ORIGINAL ARTICLE

HNF4α and *CDH1* Are Associated with Ulcerative Colitis in a Dutch Cohort

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Background: Inflammatory bowel diseases (IBDs), consisting of ulcerative colitis (UC) and Crohn's disease (CD), are complex disorders with multiple genes contributing to disease pathogenesis. A recent genome-wide association scan identified three novel susceptibility loci for UC: *HNF4α*, *CDH1*, and *LAMB1*. We performed an analysis of these three loci in an independent cohort.

Methods: In all, 821 UC patients and 1260 healthy controls of central European Caucasian descent were genotyped for single nucleotide polymorphisms (SNPs): rs6017342 (*HNF4α*), rs1728785 (*CDH1*), and rs6949033 (*LAMB1*). Differences in allele and genotype distribution in cases and controls were tested for significance with the χ^2 test.

Results: Allelic association analysis showed that SNP rs6017342 in the *HNF4α* locus was strongly associated with UC ($P = 1{,}04 \times 10^{-11}$, odds ratio [OR] = 1.56, 95% confidence interval [CI] = 1.37–1.77) and SNP rs1728785 (*CDH1*) was associated with $P = 0.01$ (OR = 1.23, 95% CI = 1.05–1.44). SNP rs6949033 in *LAMB1* was not associated in our cohort ($P = 0.12$, OR = 1.11, 95% CI = 0.97–1.26). We found an association for SNP rs6949033 (*LAMB1*) for disease limited to the rectum ($P = 0.02$). However, this association was lost after correcting for multiple testing. No further specific subphenotype associations were identified.

Conclusions: This is the first independent study to replicate the *HNF4α* and *CDH1* loci as susceptibility loci for UC. The main candidate genes in these risk loci play important roles in the maintenance of the integrity of the epithelial barrier, highlighting the importance of the mucosal barrier function for UC pathogenesis.

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Key Words: ulcerative colitis, genetics, inflammatory bowel diseases, *HNF4α*, *CDH1*

Inflammatory bowel diseases (IBDs) are common, chronic gastrointestinal inflammatory disorders with a prevalence of 100–200/100.000 in the developed countries. They comprise two major forms: Crohn's disease (CD) and ulcerative colitis (UC).[1,2] The etiology of CD and UC is complex and consists of an aberrant immune response to the commensal bacterial flora in a genetically susceptible host. It is thought that this aberrant response is due to a combination of factors, including environmental and genetic factors, causing defects in both innate and adaptive immunity and epithelial barrier function.[2]

The genetic basis of IBD has long been appreciated through family studies, with ≈30,0% concordance of IBD among monozygotic twins.[3] IBDs are complex genetic disorders with multiple genes contributing to the disease pathogenesis. Until recently the focus in genetic research in IBD was mainly on CD; however, in recent years the attention also turned to UC, with six genome-wide association studies (GWAS) identifying 18 UC-associated loci. These studies highlighted both disease-specific loci and other loci that are shared between UC and CD.[4–10]

As part of the Wellcome Trust Case Control Consortium phase 2 (WTCCC2), the UK IBD Genetics Consortium identified three novel susceptibility loci for UC, comprising *HNF4α*, *CDH1*, and *LAMB1*, which all play a role in epithelial barrier function.[4] Given the central role of the epithelium in regulating inflammatory responses, the importance of the intestinal barrier in limiting access of toxins

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and microbes to underlying tissues and the antimicrobial nature of the immune responses in UC, intestinal barrier dysfunction is an important factor in UC pathogenesis.[11]

Replication studies are important to support the differences between true-positive associations and false ones.[12] Essential in a replication study is the presence of independent populations using large sample sizes with matched controls and disease phenotypes mostly comparable with those used in the initial studies. We undertook a study in a Dutch cohort of UC patients and tested these three new associated loci (*HNF4α*, *CDH1*, *LAMB1*) in 821 UC patients and 1260 controls.

