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RESEARCH ARTICLE

Multiple myeloma, IL6, and risk of schizophrenia: A Mendelian randomization, transcriptome, and Bayesian colocalization study

Shuyang Lin[1] | **Bei Gao**[2] | **Rui Xu**[3] | **Hongming Shang**[4] | **Yan Xiong**[2] | **Jiayi Zhou**[5] | **Zhe Yang**[6] | **Chao Jiang**[7] | **Shumei Yan**[8]

[1]Division of Hematology, Department of Medicine, Washington University School of Medicine in St Louis, St Louis, Missouri, USA

[2]Division of Genetics and Genomic Medicine, Department of Pediatrics, Washington University School of Medicine in St. Louis, St Louis, Missouri, USA

[3]Affiliated Cancer Hospital & Institute of Guangzhou Medical University, Guangzhou, Guangdong, China

[4]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

[5]Department of Hematology, Fujian Medical University Union Hospital, Fuzhou, Fujian, China

[6]Department of Medicine, Southern Medical University, Guangzhou, Guangdong, China

[7]Department of Cancer Center, The People's Hospital of Baoan, Shenzhen, Guangdong, China

[8]Department of Pathology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Correspondence
Shumei Yan, Department of Pathology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, 510060, China.
Email: yanshm@sysucc.org.cn

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Abstract

Numerous 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. This exploratory study employed bidirectional Mendelian randomization (MR) analysis to investigate the causal relationships between MM and inflammatory diseases, including atherosclerosis, asthma, ankylosing spondylitis, Alzheimer's disease (AD), Parkinson's disease (PD), sarcoidosis, inflammatory bowel disease, nonalcoholic fatty liver disease, type II diabetes, and schizophrenia (SZ). Transcriptomic and genome-wide Bayesian colocalization analyses were further applied to reveal the underlying mechanism. A significant and previously unrecognized positive association was identified between genetic predisposition to MM and the risk of SZ. Two independent case reports showed that treatment-resistant psychosis is due to underlying MM and is resolved by treating MM. From our MR analyses, 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

Shuyang Lin and Bei Gao contributed equally to this work and shared first authorship.

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 the HLA-DRB1 allele has been implicated in AD and PD, further highlighting the impact of our results. Additionally, we confirmed that interleukin-6 (IL-6) is a risk factor for SZ through secondary MR, reinforcing the role of neuroinflammation in SZ etiology. 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.

KEYWORDS
Bayesian colocalization, causal relationship, HLA, inflammation, Mendelian randomization, multiple myeloma, schizophrenia, transcriptomic analysis

1 | INTRODUCTION

Characterized by aberrant clonal expansion of plasma B cells in the bone marrow, multiple myeloma (MM) is the second most common hematological malignancy with a mounting epidemic burden globally [1]. Without proper and timely intervention, MM can exacerbate progressively, leading to osteolysis, kidney injury, hypercalcemia, and other nonspecific constitutional symptoms [2]. However, the casual factors, including driver mutations, environmental factors, and familial inheritance contributing to the etiology of MM, remain poorly understood [3–10]. The clinical challenges associated with MM are compounded by diagnostic difficulty and limited treatment options. Typically, bortezomib and dexamethasone serve as the first-line treatment for MM, with selinexor reserved for refractory MM [11–12]. Patients with MM often face grim prognoses and dismal outcomes owing to the lack of curative treatment and debilitating symptoms [13].

Emerging studies suggest that inflammatory microenvironment and abnormal cytokine signaling networks are associated with the initiation and progression of MM [14–17]. Notably, dysregulated cytokine levels associated with MM form a complex, vicious cycle wherein elevated cytokine levels both potentiate MM and arise as a consequence of MM [18]. Although several correlational studies have highlighted the association between MM and various inflammatory diseases, the limitations of such studies, including insufficient statistical power and susceptibility to cofounders and reverse causality, underscore the need for more rigorous investigation. To provide more clinical insights, there is an urgent need to assess the bidirectional causal relationship between MM and inflammatory diseases. Thus, interrogating inflammation and abnormal cytokine levels as the shared pathophysiology of MM and inflammatory diseases using more robust methods are warranted to substantiate causal inference [19].

Mendelian randomization (MR), mirroring the design of randomized control trials (RCTs), emerges as a powerful tool for assessing the causal association between exposures and outcomes. By using single-nucleotide polymorphisms (SNPs) as instrumental variants (IV), MR offers a unique advantage in examining causalities impractical or unethical to explore through RCT, while minimizing the confounding effects and reverse causality typically observed in correlational studies [20].

Here, we employed MR analysis to evaluate 10 inflammatory diseases across organ systems that have been speculated to be associated with MM, including the atherosclerosis (ARS), ankylosing spondylitis (AS), asthma (AT), Parkinson's disease (PD), Alzheimer's disease (AD), schizophrenia (SZ), type II diabetes (TIID), sarcoidosis (SD), inflammatory bowel disease (IBD), and nonalcoholic fatty liver disease (NAFL) (Supporting Information Figure 1) [21–30]. Extensive literature supports the conclusion that TIID is likely not a risk factor for MM [31, 32]. Hence, the absence of a causal association between TIID and MM can be leveraged as a "negative control" for the analysis in order to demonstrate the validity of our method. Collectively, we refer to these inflammatory diseases as *forward exposure* when MM is investigated as the outcome and *reverse outcome* when MM is used as the exposure. In the forward direction, the causal effect of forward exposure on MM as the outcome can potentially justify the repurposing of drugs used originally to suppress the forward exposure and avoid risk factors for the treatment and prevention of MM, respectively. In the reverse direction, establishing MM exposure causing the reverse outcome can facilitate early detection and management of potential MM cases, especially in patients suffering from the reverse outcomes, thereby reducing the healthcare burden, and benefiting patients. Following MR analyses, we employed transcriptomic analyses and genome-wide Bayesian colocalization to offer insight into the underlying biological processes. The overall design of the study is shown in Figure 1.

