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Association of hOGG1 and APE1 gene polymorphisms with disease severity in ulcerative colitis: A case-control study

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MAIN POINTS

- The hOGG1 Ser326Cys polymorphism was significantly associated with severe ulcerative colitis activity, suggesting its potential role in disease progression.
- The APE1 Asp148Glu polymorphism showed no significant association with disease presence or severity.
- Impaired base excision repair (BER) capacity may contribute to increased oxidative DNA damage and inflammation in UC.
- The hOGG1 Ser326Cys variant could serve as a genetic biomarker for disease severity and guide personalized management in UC patients.

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ABSTRACT

Aim: Ulcerative colitis (UC) is a chronic inflammatory disease of the colon characterized by excessive oxidative stress and impaired DNA repair mechanisms. This study aimed to investigate the relationship between two key base excision repair gene polymorphisms---APE1 (Asp148Glu) and hOGG1 (Ser326Cys)---and clinical features of UC, particularly disease activity.

Materials and Methods: Ninety-nine UC patients, 50 colorectal cancer (CRC) patients, and 50 age- and gender-matched healthy controls were enrolled. Peripheral blood samples were collected for DNA extraction, and genotyping was performed using real-time PCR and melting curve analysis. Clinical data, including disease duration, location, and activity based on the Truelove-Witts index, were analyzed about genetic variants.

Results: No significant differences were found in the genotype or allele frequencies of APE1 and hOGG1 between UC, CRC, and control groups. However, the hOGG1 Ser326Cys polymorphism was significantly more frequent in UC patients with severe disease activity ($p = 0.034$), suggesting a possible role in disease progression.

Conclusion: The hOGG1 Ser326Cys polymorphism may be associated with increased disease severity in UC and could serve as a potential prognostic biomarker. Further studies are needed to validate this finding in larger cohorts.

Keywords: Ulcerative colitis, DNA repair, Genetic polymorphism, Reactive oxygen species

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disorder characterized by recurring inflammation of the colonic mucosa, often extending from the rectum to the cecum [1]. One of the key pathogenic mechanisms in UC is oxidative stress, which arises from an imbalance between prooxidant and antioxidant systems. This imbalance promotes the excessive production of reactive oxygen species (ROS) that interact with cellular components, leading to damage to DNA, proteins, and lipids [2,3].

In addition to oxidative stress and impaired DNA repair, ulcerative colitis is increasingly recognized as an autoimmune disorder driven by complex immune dysregulation. Imbalances in innate and adaptive immunity, particularly alterations in T helper subsets, regulatory T-cell dysfunction, and plasmablast-skewed humoral responses, play central roles in sustaining chronic mucosal inflammation [4,5]. Furthermore, environmental and dietary factors are now considered important modulators of oxidative stress and disease course, with evidence linking processed food intake, microbiota composition, and eating behaviors to UC pathogenesis [6-8]. Integrating genetic, immunological, and environmental perspectives therefore provides a more comprehensive framework for understanding UC pathophysiology.

DNA damage caused by ROS includes single-base modifications, strand breaks, and intra/inter-strand cross-links [3].

Under physiological conditions, such damage is counteracted by complex DNA repair systems, among which base excision repair (BER) plays a central role in repairing oxidative lesions [9–11]. Key enzymes in this pathway include apurinic/apyrimidinic endonuclease 1 (APE1) and human 8-oxoguanine DNA glycosylase (hOGG1), which recognize and excise oxidized bases to maintain genomic stability [12,13].

Genetic polymorphisms in BER enzymes may impair their activity and contribute to reduced DNA repair capacity. In particular, the APE1 Asp148Glu and hOGG1 Ser326Cys polymorphisms have been associated with altered enzymatic function [13,14]. These polymorphisms can potentially exacerbate oxidative stress by reducing DNA repair efficiency, thereby contributing to persistent inflammation and increasing susceptibility to neoplastic transformation [15,16].

Although much of the literature has focused on the role of these variants in colorectal cancer (CRC), their impact on the severity and clinical course of UC remains less clear. Given the shared pathophysiological mechanisms of oxidative stress and inflammation in UC and CRC, investigating these polymorphisms in UC may offer insights into disease progression and outcomes.

This study aims to investigate the prevalence of APE1 (Asp148Glu) and hOGG1 (Ser326Cys) polymorphisms in UC patients and to assess their associations with clinical characteristics, including disease duration, location, and activity. By comparing UC patients with CRC patients and healthy controls, this study seeks to clarify whether these DNA repair variants play a role in the clinical phenotype of UC and may serve as potential biomarkers for disease severity or prognosis.

