped using Applied Biosystem’s (Foster City, CA, USA) allele-specific TaqMan® or TaqMan-MGB assays (Table 2); ATG16L1 variant Thr300Ala (rs2241880) detection was performed using a pre-designed TaqMan® single nucleotide polymorphism (SNP) genotyping assay (ID C_9095577_20). Genotyping was performed on an automated platform using the TaqMan® (Applied Biosystems, Foster City, CA, USA) technique as previously described. All genotyped markers had a call rate greater than 95% in case and healthy control samples.

Statistical analysis

Each SNP was checked for conformance with Hardy-Weinberg equilibrium in the control group using Fisher’s exact test (P(HWE) > 0.01). Single-marker association analyses between cases and controls were performed using χ² statistics or Fisher’s exact genotypic test. The significance level of the tests for considering P-values as significant was set to < 0.05. Data were evaluated using the web interface SISA. Carriership of mutated alleles in case and control populations was estimated by direct counting.

The population attributable risk percentage (PAR%) was calculated as the attributable risk percentage (AR%) multiplied by the proportion of exposed cases, where AR% was estimated from the odds ratio (OR), assuming that the exposure of the control population to the disease-associated variant reflects the true prevalence of the variant in the general population.

RESULTS

Table 1 Summary of clinical and demographic characteristics of the IBD patients n (%)  

| Characteristics   | CD    | UC    |
|------------------|-------|-------|
| Gender (male/female) | 27/30 | 68/55 |
| Age (years ± SD)  | 40.5 ± 14.9 | 45.4 ± 16.4 |
| Age at diagnosis (years ± SD) | 31.7 ± 16.6 | 34.3 ± 14.7 |
| Familial IBD     | 0     | 0     |
| Surgery treatment | 15 (26.3) | 3 (2.4) |
| Disease extension in UC | - | 2 (21.1) |
| Proctitis        | -     | 61 (49.5) |
| Left-sided colitis| -     | 36 (29.3) |
| Disease localization in CD | Terminal ileum, L1 | 17 (29.8) |
| Colon, L1        | 16 (28.1) | -     |
| Ileocolon, L2     | 23 (40.3) | -     |
| Upper GI, L4      | 1 (1.8) | -     |
| Disease Behavior in CD | Non-stricturing, non-penetrating, B1 | 41 (71.9) |
| Stricturing, B2   | 5 (8.8) | -     |
| Penetrating, B3   | 11 (19.3) | -     |
| Perianal disease, B4 | -     | -     |
| Extraintestinal manifestations | Joints | 6 (10.5) |
| Cutaneous        | 3 (5.3) | 4 (3.3) |
| Gastrointestinal | 1 (1.8) | 0     |
| Hepatobiliary    | 0     | 2 (1.6) |

IBD: Inflammatory bowel diseases; CD: Crohn’s disease; UC: Ulcerative colitis.
Table 2  TaqMan® primer and probe sequences of NOD2 and IL23R assays

| Marker | Primers | Probes |
|--------|---------|--------|
| NOD2   | rs2066844 5′-TTCTTGGCACGCGGGGTCTGTGTC | TET-CCCTGGCAGGCAGCCCTAGCC |
|        | rs2066845 5′-ACTGGACTGCCTTGGGGGTTG | FAM-CTCTGGCAGGGCAGGGCTT |
|        | rs2066847 5′-CCCTTGCCGAGCACGCTTGGTTG | VIC-CTCTGGCAGGGCAGGGCTT |
| IL23R  | rs12189026 5′-CGAATGCTGATGATACTTTTTC | VIC-AGAATGCTGATGATACTTT |
|        | rs2066844 5′-TTCCTGGCAGGGCTGTTGTC | FAM-CTCTGGCAGGGCAGGGCTT |

The examined alleles are highlighted by bold underlined typing.