MATERIALS AND METHODS

Patients and Controls

Cases consisted of 838 Dutch UC patients. Cases were collected at the Academic Medical Center, Amsterdam ($n = 409$) the University Medical Center St. Radboud, Nijmegen ($n = 206$), and the University Medical Center Groningen, Groningen ($n = 223$), the Netherlands. Healthy controls consisted of 1260 Dutch blood bank donors collected at the University Medical Center Groningen, Groningen. All cases and controls were of European Caucasian descent. Patients were diagnosed according to accepted clinical, endoscopic, radiological, and histological findings.[2] For UC patients, phenotypes were described according to age of onset, maximum extent of disease (proctitis, left-sided, or extensive), necessity of colectomy, and the occurrence of malignancy and extraintestinal manifestations. Clinical data of the study population are presented in Table 1.

In all cases, informed consent was obtained using protocols approved by the local Institutional Review Board in all participating institutions. All patients and controls gave informed consent and DNA samples were handled anonymously.

DNA Samples and Single Nucleotide Polymorphism (SNP) Genotyping

All individuals in the study populations provided blood samples and DNA was extracted according to standard protocols.[13] Samples that displayed undetermined genotypes for all tested SNPs were excluded from analysis ($n = 17$), assuming insufficient DNA quality. All excluded samples were cases, so the final number of cases was 821.

For this study the three SNPs showing genome-wide significant association in the WTCCC2 GWA study[4] were selected: SNP rs6017342 (*HNF4α*), SNP rs1728785 (*CDH1*), and SNP rs886774 (*LAMB1*). Probably due to an unknown polymorphism in the primer, SNP rs886774 (*LAMB1*) gave technical problems: genotypes of a group of individuals could not reliably be called. This SNP was replaced by a proxy SNP rs6949033 (D' and $r^2 = 1$). Genotyping was performed at the Department of Genetics, University Medical Center Groningen, using Taqman technology and SNP genotyping assays for polymerase chain reaction (PCR) obtained from Applied Biosystems (Nieuwerkerk a/d IJssel, the Netherlands) between December 2009 and March 2010. Genotyping of the SNPs was successful with a call rate >95%.

TABLE 1. Clinical Characteristics of Ulcerative Colitis Patients and Healthy Controls

	Cases		Controls	
Total number	821		1260	
Sex[a]				
Male	393	50.4%	765	61.6%
Female	386	49.6%	476	38.4%
Age[b]				
Mean (years)	44.2		50.8	
Median (years)	42.9		52.4	
Age at diagnosis[c]				
Mean (years)	31.3			
Median (years)	29.0			
Early onset (<18 years)	71	11.0%		
Adult onset (≥18 years)	575	89.0%		
Disease extent[d]				
Proctitis	70	11.8%		
Left-sided	174	29.4%		
Extensive	339	57.4%		
Extraintestinal manifestations[e]	71	15.9%		
Colectomy[f]	167	27.5%		
Colorectal cancer[g]	2	0.5%		

[a,b]Data available for >95% of samples.
[c,d,f]Data available for >70% of samples.
[e,g]Data available for >50% of cases.

Statistical Analysis

All genotypes obtained were tested for Hardy–Weinberg equilibrium by χ^2 testing. Deviation from Hardy–Weinberg equilibrium was defined when observed genotypes differed significantly from expected genotypes. Differences in allele and genotype distribution in cases and controls were tested for significance by the χ^2 test, and odds ratios (OR) and confidence intervals (CI) were calculated.

Association between SNPs and subphenotypes were calculated using a within-cases analysis. The subphenotype analyses consisted of limited disease (proctitis) against left-sided and extensive disease, and extensive disease against proctitis and left-sided. The subphenotype analyses were also tested for statistical significance using the χ^2 test. *P*-values from the subphenotype analysis were corrected for

TABLE 2. Allelic Association Analysis for 821 UC Patients and 1260 Healthy Controls

SNP	Chr	Position[a]	Gene	Risk Allele	RAF Controls	RAF Cases	*P*-value	OR	95% CI
rs6017342	20q13.12	42.498.442	*HNF4α*	C	0.49	0.60	$\mathbf{1.04 \times 10^{-11}}$	1.56	1.37–1.77
rs1728785	16q22.1	67.148.731	*CDH1*	C	0.78	0.81	**0.01**	1.23	1.05–1.44
rs6949033[b]	7q31.1	107.282.453	*LAMB1*	A	0.42	0.44	0.12	1.11	0.97–1.26

[a]Position NCBI Build 36.1 coordinates.
[b]Proxy for rs886774 (D′ and r^2=1).
Statistically significant associations in bold.
SNP, single nucleotide polymorphism; Chr, chromosome; RAF, risk allele frequency; OR, odds ratio; CI, confidence interval.

multiple testing with Bonferroni's correction for six analyses.

