Epithelial barrier and dendritic cell function in the intestinal mucosa
Verstege, M.I.

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Single nucleotide polymorphisms in C-type lectin genes, clustered in the IBD2 and IBD6 susceptibility loci, may play a role in the pathogenesis of inflammatory bowel diseases

Simone C. Wolfkamp¹², Marleen I. Verstege¹², Sander Meisner², Pieter C. Stokkers¹, Anje A. te Velde²

1. Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam

2. Tytgat Institute for Liver and Intestinal Diseases, Academic Medical Centre, Amsterdam
Chapter 5

Abstract

The balance between microbes and host defence mechanisms at the mucosal frontier plays an important, yet unclarified role in the pathogenesis of inflammatory bowel disease (IBD). The importance of micro-organisms in IBD is supported by the association of IBD with mutations in pathogen recognition receptors (PRRs) as NOD2 and TLR4. We wanted to investigate whether polymorphisms in another type of PRRs, the so-called C-type lectin receptors (CLRs) are associated with IBD. Growing insight in the pathogenetic role of NOD2 mutations in Crohn’s disease (CD) and the fact that the majority of CLR-encoding genes are located in IBD susceptibility loci provide strong arguments for further exploration of the role of CLRs in IBD. In this study, we selected four single nucleotide polymorphisms (SNPs) in different CLRs to see whether there could be a role for these CLRs in IBD. Functional SNPs in the candidate CLRs DC-SIGN, LLT1, DCIR and MGL were investigated. Genotyping of all SNP’s was performed at the AMC. In this study a total of 1348 patients were included of which 535 CD patients, 371 ulcerative colitis (UC) patients and 442 healthy controls (HC). No association was found between our IBD cohort and the candidate SNPs for DC-SIGN (CD/HC: p=0.25 and UC/HC: p=0.36), DCIR (CD/HC: p=0.22 and UC/HC: p=0.41) and MGL (CD/HC: p=0.37 and UC/HC: p=0.25). However, polymorphisms in LLT1 were associated with our CD population (p<0.034). Our UC cohort was not associated with the variation in LLT1 (p=0.33). LLT1 is a ligand for recently discovered CD161. CD161 is a new surface marker for human IL-17 producing Th17 cells. The Th17 phenotype has been linked to CD by the fact that IL-22, IL-17 and IL-23 receptor levels are increased in CD. The signal transduction pathways involving LLT1 and CD161 are not completely clarified and currently under investigation in our laboratory.
Introduction

Inflammatory Bowel Disease (IBD) is comprised of two major disorders, knowing Crohn’s Disease (CD) and Ulcerative Colitis (UC). Both diseases are characterised by chronic, relapsing intestinal inflammation causing diarrhoea, abdominal pain and malnutrition. CD can affect any part of the gastrointestinal tract, although the most common areas are the terminal ileum and colon, whereas UC is limited to the colon. Within the last era it has become clear that next to immunological and environmental factors, genetic factors play an important role in the pathogenesis of IBD. It is suggested that there is an inadequate immune response in a genetic susceptible host. Antigen presenting cells (APCs) highly express pattern recognition receptors (PRRs) to detect highly conserved structures of microbes and altered self proteins. Dependent on which PRRs are activated by specific antigens, APCs will direct naïve T cells to differentiate into Th1, Th2, Th17 of regulatory T cells. It has been shown earlier that mutations in the PRRs NOD2 (CARD15), NALP3 (CIAS1, NLRP3) and Toll-like receptor-4 are associated with the development of CD.  