MATERIALS AND METHODS

Study design and participants

This cross-sectional study included three groups: 99 patients diagnosed with UC, 50 patients with histopathologically confirmed CRC, and 50 age- and gender-matched healthy controls. Ethical approval was obtained from the İnönü University Ethics Committee (Approval Number: 2017/58). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

The required sample size was estimated using G*Power software for a chi-square test comparing genotype distributions across three independent groups (UC, CRC, and healthy controls). Assuming a medium effect size (w = 0.3), a significance level of $\alpha = 0.05$, and a power of 0.80, the minimum recommended sample size was 108 participants (approximately 36 per group). Our study included 99 UC patients, 50 CRC patients, and 50 healthy controls, exceeding the minimum requirement for adequate statistical power.

Clinical evaluation and classification

Demographic data, including age, gender, disease duration, and disease location, were collected from hospital electronic medical records. For UC patients, disease activity was assessed using the Truelove-Witts index at the time of admission [17]. Based on clinical and laboratory parameters, disease activity was categorized as:

- *Mild disease:* ≤4 stools/day, erythrocyte sedimentation rate <30 mm/h, absence of fever and tachycardia, mild anemia.
- *Severe disease:* >6 bloody stools/day, fever >37.5°C, hemoglobin <75% of normal, tachycardia >100 bpm.
- *Moderate disease:* Findings between mild and severe presentations.

UC patients were further classified by disease extent:

- *Proctitis:* Limited to the rectum
- *Left-sided colitis:* Involving colon up to the splenic flexure
- *Extensive colitis (pancolitis):* Extending beyond the splenic flexure

CRC patients were grouped based on tumor location: rectum, left colon, or right colon.

Sample collection and DNA extraction

Peripheral blood samples (2 mL) were collected in EDTA tubes from all participants. Genomic DNA was extracted using the PureLink Genomic DNA Mini Kit (Invitrogen, Thermo Fisher Scientific) following the manufacturer's instructions.

Genotyping and polymorphism analysis

Genotyping of APE1 (Asp148Glu) and hOGG1 (Ser326Cys) polymorphisms was performed using real-time PCR and melting curve analysis on the LightCycler 2.0 system (Roche). The assays measured fluorescence during amplification, and melting curves were used to distinguish between genotypes.

- *APE1 (Asp148Glu):* A T-to-G substitution at nucleotide 2197 causes an Asp→Glu change at codon 148. Genotypes (Asp/Asp [AA], Asp/Glu [AG], Glu/Glu [GG]) were identified using LightSNiP assays (TIB-MolBiol, Berlin, Germany).
- *hOGG1 (Ser326Cys):* A C-to-G substitution at nucleotide 1245 results in a Ser→Cys change at codon 326. Genotypes (Ser/Ser [SS], Ser/Cys [SC], Cys/Cys [CC]) were determined using the same platform.

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Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (Armonk, NY: IBM Corp.). The Kolmogorov–Smirnov test was applied to assess the normality of continuous variables. Since the distribution of age was not normal, results were summarized as median (minimum–maximum), and comparisons among the three groups (UC, CRC, and controls) were conducted using the Kruskal–Wallis test. As no significant difference was detected, post-hoc pairwise analyses were not performed. Categorical variables were expressed as counts and percentages, and comparisons were performed using the Pearson Chi-Square or Fisher's exact test as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics

A total of 99 UC patients (42.4% female; median age: 46 [min:36 max:58] years), 50 CRC patients (42% female; median age: 48 [min:41 max:55] years), and 50 healthy controls (42% female; median age: 44 [min:40 max:56] years) were included. There were no statistically significant differences among the three groups in terms of age (p = 0.778) or gender distribution (p = 0.998).

Table 1. Demographic and clinical characteristics of ulcerative colitis patients.

UC patients, n	99
Age (years), median (min-max)	46 (36-58)
Female, n(%)	42 (42.4)
Disease duration, month	81.32
Location, n(%)	
• Proctitis	21 (21.2)
• Left colon	56 (56.4)
• Extensive	22 (22.2)
Truelove-Witts disease activity index, n(%)	
• Mild	71 (71.7)
• Moderate	20 (20.2)
• Severe	8 (8.1)

UC: Ulcerative colitis, SD: Standard deviation.