2 | METHODS

2.1 | Software

All MR analyses were performed in R software (version 4.3.1) with the *TwoSampleMR* package (version 0.5.7), and the *MRPRESSO* package (version 1.0). Forest plots were generated with the *Forestploter* package (version 1.1.0). Transcriptomic analysis was performed with *Limma* Package (version 3.17), *EdgeR* package (version 3.17), and visualized

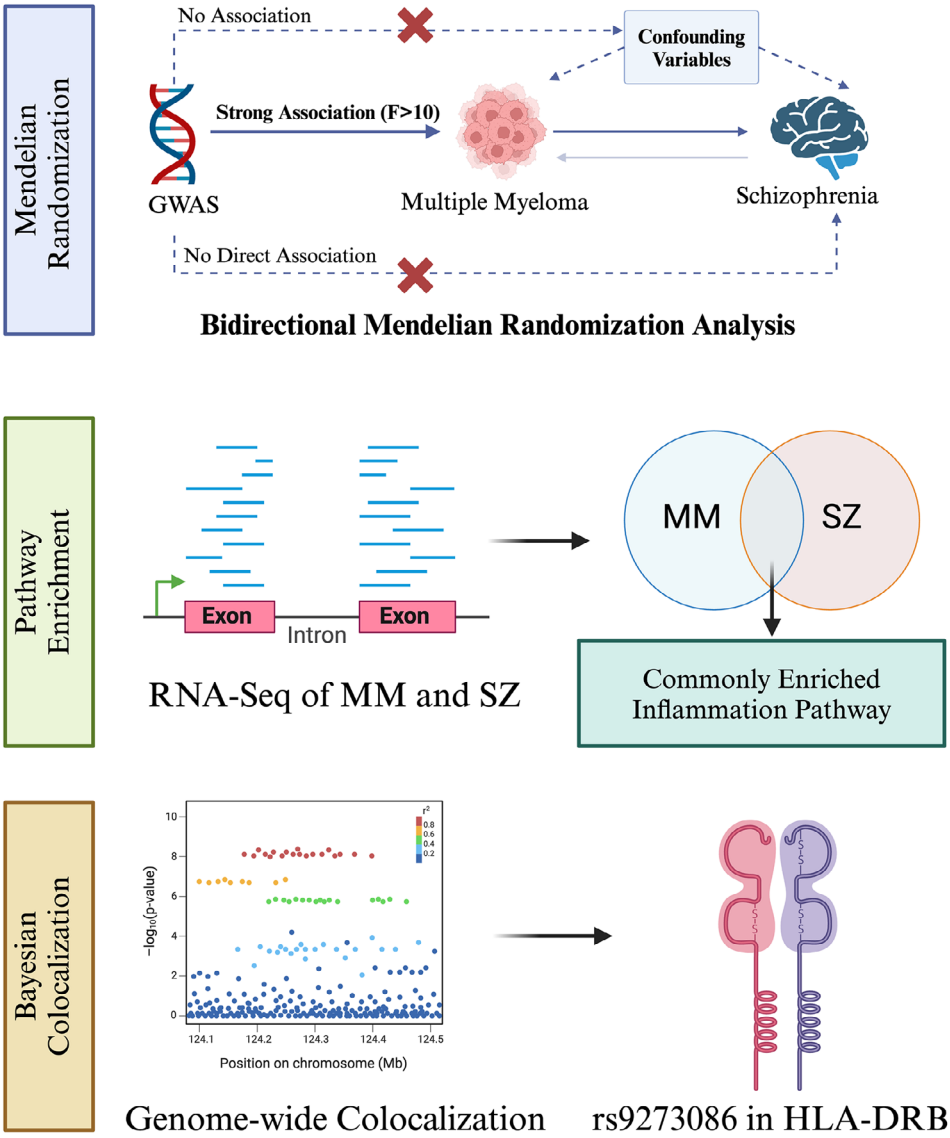

FIGURE 1 Overview of the analyses used in the study. Bidirectional two sample Mendelian randomization (MR) was first used to confirm the causal effect of multiple myeloma (MM) on schizophrenia (SZ). Subsequently, RNA-seq data from MM and SZ were analyzed to reveal commonly enriched inflammation pathways. Lastly, colocalization analysis reveals rs9273086 as the shared risk variant driving both diseases via polymorphism of HLA-DRB1. GWAS, Genome-Wide Association Studies.

with *the ggplot2* package (version 3.4.2) and *goplot* package (version 1.0.2). Bayesian localization analysis was performed with *Coloc* package (version 5.2.3).

2.2 | Data sources

Summary-level Genome-Wide Association Studies (GWAS) statistics were extracted from the *mrcieu* database (web access: https://gwas.mrcieu.ac.uk/datasets). Since MM is difficult to diagnose, only one publicly accessible GWAS from the UK Biobank consortium was available. For other inflammatory diseases, we obtained GWAS from consortiums other than UK Biobank to minimize sample overlaps. A detailed summary of the relevant information on the GWAS included in this study can be found in Supporting Information Table 1. GWAS data for 91 inflammatory proteins were obtained from Zhao et al. [33].

2.3 | Instrument variable selection

Three principal assumptions about SNPs selected as IV must be satisfied to reliably draw conclusions pertaining to the causal relationship of exposure and outcome using MR [34–37]. First, IV was assumed to be strongly correlated with exposure (relevance assumption). To meet this selection criterion, we only included SNPs with $p < 5 \times 10^{-8}$, $R^2 < 0.001$, and kb = 10,000, which indicated genetic significance. For ARS, AD, PD, SD, NAFL, and MM, we relaxed the p value threshold to a less stringent value of $p < 5 \times 10^{-6}$ to extract

