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LETTER TO THE EDITOR

Evaluating genetic insights into ulcerative colitis and anxiety: Limitations and future directions

Ying Peng, Xi-Dai Long

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Abstract

We reviewed the study by He *et al*, which investigates the genetic correlation between ulcerative colitis (UC) and anxiety using bidirectional Mendelian randomization. This study reveals a genetic link between UC and anxiety, diverging from prior research associating higher anxiety with Crohn's disease. While the study's use of large-scale genome-wide association studies data is commendable, it faces limitations such as single nucleotide polymorphism selection biases, lack of multiple testing corrections, and a reliance on European populations. Future research should address these limitations, incorporate diverse populations, and explore psychotherapeutic interventions to improve UC management and patient outcomes.

Key Words: Ulcerative colitis; Anxiety; Mendelian randomization; Genome-wide association study; Gut-brain axis; Instrumental variables; Genetic epidemiology; Pleiotropy

Core Tip: The study by He *et al* highlights significant genetic associations between ulcerative colitis and anxiety, providing valuable insights into the gut-brain axis. However, it also underscores the need for further research to validate these findings and assess their clinical relevance across diverse populations. Key areas for future investigation include the cost-effectiveness of routine screening for Mendelian traits and the development of personalized treatment strategies targeting genetic and biological mechanisms.

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TO THE EDITOR

We were intrigued by the study "Causal associations between inflammatory bowel disease and anxiety: A bidirectional Mendelian randomization study" by He *et al*[1], published in the *World Journal of Gastroenterology*. This study, employing bidirectional Mendelian randomization (MR) and genome-wide association studies (GWAS), provides notable insights into the genetic correlations between inflammatory bowel disease (IBD), specifically ulcerative colitis (UC), and anxiety. The methodological approach to uncovering the genetic underpinnings of the UC-anxiety relationship is a significant stride, particularly in its exploration of the gut-brain axis.

Nevertheless, it is essential to contextualize these findings within existing research. Prior studies have frequently indicated a bidirectional relationship between IBD and anxiety, suggesting a more prevalent occurrence of anxiety in IBD patients compared to the general population[2-4]. In contrast, He *et al*'s research[1] delineates a specific genetic link between UC and anxiety but not Crohn's disease (CD). This divergence from previous findings[5,6], where CD has often been associated with higher anxiety levels, necessitates a deeper examination of the distinct genetic and pathophysiological mechanisms differentiating UC and CD, especially in their interactions with psychiatric manifestations.

The methodology of the study, especially the use of bidirectional MR and large-scale GWAS data, is commendable[7]. However, I would like to delve into some critical aspects and potential limitations for a deeper academic discourse. A key point of consideration is the choice of single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) in MR analysis[8,9]. This selection is pivotal, as the potential for linkage disequilibrium and pleiotropy among these SNPs could introduce biases into the analysis. Despite the study reporting no significant pleiotropy or heterogeneity, several concerns arise. Primarily, the criteria for SNP elimination due to potential confounders, including smoking, body mass index, neuropsychiatric diseases, and other factors, may not be exhaustive. This raises concerns about the comprehensive adjustment for confounders, which is critical in ensuring the validity of the IVs used in MR.

Another significant oversight is the absence of a multiple testing correction in the study's MR results. In genome-wide studies, such corrections are crucial to prevent the overestimation of the significance of associations and to mitigate the risk of type I errors.

Moreover, the study's reliance on GWAS data from European populations limits its generalizability[10,11]. Given the potential variability in genetic predispositions to IBD and anxiety across different ethnicities, future research should strive to include a more diverse cohort to validate these findings on a broader scale.

Additionally, recent research has identified distinct features between UC patients with and without anxiety. Patients with anxiety show higher perceived stress and depression levels, as measured by the Perceived Stress Scale and Patient Health Questionnaire (PHQ-9). Additionally, elevated *IL17F* and *IL23A* gene expression in the intestinal mucosa correlates with increased psychological distress in these patients[12]. This suggests the need to investigate how these factors interact to exacerbate anxiety in UC, potentially guiding the development of more targeted interventions.