One of the major classes of the PRRs are the C-type lectins. C-type lectin like receptors (CLRs) are expressed on dendritic cells (DCs) and macrophages, reflecting the position of these cell types as sensors at the interface of the immune system and environment. In 1860 the first animal lectins were already described as being a substance of snake venom, but it was Drickamer in 1988 who suggested a categorisation of the lectins into structural categories. Today, the classification of lectins is based on the primary protein sequence of the carbohydrate recognition domain (CRD), the protein domain involved in carbohydrate binding and the Ca2+ mediated carbohydrate recognition, typical for CLRs. CLRs are folded according the specific C-type lectin-like fold, consisting of two anti-parallel β strands and two α helices. They can be divided into two categories based on Ca2+ ion coordination and the orientation of their N-terminus. Although carbohydrate recognition is primarily determined by the amino acid sequence of the CRD fold, it is strongly influenced by the oligomerisation of the receptor. Oligomerisation not only
strengthens the binding to a certain structure, it also limits the binding to ligands with a complementary carbohydrate density and spacing. Most CLRs are present as transmembrane proteins on APCs, mostly immature DCs, although they can also appear soluble in the cell. Antigens can be taken up through CLRs, processed and presented to major histocompatibility complex (MHC) classes I and II, thereby inducing CD4 and CD8 T-cell responses. CLRs also play a role in signalling pathways upon glycan interaction and can thereby mediate a pro- or anti-inflammatory response. These responses are also influenced by the presence of a sequence motif, found in the intracellular domain of various receptors. The motifs, termed immunoreceptor tyrosine based activation (or inhibitory) motifs, (ITAMs or ITIMs), provide the basis for two opposed signalling modules that control the balance of the immune silencing and activation. CLRs have been shown to be involved in several aspects of the immune response. Growing insight in the pathogenetic role of mutations in PRRs as NOD2 in CD and the fact that the majority of the CLR encoding genes are located in IBD susceptibility loci provide strong arguments for further exploration of the role of CLRs in IBD. We selected four CLRs in this study to see whether there could be a role for these CLR’s in IBD. All four selected CLRs, knowing DC-SIGN (DC-specific intercellular adhesion molecule 3 (ICAM-3) grabbing nonintegrin), MGL (Macrophage Galactose-type Lectin, CLEC10A, CD301), DCIR (Dendritic Cell Immunoreceptor, CLEC4A) and LLT1 (Lectin-like transcript 1, CLEC2D) were chosen based on their known function, their presence on a susceptibility locus and their association with other chronic inflammatory or autoimmune diseases.
Materials and Methods

Genotyping

In this study we genotyped our cohort for four SNP’s in different CLRs (see table 1). DNA was isolated from venous blood, which was collected over the years from patients during periodic visits. Genotyping for the SNP’s was performed by polymerase chain reaction restriction fragment length polymorphisms (PCR-RFLP). Designed primers, thermal cycling and restriction enzymes (all from New England BioLabs, Ipswich, MA) are listed in table 1. Restriction fragments were separated and visualised using 3% agarose gel containing ethydium bromide.

<table>
<thead>
<tr>
<th>C-type lectin</th>
<th>CLEC4M</th>
<th>CLEC10a</th>
<th>CLEC4a</th>
<th>CLEC2d</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs number</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward:</td>
<td>3’gccaggccaggaaggagcag 5’</td>
<td>3’gagcttgcttctccgta 5’</td>
<td>3’gctcgagagagttctggag 5’</td>
<td>3’gttagctttaatagaatgctctt 5’</td>
</tr>
<tr>
<td>Reverse:</td>
<td>3’gcctgctgcttgctgtgcttttgctta 5’</td>
<td>3’gccacctgctcaagcttggactgtgttg 5’</td>
<td>3’gtagctttaatagaatgctctt 5’</td>
<td>3’ccaccagcaggtgaatgctctt 5’</td>
</tr>
<tr>
<td>Thermal cycling</td>
<td>96°C 15 min</td>
<td>95°C 5 min</td>
<td>95°C 5 min</td>
<td>95°C 5 min</td>
</tr>
<tr>
<td>57°C 1 min</td>
<td>57°C 45 sec</td>
<td>57°C 45 sec</td>
<td>57°C 45 sec</td>
<td>57°C 45 sec</td>
</tr>
<tr>
<td>8°C ∞</td>
<td>10°C ∞</td>
<td>10°C ∞</td>
<td>10°C ∞</td>
<td>10°C ∞</td>
</tr>
<tr>
<td>Restriction enzymes</td>
<td>HpyCH4 IV</td>
<td>AvaI</td>
<td>MaeIII</td>
<td>Bsm AI</td>
</tr>
<tr>
<td>Product size</td>
<td>240 bp</td>
<td>275 bp</td>
<td>272 bp</td>
<td>328 bp</td>
</tr>
<tr>
<td>Restriction digestion patterns</td>
<td>GG: 240 bp</td>
<td>AA: 275 bp</td>
<td>AA: 272 bp</td>
<td>GG: 396, 32 bp</td>
</tr>
<tr>
<td>AA: 240, 143, 96 bp</td>
<td>AG: 275, 246 bp</td>
<td>AT: 272, 235, 37 bp</td>
<td>GC: 328, 396, 32 bp</td>
<td></td>
</tr>
<tr>
<td>AA: 143, 96 bp</td>
<td>GG: 246, 29 bp</td>
<td>TT: 235, 37 bp</td>
<td>CC: 396, 32 bp</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Designed primers, thermal cycling and restriction enzymes.
Patients and controls for genotyping