sufficient SNPs to perform M [36, 37]. Next, we performed clumping with $R^2 > 0.001$ and window size = 10,000 kb to minimize the effect of linkage disequilibrium in chosen SNPs [38]. To ensure the robustness of our selection, we calculated the *F*-statistic value to evaluate the strength of the correlation between the selected IV and the exposure. *F*-statistic was derived by the formula $F = (\frac{R^2}{1-R^2})(\frac{n-k-1}{k})$, where R^2 indicates the exposure variance of SNPs (i.e., the extent to which the exposure as a whole can be accounted for by an individual SNP), *n* denotes the sample size of SNPs, and *k* equals the number of IVs included ($k = 1$ for individual SNP). R^2 was obtained by using the formula $R^2 = \frac{\beta^2}{\beta^2 + SE^2(n)}$, where β is the effect size for the SNP and SE is the standard error for β. SNPs that are not strongly correlated with the exposure ($F < 10$) were excluded [34, 38, 39]. Additionally, SNPs with palindromic sequences were removed before harmonization [40, 41]. Second, IV was assumed to be exclusively restrictive to the exposure, that is, IV could only mediate the causal effect through the exposure and could not be strongly correlated with the outcome. Hence, we extracted SNPs that satisfied the first assumption from the outcome and excluded any exposure-correlated SNPs with $p < 5 \times 10^{-8}$ in the outcome. Third, using PhenoScanner (web access: http://www.phenoscanner.medschl.cam.ac.uk/), we screened for SNPs that are associated with possible confounders: obesity, alcohol drinking, smoking, and hypertension. If any SNPs were associated with the potential confounders with $p < 5 \times 10^{-5}$, MR analyses were re-performed after dropping these SNPs to maintain the robustness of our studies and fulfill the independence assumption. SNPs selected as IV can be found in Supporting Information Table 2.

2.4 | Mendelian randomization analyses

An outline of the MR study design can be found in Supporting Information Figure 2. We first harmonized exposure and outcome data so that the effect allele of IV on exposure and outcome corresponded to the same allele. We then performed the inverse-variance weighted (IVW) random effect method to evaluate the causal relationships between exposure and outcome. A *p* value smaller than 0.05 indicates a statistically significant causality of exposure on the outcome. Odd (Wald) ratio (OR) estimates reported 95% confidence intervals (CIs) were visualized with forest plots. The β value and the OR reflect the direction of the causality. A positive β value indicated that the exposure is a significant risk factor for the outcome and vice versa. An OR greater than 1 indicated that the exposure was a significant risk to the outcome and vice versa. An OR equal to one implies that the exposure did not affect the outcome. If the IVW-random effect method yields significant causality, we additionally performed IVW-fixed effect, maximum likelihood, MR Egger regression, weighted median, penalized weighted median, simple mode, and weighted mode methods to verify the accuracy of IVW-random effect results. If MR analyses confirmed that a causal interference was statistically significant and not biased by heterogeneity and pleiotropy effect as indicated by the sensitivity tests, we generated scatter plots to visualize the results of different MR analyses by plotting IV-outcome against IV-exposure associations while further examining pleiotropy effects.

2.5 | Sensitivity tests

To ensure that the SNPs used to carry out MR analysis satisfied the exclusion-restriction assumption, we examined the heterogeneity of SNPs used to perform the initial MR analysis by performing Cochran's *Q*-test. A *p* value greater than 0.05 indicated the absence of heterogeneity and vice versa [43]. Next, we performed the MR Egger's intercept test to evaluate the potential pleiotropy effects of the IV [40]. If either test shows a *p* value of <0.05, the MR PRESSO test was performed to correct for potential outlier underlying pleiotropy effects. If the MR PRESSO test yielded a *p* value of <0.05 even after dropping the outliers, the results were considered unreliable, and no conclusion could be drawn [42]. When appropriate, we also conduct the leave-one-out analysis to assess how individual SNP affects the overall estimates of the MR analysis result.

2.6 | Transcriptomic analyses

Gene expression of bone marrow samples obtained from MM patients versus healthy subjects (GSE47552) was downloaded from the Gene Expression Omnibus (GEO) database. Differentially Expressed Genes (DEG) lists were obtained using the *limma* package (version 3.17) and *EdgeR* package (version 3.17). DEG with Log2 fold change (LogFC) > 1 and $p < 0.05$ were extracted and used for functional annotation and enrichment analysis of transcriptomic alteration associated with the development of MM. Curated DEG lists were directly downloaded from Fillman et al., and DEG with LogFC > 1 and $p < 0.05$ were used for transcriptomic analysis of the mRNA expression in the dorsolateral prefrontal cortex of SZ patients [43]. The DEG tables can be found in Supporting information Table 3. Gene Set Enrichment Analysis (GSEA) was performed using hallmark gene sets accessed from the Molecular Signature Database (MSigDB) website (https://www.gsea-msigdb.org/gsea/msigdb/index.jsp). Results of GSEA were visualized with ggplot2 and goplot packages. Commonly upregulated DEG was visualized with Jvenn [56].

2.7 | Bayesian colocalization analysis

Genome-wide eQTL data were accessed from https://gtexportal.org/home/. By using the *coloc* package, the SZ and MM GWAS were subjected to Bayesian colocalization analysis across the genome to identify common causal variants. Five hypotheses can be generated from the Bayesian colocalization analysis. H_0: no casual SNP exists between two phenotypes. H_1: causal SNP only exists for the first phenotype. H_2: casual SNP exists only for the second phenotype. H_3: two distinct SNPs exist for both phenotypes. H_4: a common casual SNP exists for both phenotypes. A posteriori probability of $H_4 > 0.75$ indicates that

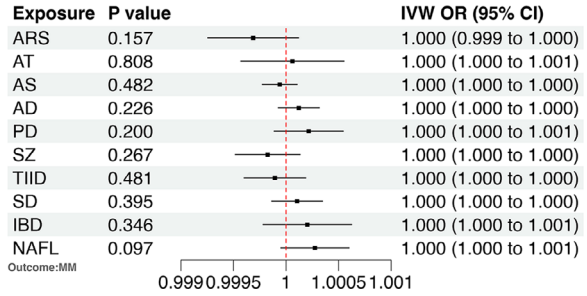

FIGURE 2 Estimates of odd ratios generated from forward Mendelian randomization (MR) analyses using the inverse-variance weighted (IVW)-random effect method. IVW-random effect method was used to acquire the odd ratio with a 95% interval and *p* value. No statistically significant association is reversed. AD, Alzheimer's disease; ARS, atherosclerosis; AS, ankylosing spondylitis; AT, asthma; IBD, inflammatory bowel disease; NAFL, nonalcoholic fatty liver disease; PD, Parkinson's disease; SD, sarcoidosis; SZ, schizophrenia; TIID, type II diabetes.