To test for interaction between two loci, an epistasis analysis was performed. Combined allele frequencies for paired SNPs were compared between cases and controls and tested for significance by χ^2 testing.

All analyses were performed using the Plink association analysis toolset.[14] All significant thresholds were set at $P < 0.05$.

RESULTS

Genotyping Success Rate and Hardy–Weinberg Equilibrium

After excluding cases with insufficient DNA quality, 97.7% of the cases and 98.0% of the controls were successfully genotyped. Controls showed no deviation from Hardy–Weinberg equilibrium for all tested SNPs.

Replication of Susceptibility Loci from the UC-GWA Study

Allelic association analysis results are shown in Table 2. SNP rs6017342 in the HNF4α locus was strongly associated with UC ($P = 1.04 \times 10^{-11}$, OR = 1.56, 95% CI = 1.37–1.77), which reached genome-wide significant association. Bases on genotype frequency, $P = 6.65 \times 10^{-11}$ (OR = 1.56, 95% CI = 1.37–1.79). Results from the sub-phenotype analyses are shown in Table 3. The association could not be specified for limited or severe UC subphenotypes in the subphenotype analysis.

SNP rs1728785 (*CDH1*) was associated with UC, with $P = 0.01$ (OR = 1.23, 95% CI = 1.05–1.44). The *P*-value for the genotype association analysis was 0.03 (OR = 1.23, 95% CI = 1.05–1.45). This locus was not associated with a distinct subphenotype.

We did not find an association of rs6949033 (*LAMB1*) with UC. We found an association for SNP rs6949033 (*LAMB1*) for disease limited to the rectum ($P = 0.02$). However, this association was lost after correcting for multiple testing.

No statistically significant epistasis was seen for the three SNPs. The strongest interaction was seen between rs1728785 (*CDH1*) and rs6017342 (*HNF4α*) with $P = 0.05$.

DISCUSSION

We confirmed the association between UC and two susceptibility loci previously identified by the WTCCC2 and UK IBD Genetics Consortium: *HNF4α* and *CDH1*. The *HNF4α* locus was also strongly associated with UC in the WTCCC2 GWA study ($P = 8.5 \times 10^{-17}$). The *CDH1* locus was associated, with $P = 2.8 \times 10^{-8}$ in the WTCCC2 GWA study, comparable to the *LAMB1* locus (*P*

TABLE 3. Subphenotype Analysis

SNP	Gene	Subphenotype Analysis	Minor Allele	*P*-value[a]	OR	95% CI
rs6949033	*LAMB1*	Limited disease	A	**0.02**	0.64	0.44–0.93
rs6949033	*LAMB1*	Extensive disease	A	0.69	0.95	0.75–1.21
rs1728785	*CDH1*	Limited disease	A	0.20	1.33	0.86–2.07
rs1728785	*CDH1*	Extensive disease	A	0.08	0.76	0.56–1.04
rs6017342	*HNF4α*	Limited disease	A	0.96	0.99	0.69–1.43
rs6017342	*HNF4α*	Extensive disease	A	0.34	1.12	0.88–1.43

[a]Uncorrected for multiple testing.
Statistically significant associations in bold.
SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

$= 3.0 \times 10^{-8}$), which could not be confirmed in the current study. The direction of the association for the associations is the same as in the WTCCC2 GWA study. However, the magnitude of association for both *HNF4α* and *CDH1* is even larger.