The study population consisted of 1572 IBD patients. All patients were recruited through the outpatient clinic at the department of Gastroenterology in the Academic Medical Centre Amsterdam, Netherlands as part of an ongoing project to investigate genetic factors that contribute to the aetiology of IBD. All phenotypic patient information has been collected in an electronic patient file. The control group consisted of in total 586 healthy volunteers, partially the partner of the patient. All patients and controls gave informed consent and the study was approved by the ethics review committees of each of the participating university hospitals. All DNA samples and data in this study were handled anonymously.

Statistics

Confirmation to Hardy-Weinberg equilibrium was tested using $\chi^2$ test. Genotypes and allele frequencies of patients and HCs were compared by $\chi^2$ test. Significance level was set at $p<0.05$. All data were analysed using Graphpad prism 4 (Graphpad Prism v. 4 for Windows, GraphPad Software, San Diego, California USA).
SNPs in C-type lectin genes may play a role in the pathogenesis of IBD

Results

DC-SIGN

In total 1354 samples were genotyped for DC-SIGN (SNP rs735239) of which were 768 IBD patients (386 CD patients vs. 382 UC patients) and 586 healthy controls (HCs). When CD patients were compared to HCs no significant difference between the genotype frequencies was found (p=0.25), with G-allele frequencies of 65.5% for CD patients and 69.1% for HCs (p=0.10) (see table 2a). Moreover, analysis of the genotype frequencies between UC patients and HCs showed no significant difference (p=0.36), with G-allele frequencies of 66.1% for UC patients and 69.1% for HCs (p=0.16) (see table 2b).

MGL

In total 1572 samples were genotyped for MGL (SNP rs90951) of which were 1017 IBD patients (560 CD patients vs. 457 UC patients) and 555 HCs. When CD patients were compared to HCs no significant difference between the genotype frequencies was found (p=0.37), with A-allele frequencies of 66.7% for CD patients and 63.9% for HCs (p=0.16) (see table 2a). Besides, analysis of the genotypes frequencies between the UC patients and the HCs showed no significant difference (p=0.25), with A-allele frequencies of 66.7% for UC patients and 63.9% for HCs (p=0.16) (see table 2b).

DCIR

In total 1349 samples were genotyped for DCIR (SNP rs2024301) of which were 830 IBD patients (531 CD patients vs. 299 UC patients) and 519 HCs. When CD patients were compared to HCs no significant difference between the genotype frequencies was found (p=0.22), with A-allele frequencies of 66.9% for CD patients and 63.6% for HCs (p=0.12) (see table 2a). Moreover, analysis of the genotypes frequencies between the UC patients and the HCs showed no significant difference
(p=0.41), with A-allele frequencies of 66.7% for UC patients and 63.6% for HCs (p=0.20) (see table 2b).