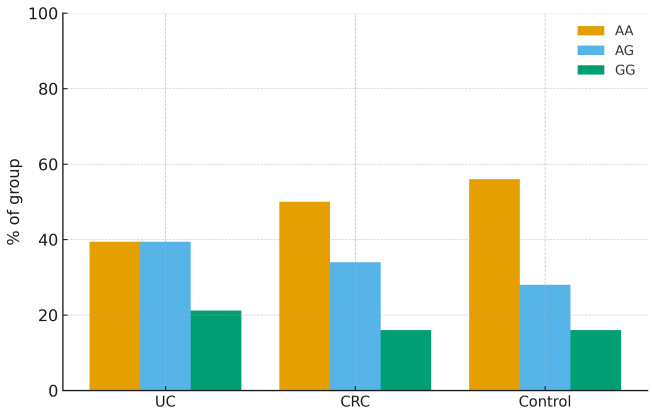

Figure 1. APE1 genotype distribution among study groups.

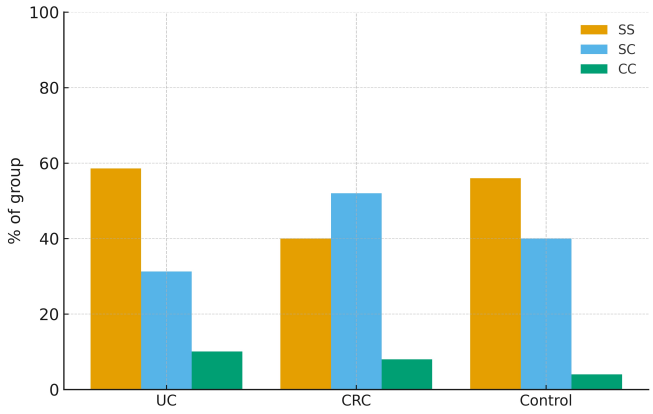

Figure 2. hOGG1 genotype distribution among study groups.

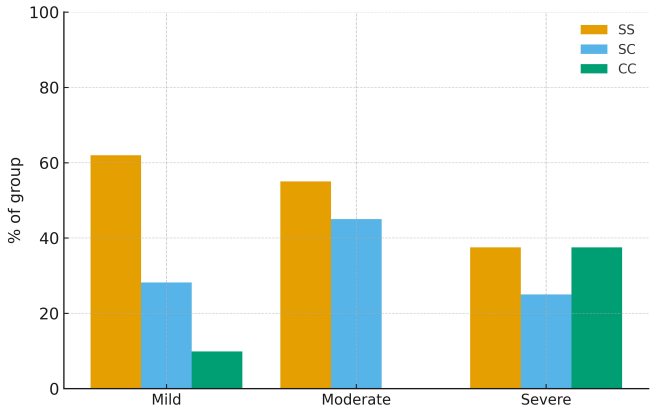

Figure 3. hOGG1 genotype distribution according to disease severity in ulcerative colitis.

The mean disease duration was 81.3 months in UC patients. UC localization was: proctitis (22%), left-sided colitis (56%), and pancolitis (22%). According to the Truelove-Witts index, disease activity was mild in 71.7%, moderate in 20.2%, and severe in 8.1% of UC patients (Table 1).

CRC group characteristics were as follows; of the 50 patients, 42% were female, and the mean age was 48 ± 2 years. The average disease duration was 62.5 months. Tumor localization showed that 58% of CRC patients had rectal involvement, 30% had tumors located in the left colon, and 12% had right-sided colon involvement.

Genotype and allele distribution of APE1 and hOGG1

In the APE1 polymorphism analysis, the distribution of genotypes across UC, CRC, and control groups was as follows; in the UC group, 39.4% had the AA genotype, 39.4% had AG, and 21.2% had GG. Among CRC patients, 50% had AA, 34% AG, and 16% GG. In the control group, the frequencies were 56% (AA), 28% (AG), and 16% (GG). No statistically significant differences were observed among the three groups regarding genotype distribution (p = 0.384) or allele frequencies (p = 0.135) (Figure 1).

Regarding the hOGG1 polymorphism; in the UC group,

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Table 2. Genotypic distribution of disease severity and APE1 and hOGG1 in UC.

Disease Severity	APE1						P-value	hOGG1						P-value
	AA		AG		GG			SS		SC		CC		
	n	%	n	%	n	%		n	%	n	%	n	%	
Mild	27	38	29	40	15	21.1		44	61.9	20	28.3	7	9.8	
Moderate	8	40	7	35	5	25	0.940	11	55	9	45	0	0	0.034*
Severe	4	50	3	37.5	1	12.5		3	37.5	2	25	3	37.5	

APE1: The apurinic/apyrimidinic endonuclease 1, A: Aspartic acid, C: Cysteine, G: Glutamic acid hOGG1: The human 8- oksoguanin DNA glycosylase, S: Serin, , *p<0.05.