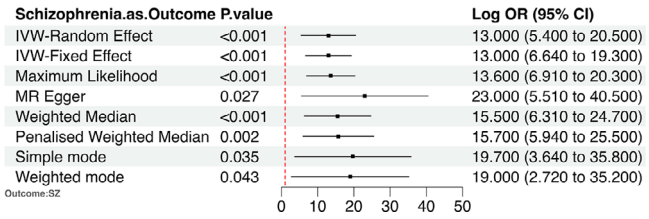

FIGURE 3 Estimates of logarithmic odd ratios generated from reverse Mendelian randomization (MR) analyses with multiple myeloma (MM) being the exposure and schizophrenia (SZ) being the outcome using multiple MR analysis methods. Different MR analysis method was used to acquire the odd ratio with a 95% interval and *p* value. All methods yield consistent directionality and statistical significance. IVW, inverse-variance weighted.

the causal SNP common to both phenotypes is statistically significant [44]. The H_4 of SNPs can be found in Supporting Information Table 4. The results of the Colocalization analysis were visualized with *Locuszoom* package online data plot tool (http://locuszoom.org/genform.php?type=yourdata).

3 | RESULTS

3.1 | Instrumental variant selection

After extracting and removing SNPs that violate the MR assumptions (see Section 2), we acquired 27 SNPs in ARS, 51 SNPs in AT, 12 SNPs in AS, 12 SNPs in AD, 12 SNPs in PD, 83 SNPs in SZ, 167 SNPs in TIID, 24 SNPs in SD, 13 SNPs in IBD, 12 SNPs in NFLD as the exposure, and 17 SNPs in MM as the exposure. Detailed information on selected SNPs is listed in Supporting Information Table 2.

3.2 | Forward MR analyses of the causal effect of forward exposures on MM

Our forward MR analyses did not reveal any causal effect of the forward exposures on the risk of MM. With the IVW-random effect method, the ORs of all inflammatory diseases as the exposure and MM as the outcome are highly proximal to 1, and none of the associated *p* values are smaller than the threshold of $p < 0.05$ (Figure 2).

3.3 | Reverse MR analyses of the causal effect of MM on reverse outcomes

The reverse MR analyses did not reveal any causal effect of MM on the risk of reverse outcomes save for AS and SZ (Supporting Information Figure 3). When AS was examined as the outcome with MM being the exposure, using the IVW-random effect method, a statistically significant association was found (Log[OR] [95% CI] 31.48 [1.62–61.34], $p = 0.038$). When SZ was evaluated as the outcome with MM being the exposure, using the IVW-random effect method, a statistically significant association was found (Log[OR] [95% CI] 13.00 [5.40–20.50], $p < 0.001$). IVW-fixed effects, maximum likelihood, MR Egger regression, weighted median, penalized weighted median, simple mode, and weighted mode methods yield (Log[OR] [95% CI] 13.00 [6.64–19.30], $p < 0.001$), (Log[OR] [95% CI] 13.60 [6.91–20.30], $p < 0.001$) (Log[OR] [95% CI] 23.00 [5.51–40.50], $p < 0.027$), (Log[OR] [95% CI] 15.50 [6.31–24.70], $p < 0.001$), (Log[OR] [95% CI] 15.70 [5.94–25.50], $p = 0.002$), (Log[OR] [95% CI] 19.70 [3.64–35.80], $p = 0.035$), (Log[OR] [95% CI] 19.00 [2.72–35.20], $p = 0.043$), respectively. All MR analysis methods have consistent directionality and statistical significance without heterogeneity or pleiotropy, supporting the conclusion that MM was a significant causal influence on SZ. These results are visualized with a forest plot (Figure 3).

3.4 | Sensitivity tests

In forward MR analysis, no heterogeneity nor pleiotropy effects were observed since all $p > 0.05$ for Cochran's *Q*-test and MR Egger intercept test (Table 1).

When AS was examined as the outcome with MM being the exposure, Cochran's *Q*-test showed a *p* value <0.05, implying a heterogeneity effect. After removing outliers, the MR PRESSO test output showed a *p* value <0.05, preventing us from concluding the causal relationship between MM and AS (Table 1). TIID, SD, and IBD also had heterogeneity when examined as the reverse outcome. MR PRESSO test showed *p* values >0.05 for them after outlier removal. No other heterogeneity nor pleiotropy effects were found in the reverse MR analysis. When SZ was examined as the outcome and MM as the exposure, no heterogeneity nor pleiotropy effects were identified because the *p* values were greater than 0.05 for both the Cochran's *Q*-test and the MR Egger intercept test. To ensure the robustness of

TABLE 1 Summary of sensitivity analysis results for two-sample Mendelian randomization (MR).

	Cochran's *Q*-test for heterogeneity (*p* value)	MR Egger's intercept for pleiotropy (*p* value)	MR PRESSO's test for distortion (after outlier removal)
Exposure with multiple myeloma (MM) as the outcome			
Atherosclerosis	0.269	0.328	Not necessary
Asthma	0.138	0.284	Not necessary
Ankylosing spondylitis	0.710	0.139	Not necessary
Alzheimer's disease	0.292	0.639	Not necessary
Parkinson's disease	0.532	0.290	Not necessary
Schizophrenia	0.999	0.609	Not necessary
Type II diabetes	0.157	0.169	Not necessary
Sarcoidosis	0.183	0.074	Not necessary
Inflammatory bowel disease	0.423	0.838	Not necessary
Nonalcoholic fatty liver disease	0.113	0.463	Not necessary
Outcome with MM as exposure			
Atherosclerosis	0.274	0.979	Not necessary
Asthma	0.804	0.372	Not necessary
Ankylosing spondylitis	<0.05	0.230	0.031
Alzheimer's disease	0.359	0.798	Not necessary
Parkinson's disease	0.515	0.541	Not necessary
Schizophrenia	0.151	0.243	Not necessary
Type II diabetes	<0.05	<0.05	0.054
Sarcoidosis	<0.05	<0.05	0.254
Inflammatory bowel disease	<0.05	0.579	Not necessary
Nonalcoholic fatty liver disease	0.787	0.447	Not necessary

our conclusion, we generated a scatter plot to examine the pleiotropy effect of different MR analysis methods (Supporting Information Figure 4). The positive slope indicates that MM is a risk factor for SZ. The *X*-intercept of all analysis methods did not deviate significantly from the origin, suggesting the absence of pleiotropy effects. Leave-one-out analysis further confirmed that no abnormal SNPs could affect the overall results (Supporting Information Figure 5). Hence, the causal inference between MM as the exposure and SZ as the outcome can be considered to be statistically significant and reliable.