Table 3  Association statistics for the NOD2, ATG16L1 and IL23R variants in the Lithuanian IBD population

| Gene marker | Minor allele | Controls (n = 186) | CD (n = 56) | UC (n = 123) |
|-------------|--------------|------------------|-------------|-------------|
|             |              | GT (11/12/22) MAF P<.05 | GT (11/12/22) MAF P<.05 | GT (11/12/22) MAF P<.05 |
| NOD2        | T            | 0/9/171 0.025 > 0.99 | 0/2/54 0.018 > 0.99 | 0/10/113 0.041 0.278 1.65 (0.66-4.13) |
| rs2066845   | C            | 1/7/169 0.025 0.099 | 4/3/53 0.027 > 0.99 | 0/1/121 0.004 0.055 0.16 (0.02-1.25) |
| rs2066847   | insC         | 2/13/166 0.047 0.048 | 4/16/36 0.214 3.687×10^-4 1.69 (2.65-10.75) | 1/8/114 0.041 0.711 0.86 (0.39-1.91) |
| ATG16L1     | G            | 44/89/53 0.476 0.560 | 16/28/11 0.546 0.199 1.32 (0.86-2.03) | 33/61/25 0.534 0.164 1.26 (0.91-1.75) |
| IL23R       | A            | 3/16/167 0.059 0.017 | 0/4/52 0.036 0.359 0.59 (0.20-1.75) | 0/11/109 0.045 0.477 0.76 (0.36-1.61) |

Minor allele frequencies (MAF), genotype counts (GT; 11 = homozygous for minor allele; 12 = heterozygous for common allele; 22 = homozygous for common allele), allelic test P values (P<.05), and odds ratios (OR, shown for the minor allele) with 95% confidence intervals (CI) are depicted for both the CD and UC case-control population.

consistent with Hardy-Weinberg equilibrium (Table 3). For each of the variants studied, the risk of carrying the variant was compared between the CD, UC and healthy controls groups. The genotype and minor allele frequencies are presented in Table 3.

As expected, none of the studied individuals were carriers of all three NOD2 risk alleles. However, two CD patients were determined as compound heterozygotes. The combined allele carriership in the group of patients with CD was much higher than in controls (41.1% vs 16.9%) and resulted in significant association (P = 2 × 10^-4, OR = 3.48, 95% CI: 1.81-6.72) whereas no significant difference was observed between UC patients and controls. The PAR% in CD patients was 29.5% for possession of one or more NOD2 variant alleles at any of the three sites.

In the allelic single marker analysis of the NOD2 variants, a significant association was detected only between CD and Leu1007insC. For this variant, both the allelic and genotypic tests revealed P-values < 10^-4 (ORallele = 5.54, 95% CI: 2.85-10.75; ORassociation = 6.12, 95% CI: 2.88-13.15), resulting from the increased minor allele frequency (MAF) in cases (21.4%) vs controls (4.7%). In the UC group, the risk allele frequency of 4.1% was almost identical with the frequency detected in the controls. The frequencies of the other two NOD2 variants: Arg702Trp and Gly908Arg were low in both controls and IBD patients groups and were not statistically significant.

The allele frequencies distribution for the IL23R and ATG16L1 disease associated variants were almost identical between cases and controls and did not demonstrate significant differences.

**DISCUSSION**

This is the first report on the prevalence of the previously defined NOD2, ATG16L1 and IL23R disease associated variants in an IBD case-control sample from Lithuania. Baltic countries still observe low IBD incidence rates, especially for CD in their populations. In Estonia (1993-1998) the incidence rate of CD was reported to be 1.4 per 100 000 inhabitants [9,10], and in Lithuania (2006) - 2.0 per 100 000 inhabitants [11]. Therefore, analysis of the genetic contribution to disease susceptibility in this region was of great interest.

Since 2001, following the identification of NOD2 as the first gene conferring susceptibility to CD [3-5], a significant number of studies have replicated the association of the Arg702Trp, Gly908Arg and Leu1007insC variants with the development of CD in populations of Caucasian origin from Europe and North America [17]. However, significant heterogeneity in the frequencies of these variants has been observed not only between ethnically divergent populations [18,19], but also within Europe [17].
Our study results add to this pattern. The carriage of at least one NOD2 variant was highest in the CD patients group (41.1%) compared to the control group (16.9%) and resulted in the OR = 3.48 (95% CI: 1.81-6.72). These data are in concordance with previously reported rates of 30%-50% in CD and 7%-20% in controls from other European regions[8,9]. The Leu1007insC variant was responsible for the major contribution of NOD2 to disease susceptibility in the Lithuanian CD population (MAF = 21.4%, OR = 5.54, 95% CI: 2.89-10.75). These data are consistent with previous reports from Central Europe and North America (MAF = 6.6%-16%) and contrast markedly with studies performed in Northern Europe, where carriage rates of Leu1007insC and other NOD2 variants are relatively low, i.e. the carriage of at least one NOD2 variant varies from 2.8% to 22%[20,21]. However, we were not able to confirm the association between Arg702Trp, Gly908Arg and IBD susceptibility in our study group. These findings are in contrast with previous reports from Southern and Central European populations, where a positive association between Arg702Trp, Gly908Arg and CD was detected. The reported alleles frequency rates in these European countries vary from 6.7% to 12.5% for Arg702Trp, from 3.3% to 6.1% for Gly908Arg, respectively, in CD patients and from 3.5% to 6.9% and from 0.6% to 3.0%, respectively, in controls[8].