58.6% had the SS genotype, 31.3% SC, and 10.1% CC. Among CRC patients, 40% had SS, 52% SC, and 8% CC. In controls, 56% were SS, 40% SC, and 4% CC. Again, there were no significant differences among the groups in genotype distribution (p = 0.110) or allele frequencies (p = 0.219) (Figure 2).

Association between polymorphisms and disease location

The distribution of APE1 and hOGG1 genotypes according to disease or tumor location was analyzed in both UC and CRC groups. Among UC patients, those with proctitis exhibited APE1 genotypes as follows: AA 47.6%, AG 38.1%, and GG 14.3%; hOGG1 genotypes were SS 52%, SC 28.6%, and CC 19%. In patients with left-sided colitis, APE1 genotypes were AA 37.5%, AG 42.9%, and GG 19.6%; hOGG1 genotypes were SS 62.5%, SC 33.9%, and CC 3.6%. In those with pancolitis, the APE1 distribution was AA 36.4%, AG 31.8%, and GG 31.8%; hOGG1 distribution was SS 54.5%, SC 27.3%, and CC 18.2%. Statistical analysis showed no significant association between genotype and disease location in UC patients for either APE1 (p = 0.724) or hOGG1 (p = 0.170).

Similarly, in the CRC group, among patients with rectal tumors, APE1 genotypes were distributed as AA 48.3%, AG 37.9%, and GG 13.8%; hOGG1 genotypes were SS 34.5%, SC 55.2%, and CC 10.3%. For left colon tumors, APE1 distribution was AA 46.7%, AG 33.3%, and GG 20%; hOGG1 distribution was SS 53.5%, SC 40%, and CC 6.7%. In patients with right colon tumors, APE1 genotypes were AA 66.7%, AG 16.7%, and GG 16.7%; hOGG1 genotypes were SS 33.3%, SC 66.7%, and CC 0%. No significant differences were observed in the distribution of genotypes by tumor location in CRC patients for either APE1 (p = 0.905) or hOGG1 (p = 0.690).

Association between gene polymorphisms and disease activity in UC

No significant association was found between APE1 genotypes and disease activity in UC patients (p = 0.940). In contrast, hOGG1 genotypes were significantly associated with disease activity (p = 0.034). The Cys/Cys genotype was more frequently observed in patients with severe UC, suggesting a potential role in disease severity (Table 2) (Figure 3). Although the overall association between hOGG1 genotype and UC disease severity was statistically significant, post-hoc pairwise Fisher's exact tests with Bonferroni adjustment did not reveal significant differences between specific severity categories. The strongest trend was observed between the moderate and severe groups (p=0.051, adjusted), where the Cys/Cys genotype was more frequent in severe UC.

Allele frequencies by disease severity

Although the frequency of the C allele of hOGG1 appeared higher in patients with severe disease (50%) compared to those with mild (23.9%) or moderate (22.5%) disease, this trend did not reach statistical significance (p = 0.680).

DISCUSSION

In this case-control study, we evaluated the association between two critical base excision repair (BER) gene polymorphisms—APE1 (Asp148Glu) and hOGG1 (Ser326Cys)—and clinical characteristics of ulcerative colitis (UC), particularly disease activity. Although no significant differences were observed in the overall distribution of these polymorphisms between UC, colorectal cancer (CRC), and healthy control groups, our results revealed a statistically significant association between the hOGG1 Cys/Cys genotype and severe UC activity. These findings highlight the possible role of impaired DNA repair mechanisms in modulating disease severity in UC.

The hOGG1 enzyme plays a pivotal role in excising 8-oxoguanine, one of the most mutagenic oxidative DNA lesions generated by reactive oxygen species (ROS) during chronic inflammation. The Ser326Cys polymorphism, which causes a serine-to-cysteine substitution at codon 326, has been shown to reduce hOGG1 enzymatic efficiency, impairing the repair of oxidative DNA damage [11,13]. This reduction in DNA repair capacity can lead to the accumulation of oxidative lesions in epithelial cells, which in turn sustains inflammation, disrupts mucosal integrity, and may drive more severe clinical manifestations in UC. Our finding that the Cys/Cys genotype is significantly more frequent among patients with severe UC activity supports this proposed mechanism.