3.5 | Transcriptomic analyses

Given our finding that MM has a casual effect on the risk of SZ, we sought to reveal the underlying biological processes. We obtained two lists of DEGs for significant upregulated genes in MM and SZ (see Section 2 for details). GSEA revealed enrichment of hypoxia (p value $= 5.8 \times 10^{-7}$), inflammatory responses (p value $= 5.94 \times 10^{-6}$), KRAS signaling (p value $= 5.37 \times 10^{-5}$), TNFα signaling via NFκB (p value $= 5.37 \times 10^{-5}$), IL6-JAK-STAT3 signaling (p value $= 8.25 \times 10^{-4}$), apoptosis (p value $= 1.1 \times 10^{-3}$), allograft rejection (p value $= 2.83 \times 10^{-3}$), epithelial mesenchymal transition (p value $= 2.83 \times 10^{-3}$), and coagulation (p value $= 4.44 \times 10^{-3}$) pathways in SZ upregulated DEG, ranked by rich score (Figure 4A). GSEA further showed enrichment of TNFα signaling via NFκB (p value $= 1.77 \times 10^{-22}$), interferon-gamma response (p value $= 6.4 \times 10^{-13}$), oxidative phosphorylation (p value $= 6.4 \times 10^{-13}$), interferon alpha response (p value $= 1.01 \times 10^{-12}$), apoptosis (p value $= 2.61 \times 10^{-10}$), inflammatory response (p value $= 2.61 \times 10^{-9}$), P53 (p value $= 2.61 \times 10^{-9}$), hypoxia (p value $= 3.46 \times 10^{-8}$), mTORC1 signaling (p value $= 3.46 \times 10^{-8}$), and UV response up (p value $= 7.61 \times 10^{-7}$) pathways in MM upregulated DEGs, ranked by rich score (Figure 4B). Moreover, we visualized significant DEG of SZ (26 DEG) and MM (63 DEG) corresponding to each enriched pathway with chord diagrams (Figure 4C,D), ranked by LogFC. Collectively, GSEA showed that hypoxia, TNFα signaling via NFκB, inflammatory responses, and apoptosis pathways were commonly enriched in both MM and SZ (Figure 4E). By performing intersection analysis, we further show that ADM, G0S2, and PPP1R15A are commonly regulated DEGs found in MM and SZ patients (Supporting Information Table 6 and Figure 4F). These proteins are involved in the regulation of cell cycle and cell proliferation, which are hallmarks of cancer.