**LLT1**

In total 1511 samples were genotyped for LLT1 (SNP rs3764022) of which were 1025 IBD patients (621 CD patients vs. 404 UC patients) and 486 HCs. When CD patients were compared to HCs a significant difference between the genotype frequencies was found with a p-value of 0.03. However, comparison of the allele frequencies (G-allele: 68.0% for CD and 65.6% for HCs) showed no significant difference (p=0.23) (see table 2a). Analysis of the genotype frequencies between the UC patients and the HCs showed no significant difference (p=0.33). When allele frequencies were assessed, no significant difference (p=0.52) was found (G-allele: 67.1% for UC patients and 65.6% for HCs) (see table 2b).
SNPs in C-type lectin genes may play a role in the pathogenesis of IBD.

<table>
<thead>
<tr>
<th>Gene</th>
<th>CD Genotype n (%)</th>
<th>CD Allelefreq. n (%)</th>
<th>HC Genotype n (%)</th>
<th>HC Allelefreq. n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GG</td>
<td>G 506 (65.5)</td>
<td>GG</td>
<td>G 810 (69.1)</td>
<td>P = 0.25</td>
</tr>
<tr>
<td>DC-SIGN</td>
<td>GA</td>
<td>A 266 (34.5)</td>
<td>GA</td>
<td>A 362 (30.9)</td>
<td>P = 0.10</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>A 46 (11.9)</td>
<td>AA</td>
<td>A 59 (10.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>A 747 (66.7)</td>
<td>AA</td>
<td>A 709 (63.9)</td>
<td>P = 0.37</td>
</tr>
<tr>
<td>MGL</td>
<td>AG</td>
<td>G 373 (33.3)</td>
<td>AG</td>
<td>G 401 (36.1)</td>
<td>P = 0.16</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>G 69 (12.3)</td>
<td>GG</td>
<td>G 83 (15.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>A 239 (45.0)</td>
<td>AA</td>
<td>A 660 (63.6)</td>
<td>P = 0.22</td>
</tr>
<tr>
<td>DCIR</td>
<td>AT</td>
<td>T 352 (33.1)</td>
<td>AT</td>
<td>T 378 (36.4)</td>
<td>P = 0.12</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>T 60 (11.3)</td>
<td>TT</td>
<td>T 77 (14.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>G 845 (68.0)</td>
<td>GG</td>
<td>G 638 (65.6)</td>
<td>P = 0.03*</td>
</tr>
<tr>
<td>LLT1</td>
<td>GC</td>
<td>C 397 (32.0)</td>
<td>GC</td>
<td>C 334 (34.4)</td>
<td>P = 0.23</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>C 53 (8.5)</td>
<td>CC</td>
<td>C 64 (13.2)</td>
<td></td>
</tr>
</tbody>
</table>

*Table 2a. Genotype frequencies and allele frequencies of CD patients compared to HCs. n = number of patients, % = percentage, P = genotype frequency p-value, 2 p = allele frequency p-value.*
<table>
<thead>
<tr>
<th>Genotype</th>
<th>Allelefreq.</th>
<th>Genotype</th>
<th>Allelefreq.</th>
<th>P–value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG 167 (43,7) G 505 (66,1)</td>
<td>GG 283 (48,3) G 810 (69,1)</td>
<td>1 P = 0.36</td>
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<td></td>
</tr>
<tr>
<td>DC-SIGN GA 171 (44,8) A 259 (33,9)</td>
<td>GA 244 (41,6) A 362 (33,9)</td>
<td>2 P = 0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA 44 (11,5)</td>
<td>AA 59 (10,1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA 205 (44,9) A 610 (66,7)</td>
<td>AA 237 (42,7) A 709 (63,9)</td>
<td>1 P = 0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGL AG 200 (43,8) G 304 (33,3)</td>
<td>AG 235 (42,3) G 401 (36,1)</td>
<td>2 P = 0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG 52 (11,4)</td>
<td>GG 83 (15,0)</td>
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<tr>
<td>DCIR AT 129 (43,1) T 199 (33,3)</td>
<td>AT 224 (43,2) T 378 (36,4)</td>
<td>2 P = 0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT 35 (11,7)</td>
<td>TT 77 (14,8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LLT1 GC 184 (45,5) C 266 (32,9)</td>
<td>GC 206 (42,4) C 334 (34,4)</td>
<td>2 P = 0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC 41 (10,1)</td>
<td>CC 64 (13,2)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Table 2b. Genotype frequencies and allele frequencies of UC patients compared to HCs. \( n \) = number of patients, \% = percentage, \(^1\) p = genotype frequency p-value, \(^2\) p = allele frequency p-value.
SNPs in C-type lectin genes may play a role in the pathogenesis of IBD

