Title: Multiple Myeloma, IL6, and Risk of Schizophrenia: A Mendelian Randomization, Transcriptome, and Bayesian Colocalization Study

Introduction:

Clinical studies speculated the association between multiple myeloma (MM) and inflammatory diseases; however, there is limited validation of these claims via establishing a causal relationship and revealing the underlying mechanism.

Method:

This exploratory study employed bidirectional Mendelian Randomization (MR) analysis to investigate the causal relationships between MM and inflammatory diseases, including atherosclerosis (ARS), asthma (AT), ankylosing spondylitis (AS), Alzheimer’s disease (AD), Parkinson’s disease (PD), sarcoidosis (SD), inflammatory bowel disease (IBD), nonalcoholic fatty liver disease (NAFL), type II diabetes (TIID) and schizophrenia (SZ). Transcriptomic and genome-wide Bayesian colocalization analyses were further applied to reveal the underlying mechanism.

Results:

A significant and previously unrecognized positive association was identified between genetic predisposition to MM and the risk of schizophrenia (SZ). During the preparation of this manuscript, additional clinical reports on psychosis as a preceding symptom leading to the diagnosis of M are emerging, signifying the impact of our study in revealing the genetic mechanism of SZ in mediating MM. Various statistical methods confirmed this association without detecting heterogeneity or pleiotropy effects. Transcriptomic analysis revealed shared inflammation-relevant pathways in MM and SZ patients, suggesting inflammation as a potential pathophysiological mediator of MM's causal effect on SZ. Bayesian colocalization analysis identified rs9273086, which maps to the protein-coding region of HLA-DRB1, as a common risk variant for both MM and SZ. Polymorphism of HLA-DRB1 allele has been implicated in Alzheimer’s and Parkinson’s diseases among other neuropsychiatric disorders, further highlighting the validity and impact of our results. Additionally, we confirmed that interleukin-6 (IL-6) is a risk factor for SZ through an inflammatory-proteome-wide MR, reinforcing the role of neuroinflammation in SZ etiology.

Conclusion:

Overall, our findings showed that genetic predisposition to MM, HLA-DRB1 polymorphism, and enhanced IL-6 signaling are associated with the increased risk of SZ, providing evidence for a causal role for neuroinflammation in SZ etiology.

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