Moreover, the PAR%, an indication of the contribution of a mutation to the disease in a specific area, was 29.5% in the present study and contrasts with the other Northern European populations reporting lowest PAR% (range: 1.88%-11%)[20,21]. The PAR% measured in the Central European populations and North America was around 30%[15,17]. Therefore, the results of our study indicate that CD in Lithuania has a strong genetic background that is related partially to NOD2 susceptibility variants. Interestingly, the relatively high carrierness frequency of any of the three NOD2 alleles in the healthy controls (16.9%) in our study is in contrast with data of low CD incidence in Lithuania[9]. This indicates the importance of environmental factors (e.g. diet, lifestyle) in disease development.

The first two genome wide association studies identified genetic alterations within IL23R[8], a component of the adaptive immune system - and ATG16L1[9] - a protein involved in autphagic processes - to be associated with IBD susceptibility and adaptive immune system - and contributable risk of the associations with findings. We were just able to observe trends for possible population we were not able to confirm any of these failed to replicate these results, supporting the previously standing of the different pathways that are involved in the development of complex diseases. Future studies in larger study groups

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COMMENTS

Background

Numerous genome-wide and linkage studies have identified and replicated significant association between inflammatory bowel disease (IBD) development and polymorphisms of genes attributed to recognition of bacterial products (CARD15), adaptive immune responses (IL23R), and autophagosome pathways (ATG16L1). However, there has been reported a heterogeneity in allele frequencies of genetic factors involved in the pathogenesis of IBD in different European populations. The genetic association with IBD susceptibility has never been investigated in Lithuania previously.

Research frontiers

The research was performed to obtain data about the frequency of NOD2, IL23R and ATG16L1 genetic variants in a case-control study group for IBD from Lithuania.

Innovations and breakthroughs

The results of the authors’ study indicate that Crohn’s disease (CD) in Lithuania has a strong genetic background that relates partially to NOD2 susceptibility variants, especially Leu1007insC. The relatively high carrierness frequency of any of the three NOD2 alleles in the healthy controls (16.9%) in this study is in contrast with the data of low CD incidence in Lithuania. This indicates the importance of environmental factors (e.g. diet, lifestyle) in disease development.

Applications

This is one of the first studies investigating the genetic association with IBD in a North-Eastern European country. The results of this study confirm that the heterogeneity of variants might be observed within Europe and will further help to understand the role of interplay between genetic and environmental factors in the development of complex diseases. Future studies in larger study groups
and further analysis of the biological functions of the identified variants are required to understand their role in determining the risk of CD and ulcerative colitis in ethnically divergent populations.

Terminology

NOD2 is a member of the NACHT-LRR receptor (NLR) protein family, which is known to be involved in recognition of microbial structures. ATG16L1 encodes a protein which is part of a larger family of proteins that are required for the intracellular degradation system - autophagy process. IL23R encodes a protein which is a subunit of the receptor for IL23A/IL23 and participates in JAK-STAT3 signaling pathway.

Peer review

The authors concluded that the NOD2 Leu1007InsC variant increases susceptibility to CD in the Lithuanian study population, whereas associations of IL23R and ATG16L1 variants with any of the distinct IBD subtypes need to be further evaluated in larger Eastern European IBD sample collections. The study was conducted with good design and convincing analysis, and the manuscript has been well written and solid conclusions have been drawn.