This result aligns with prior research showing increased expression of OGG1 in inflamed and dysplastic colonic mucosa of UC patients and in tissues undergoing malignant transformation [18,19]. The accumulation of unrepaired oxidative

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DNA damage in individuals with the Cys/Cys genotype may contribute to enhanced activation of DNA damage response pathways such as p53, NF-κB, and STAT3, thereby amplifying the inflammatory process and mucosal injury. Moreover, oxidative stress in UC has been implicated in epithelial apoptosis, barrier dysfunction, and dysbiosis—all of which are hallmarks of severe disease. These mechanistic links between impaired DNA repair and inflammation offer a plausible biological explanation for our observed genotype-phenotype association.

In contrast, the APE1 (Asp148Glu) polymorphism did not demonstrate a significant association with UC severity or with the presence of disease in our cohort. While APE1 is a crucial enzyme in the BER pathway responsible for cleaving the DNA backbone at abasic sites, the functional consequences of the Asp148Glu variant are more nuanced and may be tissue- or context-specific. Some studies have reported increased risk of UC with this variant, particularly in cohorts with high inflammatory activity [20]. However, our cohort included a relatively low proportion of patients with severe disease, which may have limited the statistical power to detect subtle associations.

Additionally, APE1 has dual roles—not only in DNA repair but also in redox regulation of transcription factors involved in inflammation. These regulatory functions may be differentially expressed in colonic tissue compared to peripheral blood, which we used for genotyping. Studies using colonic biopsies have demonstrated increased APE1 expression in inflamed mucosa, suggesting that tissue-level post-translational modifications or epigenetic changes may influence the functional impact of this polymorphism [21]. Therefore, the lack of association in our study may reflect the importance of local tissue environment and dynamic gene expression over static germline variants.

Although our study design included a CRC group due to the shared pathogenic features with UC, particularly oxidative stress and chronic inflammation, neither polymorphism was significantly enriched in CRC patients compared to controls. This may be due to the relatively small sample size or to the multifactorial nature of CRC, where cumulative somatic mutations, microsatellite instability, and environmental exposures play a dominant role beyond single-gene polymorphisms. Nevertheless, the overlap between pathways implicated in UC and CRC—especially those involving ROS and DNA repair—warrants further longitudinal studies to explore whether hOGG1 variants in UC patients could predict neoplastic transformation risk over time.

The identification of the hOGG1 Ser326Cys variant as a potential marker of severe UC activity has clinical implications. First, it supports the hypothesis that genetic susceptibility related to oxidative DNA damage modulates disease progression. Second, it highlights the need for genotype-guided risk stratification in UC management. Patients with the Cys/Cys genotype may benefit from closer endoscopic surveillance and more aggressive anti-inflammatory or antioxidant therapies. Third, this variant may represent a candidate biomarker for identifying individuals at increased risk of complications such as treatment resistance or CRC development.

Identification of UC patients carrying the hOGG1 Ser326Cys variant, particularly the Cys/Cys genotype, may provide valuable information for individualized disease management. Since these patients appear to be more prone to severe disease activity, clinicians could consider closer clinical and endoscopic monitoring, earlier escalation of medical therapy, and stricter surveillance for complications such as treatment resistance or colorectal neoplasia. Integrating genetic risk markers like hOGG1 into follow-up strategies may therefore improve prognostic stratification and guide more personalized approaches to long-term UC care.

Limitations

Our study has several limitations. The relatively small number of patients with severe UC limits the generalizability of our findings. The cross-sectional design precludes causal inference, and functional assays of hOGG1 or APE1 activity were not performed. Furthermore, environmental factors such as smoking, diet, or microbiome composition—which can modulate oxidative stress—were not controlled for. Future studies should include mucosal tissue analysis, longitudinal follow-up, and integration of transcriptomic or epigenetic data to clarify the functional consequences of these polymorphisms. In addition, environmental and dietary factors, which are known to influence oxidative stress and inflammatory responses, were not assessed in our study. As such, we cannot exclude the possibility that these unmeasured variables may have contributed to the observed genotype–phenotype correlations.

CONCLUSION

In summary, our study suggests that the hOGG1 Ser326Cys polymorphism is associated with increased disease severity in ulcerative colitis, potentially due to impaired DNA repair and enhanced oxidative stress. While the APE1 Asp148Glu variant did not show a similar association, its context-dependent role warrants further investigation. These findings underscore the relevance of BER gene variants in UC pathogenesis and may inform future biomarker development for prognostic and therapeutic purposes.

Ethics Committee Approval: Ethical approval was obtained from the İnönü University Ethics Committee (Approval Number: 2017/58).

Informed Consent: Written informed consent was obtained from all participants included in the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

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