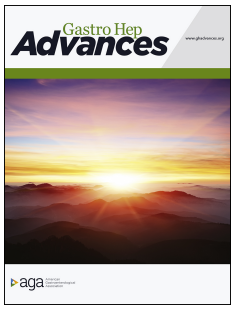

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CYP2C19 Genotype Is Not Associated with Risk of Microscopic Colitis

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Abbreviations:
BMI, body mass index; EM, extensive metabolizers; H2RA, histamine 2 receptor antagonists; IM, intermediate metabolizers; MC, microscopic colitis; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; UM, ultra-rapid metabolizers

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Data transparency: Data will be available to other researchers

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Microscopic colitis (MC) is a cause of chronic diarrhea, defined by grossly normal appearing mucosa with lymphocytic invasion or collagen deposition on histology. [1] The pathophysiology of MC remains unclear. Medications from diverse classes, including proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), histamine 2 receptor antagonists (H2RAs), HMG-CoA reductase inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs), have been described as potential causes of MC. [2-4]

These medications have varied mechanisms of action. As such, we hypothesized that altered drug metabolism may be the unifying feature to explain a potential association between medications and MC risk. A number of these drugs (PPIs, H2RAs, and SSRIs) are metabolized by the cytochrome P450 isoform, CYP2C19. CYP2C19 genetic variants have been shown to alter enzyme activity, and have been linked to differential therapeutic response. For *H pylori* treatment, individuals with CYP2C19 variants which result in "slow metabolism" of PPIs had 4 times the odds of eradication of *H pylori* as compared to individuals with "normal metabolism" (95% CI 1.35 – 13.05).[5] Among patients with reflux esophagitis, CYP2C19 "rapid metabolism" phenotype was associated with 1.66 times the odds of lack of response to PPI (95% CI 1.02 – 2.66) as compared to "normal metabolism." [6] In this study, we assessed whether the CYP2C19 genotype was associated with the odds of MC.

To investigate the relationship between CYP2C19 and MC, we performed a case control study, as previously described.[7] Participants were identified among patients referred to University of North Carolina Hospitals for elective outpatient colonoscopy for indication of diarrhea. Patients had to report loose to watery stool consistency during the week prior to colonoscopy to be

included. We excluded patients with history of inflammatory bowel disease, evidence of gross inflammation on endoscopy, or clinical biopsies with neutrophilic or eosinophilic colitis. Participants completed detailed surveys with information on demographics, medical, surgical and reproductive history, prescription and over-the-counter medication use in the prior year. Patients were classified as microscopic colitis cases or controls based on the reading of the study pathologist. Genotype of CYP2C19 was measured on consecutive cases and controls who had blood collected and completed the interview. Participants were categorized as extensive metabolizers (EM), intermediate metabolizers (IM), or ultra-rapid metabolizers (UM) based on CYP2C19 genotype, as previously described (Supplemental Text). [8] "Extensive metabolizers" were considered the reference group. Data analysis was conducted using Stata 17.0. [9] Exposure variables were examined in univariate analysis using chi-square (categorical) or t tests (continuous). We used logistic regression to calculate crude and adjusted odds ratios for microscopic colitis risk by CYP2C19 phenotype.

CYP2C19 genotype information was obtained on 45 cases of MC and 162 controls. The cases were older (mean age 64.3 years (standard deviation (SD) 12.0) vs 54.8 years (SD 11.9)) and had a higher level of education (72.1% college or postgrad vs 63%) than controls. Cases were more likely to be female (82.2% vs 69.1%), to identify as White race (97.7% vs 87.7%) and to have lower body mass index (mean BMI 25.3 kg/m^2 (SE 7.2) vs 29.4 kg/m^2 (SE 7.2)) compared to controls. Non-MC controls were more likely to be current smokers (25.9% vs 14.0%). Marital status was not different between groups. Controls were more likely to use PPIs (50% vs 32.6%), NSAIDs (52.9% vs 44.2%) and H2RAs (20.3% vs 11.6%) compared to MC cases; however, these differences were not statistically significant after adjusting for age, sex and education as

previously reported. [5] SSRI and HMG-CoA reductase inhibitor use was not different between groups (Supplementary Table 1).

We next examined the relationship between CYP2C19 phenotype and case control status. There was no association between CYP2C19 phenotype by case control status (p = 0.126). In an unadjusted model of CYP2C19 phenotype, patients with ultra-rapid metabolism (UM) had twice the odds of microscopic colitis than patients with extensive metabolism (EM) (OR 2.21, 95% CI 1.01 – 4.84). The association was not significant when controlling for age, education and body mass index (aOR 1.91, 95% CI 0.76-4.78) (Table 1). Combining UM and IM to compare to EM further diminished the relationship (aOR 1.65, 95% C1 0.71-3.81) (Supplementary Table 2).

Finally, we examined the relationship between CYP2C19 phenotype and medication use. There were no significant differences in odds of MC for those who reported using medications metabolized by CYP2C19 (PPI, H2RA or SSRI) compared to those who did not use those medications (Supplementary Table 3). This was true for all CYP2C19 subgroups: ultrarapid metabolizers, intermediate metabolizer, and extensive metabolizers, and across all medication groups.

Previous studies defining the degree of effect of medications on MC risk is inconsistent. For PPI, ORs range anywhere from 0.64[10] to 7.04,[3] with some variation attributable to selection of controls. Overall, the results in this study are consistent with our primary analysis, which showed no association between medication use and MC risk. [7] Stratification by CYP2C19 genotype to examine for more specific differences in odds of MC did not modify this relationship.

This study was limited by modest sample size and self-report of medication use. A larger sample size would allow for comparisons of interactions among drugs, such as in NSAIDs and PPIs. The modest sample size also limits the ability to detect small differences which may be clinically meaningful. A future study could examine more genotypes, including those termed "poor metabolizers," which are not currently represented. [8] Finally, we examined only one of the cytochrome P450 isoforms; CYP3A4, CYP2C9 and CYP2D6 may be of interest because of their role in metabolism of HMG-CoA reductase inhibitors, NSAIDs, and beta blockers, respectively.

In conclusion, we conducted a case-control study of patients with microscopic colitis compared to controls with diarrhea to identify factors that may increase risk of MC. We hypothesized that CYP2C19 genotype might explain a potential relationship between medication use and odds of MC. After adjusting for potentially confounding variables, we did not identity a relationship between CYP2C19 genotype and MC overall or stratified by medications. In the continued absence of a biological mechanism to explain why so many different classes of medicine are linked with MC, one might question whether these associations are true.

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Table 1. Odds of Microscopic Colitis by CYP2C19 phenotype

Phenotype	**Number of Cases**	**Number of Controls**	**Odds Ratio**	**95% Confidence Interval**	**Adjusted Odds Ratio***	**95% Confidence Interval**
Extensive metabolizer	13	70	Reference	-	Reference	-
Intermediate metabolizer	11	41	1.44	0.59-3.52	1.29	0.45-3.71
Ultra-rapid metabolizer	21	51	**2.21**	1.01-4.84	1.91	0.76-4.78

*Adjusted for age, education, and body mass index