REFERENCES

1. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; 126: 1504-1517
2. Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. *Nat Rev Immunol* 2003; 3: 521-533
3. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cézard JP, Belaiche J, Almer S, Tysk C, O’Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Cervera-Rousselot C, Mcry J, Colombel JF, Sahabatou M, Thomas G. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn’s disease. *Nature* 2001; 411: 599-603
4. Ogura Y, Bonen DK, Inohara N, Nicolae DL, Chen FF, Ramos R, Britton H, Moran T, Karaliuskas R, Duerr RH, Ackhar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G, Cho JH. A framshift mutation in NOD2 associated with susceptibility to Crohn’s disease. *Nature* 2001; 411: 603-606
5. Hampe J, Cuthbert A, Croucher PJ, Mirza MM, Mascheretti S, Fisher S, Frenzel H, King K, Hasselmeyer A, MacPherson AJ, Bridger S, van Deventer S, Forbes A, Nikolaus S, Lennard-Jones JE, Foelsch UR, Krawczak M, Lewis C, Schreiber S, Mathew CG. Association between insertion mutation in NOD2 gene and Crohn’s disease in German and British populations. *Lancet* 2001; 357: 1925-1928
6. Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhardt AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barmada MA, Achkar JP, Brant SR, Bayless TM, Kirschner BS, Hanauer SB, Nunez G, Cho JH. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Nat Rev Immunol* 2007; 3: 682-691
7. Prescott NJ, Fisher SA, Franke A, Hampe J, Onnie CM, Soars D, Bagnall R, Mirza MM, Sanderson J, Forbes A, Mansfield S, Lewis CJ, Lewis CM, Schreiber S, Mathew CG. A nonsynonymous SNP in ATG16L1 predisposes to ileal Crohn’s disease-assOCIated polymorphisms between German and Norwegian populations. *J Exp Med* 2006; 145: 459-468
8. Vind I, Vieira A, Houg L, Tavares L, Riis L, Andersen FS, Locht H, Freitas J, Monteiro I, Christensen IJ, Munkholm P. NOD2/CARD15 gene polymorphisms in Crohn’s disease: A meta-analysis. *J Exp Med* 2003; 2011; 6: 1-16
9. Medici V, Mascheretti S, Croucher PJ, Stoll M, Hampe J, Grebe J, Sturmiolo CC, Solberg C, Jahnse N, Joum M, Schreiber S, Vain MH. Extreme heterogeneity in CARD15 and DLG5 Crohn disease-associated polymorphisms between German and Norwegian populations. *J Exp Med* 2006; 145: 459-468
10. Podolsky DK. Inflammatory bowel disease (I). *N Engl J Med* 1991; 325: 928-937
11. 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 Jr. EV, Peto AS, Riddell RH, Sachar DB, Schreiber S, Steinhardt 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: 5-36
12. Hampe J, Wollstein A, Lu T, Frevel HJ, Will M, Manaster C, Schreiber S. An integrated system for high throughput TaqMan based SNP genotyping. *Bioinformatics* 2001; 17: 654-655
13. Uittenbroek DG. SISA-Binomial. 1997. Available from: URL: http://www.quantitativeskills.com/sisa/distributions/binomial.htm
14. Hennekens CH, Buring JE. Epidemiology in Medicine. 1st ed. Philadelphia: Lippincott Williams and Wilkins, 1987: 87-93
15. Salupere R. Inflammatory bowel disease in Estonia: A prospective epidemiologic study 1993-1998. *World J Gastroenterol* 2001; 7: 387-388
16. Economou M, Trikalinos TA, Loizou KT, Tsianos EV, Ioannidis JP. Differential effects of NOD2 variants on Crohn’s disease risk and phenotype in diverse populations: a meta-analysis. *Am J Gastroenterol* 2004; 99: 2393-2404
17. Yamazaki K, Takezoe M, Tanaka T, Kazumori T, Nakamura Y. Absence of mutation in the NOD2/CARD15 gene among 483 Japanese patients with Crohn’s disease. *J Hum Genet* 2002; 47: 469-472
18. Croucher PJ, Mascheretti S, Hampe J, Huse K, Frenzel H, Stoll M, Lu T, Nikolaus S, Yang SK, Krawczak M, Kim WH, Schreiber S. Haplotype structure and association to Crohn’s disease of CARD15 mutations in two ethnically divergent populations. *Eur J Hum Genet* 2003; 11: 6:16
19. Glus J, Konrad A, Schmelch S, Dambacher J, Seiderer J, Schropp F, Wetzke M, Roeseke D, Török HP, Tonenchi L, Pfenning S, Haller D, Griga T, Klein W, Epplen JT, Wolczynski C, Lobbe P, Gökke B, Oehsenkühn T, Mussack T, Wolczynski M, Müller-Myhsok B, Brand S, The ATG16L1 gene variants rs2241879 and rs2241880 (T300A) are strongly associated with susceptibility to Crohn’s disease in the German population. *Am J Gastroenterol* 2008; 103: 682-691
20. Prescott NJ, Fisher SA, Franke A, Hampe J, Onnie CM, Soars D, Bagnall R, Mirza MM, Sanderson J, Forbes A, Mansfield S, Lewis CJ, Lewis CM, Schreiber S, Mathew CG. A nonsynonymous SNP in ATG16L1 predisposes to ileal Crohn’s disease and is independent of CARD15 and IBD5. *Gastroenterology* 2007; 132: 1665-1671
21. Bucin C, Durnus T, Mohnar T, de Jong D, Drenth JPH, Fiedler T, Gentz E, Todorov T, Haas V, Buhner S, Sturm A, Baumgart DC, Nagy F, Lonovics J, Landt O, Kage A, Buning H, Nickel R, Buttner J, Locs H, Schmidt HHJ, Witt H. A study in three European IBD cohorts confirms that the ATG16L1 c.898A > G (p.Thr300Ala) variant is a susceptibility factor for Crohn’s disease. *J Crohn’s Colitis* 2007; 1: 70-76
Cummings JR, Cooney R, Pathan S, Anderson CA, Barrett JC, Beckly J, Geremia A, Hancock L, Guo C, Ahmadi T, Cardon LR, Jewell DP. Confirmation of the role of ATG16L1 as a Crohn’s disease susceptibility gene. Inflamm Bowel Dis 2007; 13: 941-946