Discussion and Conclusion

In this study we hypothesised that mutations in CLRs as innate sensors of DCs are associated with IBD. All chosen CLRs are located on IBD susceptibility loci and are associated with other chronic inflammatory or autoimmune diseases. The most studied CLR of the four is the Ca\(^2+\)-dependent type II C-type lectin DC-SIGN, encoded by a member of the CD209 gene family on chromosome 19p13. This receptor binds the natural ligands ICAM-2 on endothelial cells and ICAM-3 on T cells resulting in close cell-cell contact, required for extravasation and antigen presentation respectively. Moreover, it may represent a common thread in many inflammatory diseases as IBD, as it has also been shown to facilitate direct infection of DCs by a range of infectious agents, such as HIV-1, Dengue virus, Ebola virus, human cytomegalovirus, *Leishmania pifanoi* amastigotes and *Mycobacterium tuberculosis*. Studies using anti-DC-SIGN antibodies as antigen indicate that DC-SIGN functions as a receptor that mediates antigen uptake for presentation to T cells. Hardly any data demonstrate that pathogen internalisation through DC-SIGN leads to enhanced pathogen-specific T cell responses. The general finding is that several pathogens target CLRs on DCs to evade immune responses, such as HIV-1 or the secreted product ManLAM of *M. tuberculosis* that inhibits DC maturation and enhances the production of IL-10. *Lactobacilli* modulate DCs to stimulate the development of regulatory T cells via DC-SIGN. In addition, other bacteria binding to DC-SIGN induce a skewing of the immune response to a Th1- or Th2-like cytokine profile. The general thought is that antigen uptake via CLRs in the absence of danger signals via Toll-like receptors does not lead to effective immunity, but instead to the induction of tolerogenic T cells. It has been suggested by Nunez *et al.*, that another functional variant in the CD209 gene, rs4804803, could be involved in the aetiology or pathology of UC in HLA-DR3-positive individuals. These findings suggest a role potential role for DC-SIGN in the pathophysiology of IBD. However, in this study we were unable to find associations between polymorphisms in DC-SIGN and any of our IBD patient groups.
Macrophage galactose-type lectin (MGL, CLEC10A, CD301), located on chromosome 17p13, is a CLR expressed on monocyte-derived immature DCs and an intermediate stage of macrophage differentiation \(^{22,22-24}\). It has been identified on dermal, gut, thymus and lymph node APCs. MGL is not expressed by monocytes, lymphocytes, plasmacytoid DC’s and resident Langerhans cells \(^{24}\). Moreover, MGL is upregulated during chronic inflammatory conditions such as rheumatoid arthritis on APCs in the affected tissue, maybe linking MGL to IBD. MGL has a specific CRD for terminal Ga1NAc moieties, parts of glycoproteins or glycolipids that function as ligands for MGL \(^{25}\). As PRR, MGL can bind to CD45, thereby down-regulating the T cell activation via APCs, which results in decreasing cytokine and proliferative responses and T cell death \(^{26}\). Homeostatic control of T cells involves tight regulation of effector T cells to prevent excessive activation that can cause tissue damage and autoimmunity, also thereby linking MGL to IBD as an autoimmune disease. Up until today there are no signalling pathways established for MGL. However, van Vliet et al. suggested that MGL may play a role in negative regulation of effector T-cells and negatively regulates DC maturation \(^{26,27}\). The fact that MGL can be linked to both chronic inflammatory diseases as well as autoimmune diseases resulted in this study to associate SNPs in MGL with IBD. Unfortunately, we were unable to detect an association of polymorphisms in MGL with our IBD patient cohort.