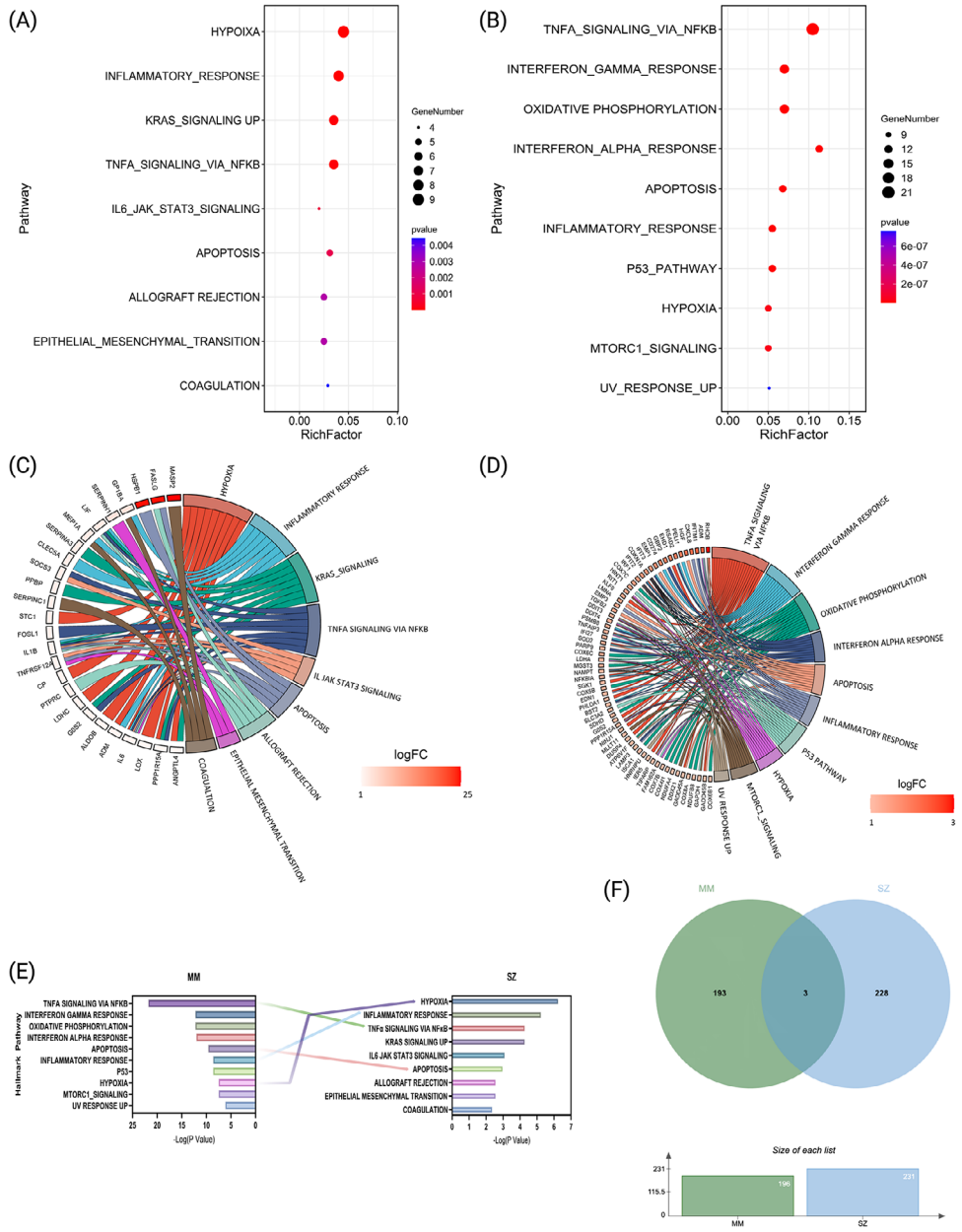

FIGURE 4 Gene Set Enrichment Analysis (GSEA) of significantly upregulated DEG in multiple myeloma (MM) and schizophrenia (SZ) patients. Figures A and B are gradient plots showing significantly enriched pathways in MM and SZ patient RNA-seq data. Figures C and D are chord diagrams showing individual genes contributing to the enriched pathways. Figure E illustrates commonly enriched pathways between MM and SZ patients. Figure F shows that commonly upregulated individual DEGs. Created with GraphPad Prism (version 9.5.1), Biorender.com, and Jvenn.

3.6 | Bayesian colocalization between MM and SZ

Although our initial MR analysis and transcriptomic analysis findings suggest that MM increases the risk for SZ possibly through proinflammatory pathways, showing that there is a common causal SNP to both diseases can further increase the robustness of our study. To this end, we performed a genome-wide Bayesian colocalization analysis to examine whether MM and SZ share a risk variant localized in the genomic region. SNP to phenotype associations were included in Supporting Information Table 7. We identified rs9273086 as a common risk variant for both disease phenotypes with an H_4 value of 0.923 (Figure 5 and Supporting Information Table 4). Rs9273086 maps to the protein-coding region of HLA-DRB1 (major histocompatibility complex, class II, DR beta 1) in chromosome 6 based on the SZGR platform, a comprehensive SZ gene resource [57].

3.7 | Inflammatory protein–SZ MR analysis

Since the transcriptomic analysis revealed an upregulated IL6 signaling pathway in SZ patients in addition to numerous correlational studies showing that IL6 is a risk factor for SZ [46–50], we became interested in

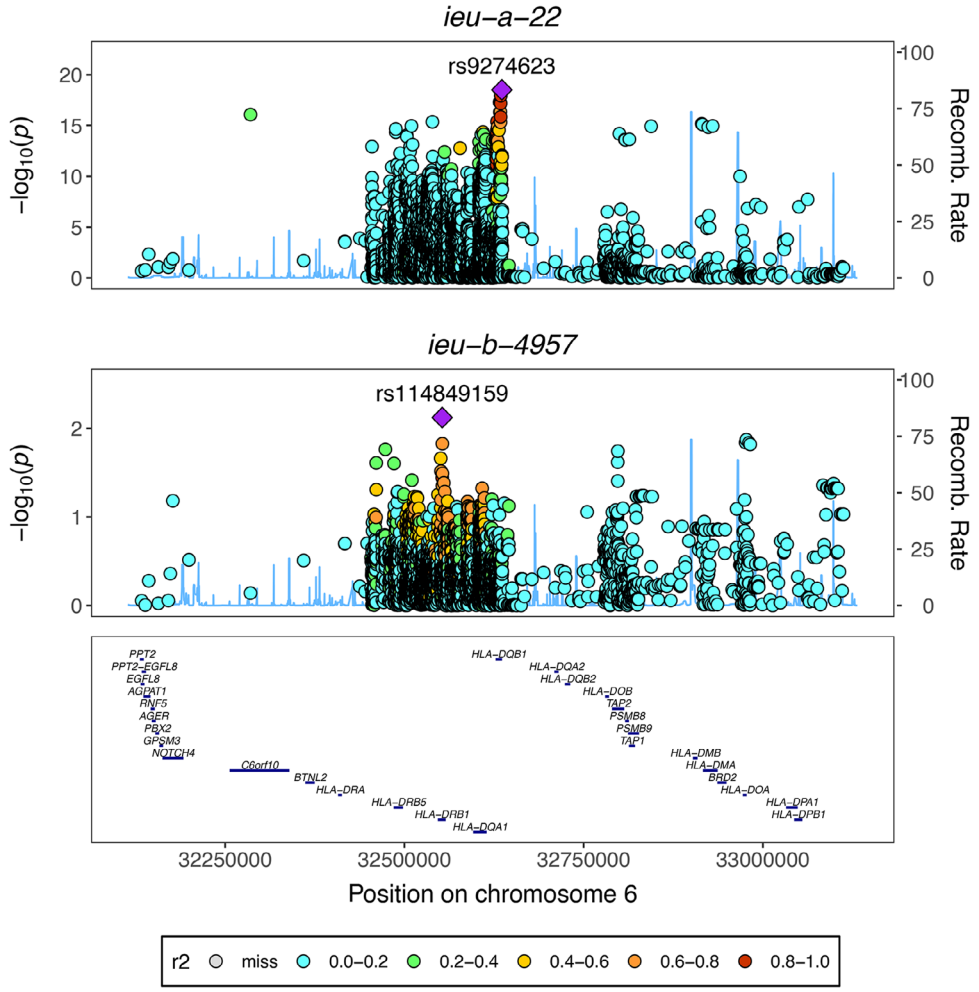

FIGURE 5 Bayesian colocalization between multiple myeloma (MM) and schizophrenia (SZ). Bayesian colocalization reveals rs9273086 as a common risk variant for MM and SZ mapping to the protein-coding region of HLA-DRB1.

extending the scope of our study by elucidating the causal role of IL6 on the etiology of SZ. Thus, we performed secondary MR analysis by using inflammatory proteins as the exposure and SZ as the outcome. Indeed, our secondary MR analysis showed that genetically predicted levels of IL6 (IVW-OR [95% CI] 1.12 [1.02–1.23], p value = 0.01), along with CD40L receptor, TGFα, and stem cell factor, were significant risk factors for SZ, further corroborating the role of cytokine dysregulation as a causal mechanism for SZ etiology (Figure 6A,B and Supporting Information Table 5). No pleiotropy and heterogeneity were identified for the association between IL6 and SZ (Supporting Information Table 8).