Lakatos PL, Szamosi T, Szilvasi A, Molnar E, Lakatos L, Kovacs A, Molnar T, Altorjai I, Papp M, Tullassay Z, Miheller P, Papp J, Tordai A, Andrikovics H; Hungarian IBD Study Group. ATG16L1 and IL23 receptor (IL23R) genes are associated with disease susceptibility in Hungarian CD patients. Dig Liver Dis 2008; 40: 867-873

Weersma RK, Zhernakova A, Nolte IM, Lefebvre C, Rioux JD, Mulder F, van Dullemen HM, Kleibeuker JH, Wijmenga C, Di Ixkra G. ATG16L1 and IL23R are associated with inflammatory bowel diseases but not with celiac disease in the Netherlands. Am J Gastroenterol 2008; 103: 621-627

Büning C, Schmidt HH, Molnar T, De Jong DJ, Fiedler T, Bührer S, Baumgart DC, Nagy F, Lefebvre C, Rioux JD, Mulder F, van Dullemen HM, Kleibeuker JH, Wijmenga C, Di Ixkra G. ATG16L1 and IL23R are associated with inflammatory bowel diseases but not with celiac disease in the Netherlands. Am J Gastroenterol 2008; 103: 621-627

Einarsdottir E, Koskinen LL, Dukes E, Kainu K, Suomela S, Lappalainen M, Ziberna F, Korponay-Szabo IR, Kurppa K, Kaukinen K, Adány R, Pocsai Z, Széles G, Färkkilä M, Kontula K, Paavola-Sakki P. Association of IL23R gene polymorphism with inflammatory bowel disease. Clin Gastroenterol Hepatol 2007; 5: 977-981, 981.e1-e2

Tremelling M, Cummings F, Fisher SA, Mansfield J, Gwilliam R, Penney A, Nimmo ER, Drummond H, Orrin CM, Prescott NJ, Sanderson J, Bredin F, Berzuini C, Forbes A, Lewis CM, Cardon L, Deloukas P, Jewell D, Mathew CG, Parkes M, Satsangi J. IL23R variation determines susceptibility but not disease phenotype in inflammatory bowel disease. Gastroenterology 2007; 132: 1657-1664

Yamazaki K, Onouchi Y, Takazoe M, Kubo M, Nakamura Y, Hata A. Association analysis of genetic variants in IL23R, ATG16L1 and 5p13.1 loci with Crohn’s disease in Japanese patients. J Hum Genet 2007; 52: 575-583