DCIR (CLED4A) located on chromosome 12p13, was originally presented by Bates in 1999 as molecular homologue of asialoglycoprotein receptor (ASGPR) and macrophage lectin \(^{11,28}\). It is a C-type lectin expressed on DC’s, granulocytes, monocytes, macrophages and B-cells. DCIR has an ITIM motif, which has shown to inhibit signal transduction when activated and it is present in the cytoplasmic tail of the C-type lectin-like molecules. After stimulation with LPS or the pro-inflammatory cytokines TNF-\(\alpha\) and IL-1\(\beta\), DCIR was down-regulated during inflammation, although stimulation with other cytokines as GM-CSF, IL-3, IL-4 and IL-13 showed accumulation of a short form of DCIR mRNA, which encodes a putative non-functional protein which may act as an antagonist to the full length...
SNPs in C-type lectin genes may play a role in the pathogenesis of IBD. The presence of the ITIM and the down-regulation of DCIR in pro-inflammatory settings, suggest a regulatory role for this receptor. Furthermore, Fujikado et al. showed that DCIR also plays a role in controlling autoimmune diseases. Aged DCIR-deficient mice developed joint abnormalities, had elevated levels of auto-antibodies and showed higher levels of CD11c+ DCs and proportional expansion of T cell populations in their lymph nodes. Young DCIR-deficient mice were found to develop more severe disease than their wild type littermates, suggesting a protective effect of DCIR. Also, the DCIR receptor was found abundantly in synovial fluid of patients with rheumatoid arthritis. This was the opposite in the control group, suggesting a role for DCIR in the development of autoimmune diseases. These last two findings suggest both an anti-inflammatory as well as an autoimmune role for DCIR, thereby linking it to IBD. We were unable to establish a role for variants of DCIR in our IBD patient cohort.

The last CLR genotyped for its SNP was LLT1, also known as CLEC2D. This CLR is located on IBD locus 2 and is expressed on activated B cells and DCs. Furthermore, LLT1 is expressed on peripheral blood mononuclear cells after stimulation through several Toll-like receptors. We found an association between LLT1 and our CD population (p<0.034). Since the homozygous mutant is less common in the CD cohort, it is likely that this polymorphism protects against the development of CD. Our UC cohort was not associated with the variation in LLT1 (p=0.33). LLT1 is a ligand for CD161 and as a complex it inhibits NK cell-mediated cytotoxicity and cytokine production. CD161 is a new surface marker for human IL-17 producing Th17 cells. The Th17 phenotype has recently been linked to CD by the fact that IL-22, IL-17 and IL-23 receptor levels are increased in CD. Further studies will analyse the role of CD161 in our IBD patient cohort.

Although we were unable to associate three of the four candidate SNPs to our IBD patient cohort, this does not mean that CLRs do not play a role in the pathophysiology of IBD. This is illustrated by the recent finding of Thebault et al. who demonstrate that CLEC-1 is associated with a higher production of IL-17.
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CLEC-1, expressed by myeloid cells and endothelial cells, is enhanced by regulatory mediators and moderates Th17 differentiation and thereby involved in processes of autoimmunity and thus IBD. Further studies and extensive SNP analysis in ongoing Genome Wide Association Studies will clarify the role of CLRs in autoimmunity.

Acknowledgements

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SNPs in C-type lectin genes may play a role in the pathogenesis of IBD

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