Advancements in psychotherapeutic treatments, such as acceptance & commitment therapy (ACT) and cognitive behavioral therapy (CBT), have demonstrated efficacy in managing IBD and psychological distress[13]. ACT, in particular, has been shown to improve health-related quality of life and reduce CD activity more effectively than CBT-informed psychoeducation. These findings underscore the value of integrating such therapies into comprehensive IBD management strategies to address both physical and mental health aspects.

Furthermore, while the study advances our understanding of the genetic links between UC and anxiety, it does not delve deeply into the complex biological mechanisms underpinning this association. The role of the microbiome, immune response, and neuronal signaling within the gut-brain axis remains to be comprehensively explored. A deeper exploration into how these factors interact and contribute to the development of anxiety in UC patients is essential. For instance, understanding the specific microbial profiles that may be implicated in UC and their influence on neuroimmune pathways could provide vital insights into the mechanisms of disease progression and symptom manifestation[14-16]. The study also treats anxiety as a singular phenotype, which might oversimplify the heterogeneity and complexity inherent in psychiatric disorders.

MR serves as an approximation of randomized controlled trials; however, its results are based on theoretical assumptions rather than actual observational data. Discrepancies between MR findings and observational studies are frequently observed[9,17]. In a clinical context, translating these genetic associations into effective management strategies for UC patients with comorbid anxiety requires further investigation. The study paves the way for potential targeted

interventions but stops short of providing a direct clinical application pathway. Routine screening for Mendelian traits in UC patients may be costly and may not always yield clinically actionable results. Despite the potential insights from Mendelian traits, such as those involving the *MEFV* gene and its association with CD severity[18], their role in routine UC management remains unclear and may not justify the expense at this stage[18].

Moreover, research on prognosis in UC associated with Mendelian traits suggests that while some genetic variants are linked to disease severity, such as the SNPs identified in medically refractory UC (MRUC) studies[19], a comprehensive understanding of their prognostic value in routine clinical practice is still developing. Studies indicate significant differences in SNPs associated with MRUC compared to non- MRUC[19], but translating these findings into practical screening protocols requires further validation.

A more detailed analysis of how these genetic findings can be translated into personalized treatment plans, potentially incorporating interventions targeting the microbiome or neuroimmune pathways, is necessary[20]. This could lead to more effective, tailored approaches to managing anxiety in UC patients, improving both their physical and mental health outcomes.

In conclusion, the study by He *et al*[1] represents a significant advancement in understanding the genetic connections between UC and anxiety. It provides valuable insights into the genetic underpinnings of these conditions, particularly through bidirectional MR and GWAS methodologies. However, several key aspects warrant further attention.

The findings underscore the necessity for a nuanced approach to integrating Mendelian trait data into UC management strategies. Routine screening for Mendelian traits, while potentially informative, may be costly and may not always provide actionable clinical benefits at this stage. The potential insights from Mendelian traits, such as those involving the *MEFV* gene and its association with CD severity[18], illustrate the need for cautious evaluation before widespread implementation in UC management. Additionally, research on prognosis in UC associated with Mendelian traits, such as those identified in MRUC studies[19], highlights significant differences between medically refractory and non-medically refractory cases. This indicates that while some genetic variants are linked to disease severity, their practical application in routine clinical screening and management requires further validation and development.

Future research should focus on validating the clinical relevance of Mendelian traits in UC and exploring their potential for personalized treatment approaches. This includes assessing the cost-effectiveness of routine screening and the prognostic value of identified genetic variants. A comprehensive understanding of how genetic findings can be translated into actionable clinical interventions, particularly those targeting the microbiome or neuroimmune pathways, is essential for improving both physical and mental health outcomes in UC patients. Integrating a broader range of populations and refining genetic analyses will be crucial for advancing our understanding and application of these findings in clinical practice.

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