4 | DISCUSSION

Current knowledge of the possible association between inflammatory diseases and MM is confined to correlational studies and case reports. The novelty and significance of our study is that we are the first study to interrogate the bidirectional causal inference between these inflammatory diseases and MM using MR. After MR analyses, we did not find any statistically significant causal association of the forward exposures included in this study with MM since the p value generated from all methods is greater than the threshold of p value <0.05. Specifically, while case reports and correlational studies indicated the possible existence of the causal relationship between IBD, AS, SD, AT, PD, AD, and MM, our MR analyses suggest the lack of such relationships. The discrepancy between our findings and other studies can presumably be attributed to the limitations of correlational studies. These observations are likely due to random isolated incidence rather than generalizable causal inference underlying the comorbidity. Our results are consistent with the extensively supported conclusion that TIID is not associated with an increased risk of MM and vice versa. The absence of a causal relationship between TIID and MM serves as a "negative control" that reflects the validity of our methods.

Interestingly, we unveiled a previously unrecognized causal effect of MM on SZ. Having a familial history of SZ is a significant risk factor, but other factors besides genetic vulnerability cannot be ruled out. For example, risk factors such as the use of cannabis, childhood trauma, and vitamin D deficiency have been hypothesized to increase the likelihood of the development of SZ [52]. To ensure the robustness of our study, we further performed Bayesian colocalization to identify

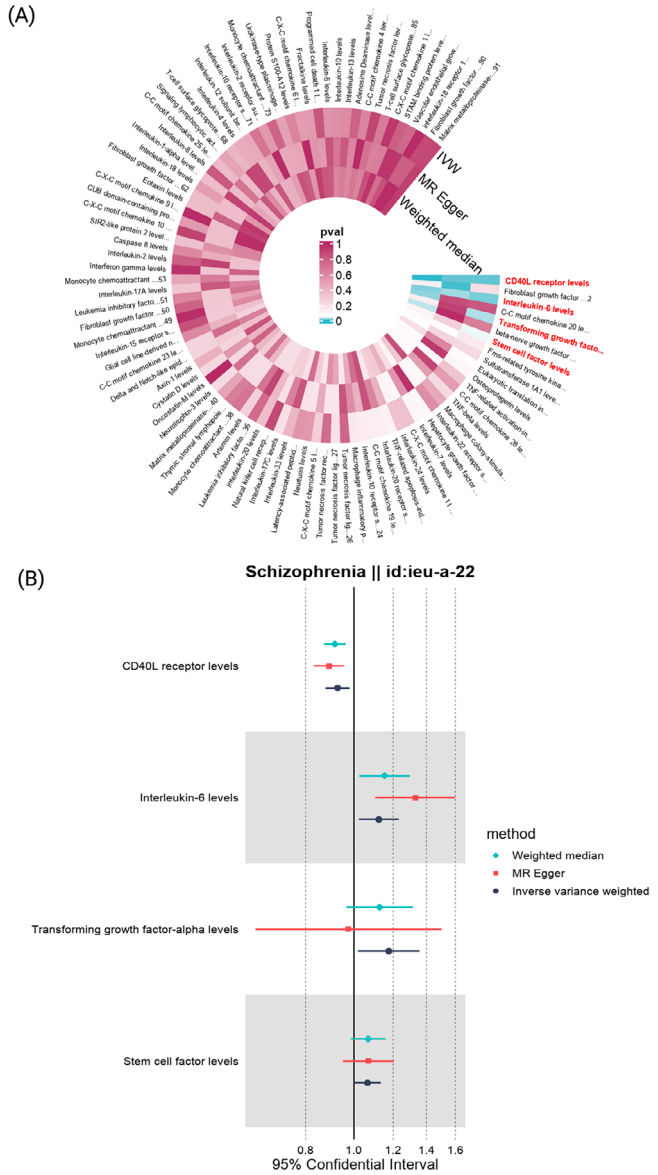

FIGURE 6 Mendelian randomization (MR) analysis of inflammatory protein and schizophrenia (SZ). Circulating inflammatory proteins were used as exposure to perform MR analysis with SZ as the outcome. Inverse-variance weighted (IVW), weighted median, and MR Egger methods were performed.

possible risk variants common to both MM and SZ. We have identified rs9273086 as a shared casual SNP between MM and SZ. This SNP maps to the protein-coding region of HLA-DRB1. Presentation of extracellular proteins via HLA-DRB1 is thought to play essential role in immune system and polymorphism of its allele is commonly associated with numerous inflammatory diseases such as rheumatoid arthritis, AD and PD, inviting future exploration of its functional relevance in both MM and SZ [53, 54].

Recent literature suggests that oversecretion of proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and TNFα is associated with an increased risk of development of SZ [45–49]. Specifically, treatment-resistant SZ has been found to be associated with increase serum IL-6 [58]. Building on our initial MR and transcriptomic analyses, we delved into the causal role of IL6 on SZ development. As expected, our secondary MR analysis between 91 inflammatory proteins and SZ confirmed the causal role of IL6 in increasing the risk for SZ, collaborating with our transcriptomic finding as well as previous correlational studies. These insights suggest that individuals with treatment-resistant SZ may potentially benefit from IL-6 receptor antagonists like sarilumab, opening avenues for targeted therapeutic interventions [50].

While B cells themselves do not directly secrete these cytokines, IL-6 has been shown to promote osteolysis and create a favorable tumor microenvironment for the initiation and progression of MM [51, 59]. Our transcriptomic analysis of MM patients confirms the enrichment of multiple inflammatory hallmark pathways including the interferon-alpha response, interferon-gamma response, inflammatory response, and TNFα signaling via NFκB. The "chicken and egg" causality dilemma of inflammation and MM remains to be deciphered. The sustained and heightened release of proinflammatory cytokines associated with MM development emerges as a plausible pathophysiological mediator, potentially contributing to the elevated risk of SZ.