The *HNF4α* locus showed the strongest association with UC. This locus was also the most associated locus in the WTCCC2 and UK IBD Consortium GWA study. It is extraordinary to discover a locus this strongly associated with UC after so many performed GWA studies. This can be explained by the simple fact that this SNP was not tested on previously used platforms.[6,7] The *HNF4α*, or hepatocyte nuclear factor 4 alpha gene is the most likely candidate gene in this locus at 20q13. HNF4α is a nuclear transcription factor, controlling expression of multiple genes.[15] From a functional perspective, HNF4α is important for epithelium homeostasis, cell function, and cell architecture in the liver and the gastrointestinal tract.[16–19] In the gastrointestinal tract, the protein controls the expression of several components of the cell–cell junction in the intestinal epithelium. In mice, loss of *HNF4α* leads to increased paracellular permeability through impairment of cell–cell junctions, indicating that HNF4α is crucial for the barrier function of the intestinal mucosa.[18] Another important function of *HNF4α* is its role as a transcriptional regulator of ion transport: loss of *HNF4α* in mice initiates loss of mucosal homeostasis through a decline in mucosal ion transport. This loss of mucosal homeostasis triggers a chronic inflammatory response in the colon of the mice and worsens tissue damage in experimental colitis.[20,21] Both the impairment of the integrity of the intestinal epithelium and loss of mucosal homeostasis have been shown to be primary events in UC pathogenesis, which makes *HNF4α* a very attractive candidate gene for the disease. Other genes surrounding *HNF4α* are *TTPAL*, *ADA*, *SERINC3*, and *PKIG*. *ADA* (adenosine deaminase) has been associated with severe combined immunodeficiency disease (SCID), causing a dysfunction of both B and T lymphocytes with impaired cellular immunity and decreased production of immunoglobulins.[22] However, neither *ADA* nor the other genes are functionally as interesting as *HNF4α*.

The second UC-associated locus we confirmed is the *CDH1* locus. The *CDH1* locus at 16q22 comprises three genes, of which *CDH1* is the most plausible candidate gene. *CDH1* encodes E-cadherin, a protein that plays an important role in cell–cell adhesions.[23] Several studies suggest that loss or mislocalization of E-cadherin causes IBD through disruption of cell–cell contacts and increased permeability.[24,25] Interestingly, different bacteria are able to mediate adhesion to epithelial cells and disrupt the cell–cell adhesions by means of downregulating E-cadherin.[26] In this way E-cadherin is important for invasion and adhesion of pathogens, which may contribute to IBD pathogenesis. Furthermore, *CDH1* mutations are associated with multiple epithelial tumors, like gastric cancer, esophageal cancer, and colorectal cancer.[27–29] In these tumors, loss of E-cadherin causes increased proliferation, invasion, and metastasis.[30,31] Especially the association between *CDH1* mutations and colorectal cancer (CRC) is interesting because patients with UC are more prone to develop CRC.[32] The association between *CDH1* and both traits gives us an indication that there might be a shared genetic background between the two diseases.

CDH3, encoding P-cadherin, is the second gene in the 16q22 locus. P-cadherin, like E-cadherin, is a member of the cadherin superfamily. In contrast to E-cadherin, P-cadherin has not been related to IBD in functional studies; therefore, *CDH1* was selected as the most probable candidate gene in the original GWAS study.[4] The third gene in this locus is a zinc finger protein, *ZFP90*; no specific function for this gene is known. Fine mapping of this region and additional functional studies are needed to clarify which gene is actually the causative gene within the locus.

Interestingly, E-cadherin and *HNF4α* interact in the Wnt/*β*-catenin signaling pathway. Loss of *HNF4α* induces mislocalization of E-cadherin, which results in destabilized cell–cell junctions and increased intestinal permeability.[18] These findings suggest that having defects in both genes would destabilize cell–cell junction further, increasing the risk of IBD. We did not see epistasis between the *HNF4α* and *CDH1* risk variants in our dataset, but this could be explained by lack of statistical power. The fact that we could not replicate the association between the *LAMB1* locus and UC could be due to the lack of statistical power. Post-hoc power analysis revealed that for *LAMB1* the power to detect an association with an OR of 1.11 was only 32%. Other possible causes are genetic heterogeneity, or a difference in disease phenotypes between the British discovery cohort and our Dutch cohort. Cases in this study more often have extensive disease than the population in the WTCCC2 GWA study. Also, cases described in our study have a lower age at diagnosis, and undergo colectomy more often than the British cases. These differences are statistically significant ($P < 0.0001$). Differences might have arisen because the Dutch cases were all selected at tertiary referral centers. Moreover, in the subphenotype analysis we found a trend towards association for less extensive disease. These observations suggest that our negative findings were due to more severe disease phenotypes in our cohort and that *LAMB1* mostly influences risk for mild UC.

In conclusion, this is the first independent study to replicate the *HNF4α* and *CDH1* loci as susceptibility loci for UC. The main candidate genes in these risk loci play important roles in the maintenance of the integrity of the

epithelial barrier, highlighting the importance of the mucosal barrier function for UC pathogenesis.

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