Despite the brain is protected by the blood–brain barrier (BBB), leukocytes and other immune cells may infiltrate the BBB following chemokine receptor activation [55]. Thus, the development of MM may induce the transmigration of immune cells across the BBB via the overactivation of the chemokine receptor. The intruded immune cells subsequently release proinflammatory cytokine, causing neuroinflammation that potentiates SZ. In sum, our study demonstrates a potential mechanism by which genetic predisposition to MM increases the risk of developing SZ via the oversecretion of proinflammatory cytokine (Supporting Information Figure 6). Consistently, a case report by Flynn et al. presented that a patient who was resistant to standard antipsychotic treatment showed significant improvement following a formal diagnosis of MM and treatment with dexamethasone [30]. By a similar account, a separate case report from Oldak et al presented a patient who had treatment-resistant psychosis, leading to a subsequent diagnosis of MM and prompt receding of the psychotic symptoms following dexamethasone, cyclosporin, and bortezomib treatment [60]. Flynn et al. hypothesized that the increased cytokine levels underlying MM may be neurotoxic long before the emergence of overt symptoms of MM such as osteolysis and hypercalcemia. On the other hand, the patient presented in Oldak et al.'s case report already had concurrent hypercalcemia. They hypothesized that hypercalcemia may play a role in monoamine metabolism that directly impacts mood and cognition. These case reports provide clinical evidence for the association between SZ and MM as a rare but important differential diagnosis and treatment plan to consider. Observational studies are confounded by ambiguous temporal order and do not reveal the underlying biological processes. Through a genetic approach, our findings confirmed the forward causal effect of MM on the increased risk of SZ and revealed potential underlying pathophysiology, providing a potential guideline for clinicians to include diagnostics tests for MM when assessing treatment-resistant SZ patients. The early detection of MM as the possible mechanism underlying treatment

resistance can provide patients with a better prognosis and quality of life.

Our study has several strengths. First, to fulfill the three principal assumptions and minimize biases, we had multiple layers of selection criteria to ensure that the SNPs were critically selected for reliable downstream analyses. Second, for the causal effect of MM on SZ, we employed multiple methods, including the commonly used IVW-random effect method. The directionality and statistical significance of these results were consistent with each other, verifying the accuracy of our conclusion. Third, our sensitivity analyses show that there is minimal heterogeneity, pleiotropy, or outlier effect. Fourth, we implemented transcriptomic analysis of MM and SZ patients, revealing shared enrichment in inflammation-related pathways, supporting the role of hyperinflammation in both diseases. Fifth, we performed Bayesian colocalization and reveals rs9273086, a SNP of HLA-DRB1, as a common risk variant to both MM and SZ, strengthening our conclusion that MM is associated with an increased risk of SZ possibly via immunological dysregulation. Lastly, we performed a secondary MR analysis between 91 inflammatory proteins and SZ. This unbiased screen consolidated the implied role of IL6 signaling in the etiology of SZ, reflecting our transcriptomic analysis findings and numerous previous observational studies.

Admittedly, our study is not free from limitations. First, the case number of our MM GWAS is relatively suboptimal. The smaller sample size weakens the statistical power of our analyses, potentially obscuring causal inferences that could have been revealed with a greater sample size. Second, since our GWAS were sourced from individuals with European ancestry, we should caution against generalizing the findings to all populations. Third, although our sensitivity analysis showed neither heterogeneity nor pleiotropy effects, we cannot guarantee that these confounding effects do not affect the conclusion of our studies. Fourth, our knowledge of phenotypes associated with the selected SNPs is not infallible nor exhaustive. For example, we have discovered rs9273086 as a causal SNP common to both MM and SZ, but it is not extensively characterized, preventing us from conducting further analysis to elucidate its contribution to MM and SZ. Given the limitation of our study, our findings should serve as a starting point for more extensive correlational studies, MR analyses with larger GWAS, as well as more robust mechanistic studies to understand the link between MM and SZ fully.

AUTHOR CONTRIBUTIONS

Conceptualization: Shuyang Lin, Bei Gao, and Shumei Yan. Methodology: Shuyang Lin, Bei Gao, and Rui Xu. Software: Shuyang Lin and Bei Gao. Formal Analysis: Shuyang Lin, Bei Gao, Rui Xu, Hongming Shang, Yan Xiong, Zhe Yang, and Jiayi Zhou. Investigation: Shuyang Lin, Bei Gao, Rui Xu, Zhe Yang, and Jiayi Zhou. Resources: Shuyang Lin, Bei Gao, Rui Xu, Hongming Shang, Yan Xiong, Zhe Yang, and Jiayi Zhou. Data Curation: Shuyang Lin, Bei Gao, Rui Xu, Hongming Shang, Yan Xiong, Zhe Yang, and Jiayi Zhou. Writing—original draft: Shuyang Lin and Bei Gao. Writing—review and editing: Shuyang Lin, Bei Gao, and Shumei Yan. Visualization: Shuyang Lin and Bei Gao. Supervision: Shumei Yan. Project administration: Shumei Yan. Funding acquisition: Shumei Yan.

Shumei Yan, Shuyang Lin, and Bei Gao conceived the project. All the authors participated in the data analysis process. Shuyang Lin and Bei Gao wrote the original manuscript with input from all authors. All the authors have read and consented to the submission of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All Genome-Wide Association Studies (GWAS) datasets were downloaded from https://gwas.mrcieu.ac.uk/datasets. Transcriptomic data for MM patients were downloaded from the GEO database (GSE47552). The list of DEG for SZ patients was directly downloaded from Fillman et al. [43]. GWAS for 91 inflammatory proteins were downloaded from Zhao et al. [33].

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

ETHICS STATEMENT

No ethical approval is needed as the study is performed with publicly available data.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

N/A.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

CODE AVAILABILITY

Codes are made available upon reasonable request from the corresponding author.

ORCID

Shuyang Lin https://orcid.org/0000-0002-9522-7798

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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