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Genetic evidence supporting the causal link between optic neuritis and rheumatoid arthritis

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Abstract. Background: Previous studies have observed an association between optic neuritis (ON) and rheumatoid arthritis (RA). However, the causal relationship between these two conditions remains ambiguous. This study aimed to explore the causal effect between ON and RA using Mendelian randomization (MR) analysis. Methods: Summary statistics for RA (14,361 RA cases and 43,923 healthy controls (HCs)) and ON (582 cases and 217,491 HCs) were obtained from an available meta-analysis of published genome-wide association studies (GWAS).Bidirectional MR was performed using inverse-variance weighting, MR-Egger regression, and weighted-median analysis. Additionally, sensitivity tests including the leave-one-out analysis, MR-PRESSO, and Cochran's Q test were conducted to assess the robustness and validity of the results. Results: The presence of ON may increase the risk of RA by 5.1% genetically (OR = 1.051, 95%CI: 0.003-0.100; p = 0.039). Sensitivity analyses provided no indications of heterogeneity (Cochran's Q = 3.173, p = 0.787) or pleiotropy (intercept of 0.015, p = 0.533). No strong evidence that RA had a causal effect on ON risk (OR = 0.937, 95%CI: 0.830-1.057; p = 0.292). Sensitivity analyses provided no indications of heterogeneity (Cochran's Q = 100.438, p = 0.081) or pleiotropy (intercept of 0.028, p = 0.091). Conclusion: This study provides genetic evidence suggesting that ON may contribute to the development of RA. These findings have potential implications for the management of RA.

Keywords: Rheumatoid Arthritis, Optic Neuritis, Genome-Wide Association Study, Causal relationship.

1. Background

Rheumatoid arthritis (RA) is categorized as a systemic chronic autoimmune disease [1]. The occurrence of RA not only affects the quality of life of patients but also brings huge economic losses to society [2, 3]. Although the etiology of RA is still unclear, many studies agree that it involves multiple genetic and environmental factors[4]. Identifying these risk factors is crucial in preventing and treating the disease.

In recent years, researchers have paid increasing attention to other risk factors for RA including inflammatory diseases like optic neuritis (ON)[5]. ON is an inflammatory condition that affects the optic nerve, commonly presenting as painful monocular vision loss in young adults, particularly females [6, 7]. Various causes, such as infections, autoimmune and inflammatory conditions, metabolic abnormalities, and medication reactions, have been associated with ON [8]. Observational studies have suggested a link between autoimmune diseases and ON, indicating a potential association between ON and RA [9]. An observational study showed that patients with ON had a higher cumulative incidence of autoimmune disease than those without [10]. However, it's important

to note that correlation does not imply causation, and further investigation is required to understand the relationship between ON and RA [11].

Mendelian randomization (MR) refers to an analytical method for assessing the causality of associations between observed modifiable exposures or risk factors and clinically relevant outcomes [12]. This approach can help minimize confounding factors and eliminate reverse causation [13]. Leveraging the extensive genome-wide association study (GWAS) data on RA, we conducted a two-sample MR study to investigate the bidirectional causal relationship between ON and RA, aiming to enhance our understanding of their connection.

2. Methods

2.1. Study overview

Summary data were obtained from GWAS for single nucleotide polymorphisms (SNPs) as instrumental variable(IV) [14]. The entire process satisfied the three main hypotheses of classical MR analysis: Assumption 1, genetic variants should be strongly associated with the exposure; Assumption 2, genetic variants extracted for exposure should be independent of any confounder which is associated with both exposure and outcome; and Assumption 3, the genetic variants affect the outcome only through the exposure. Additionally, ethical approval was not necessary for this MR study. An overview of the research design is presented in Figure 1.

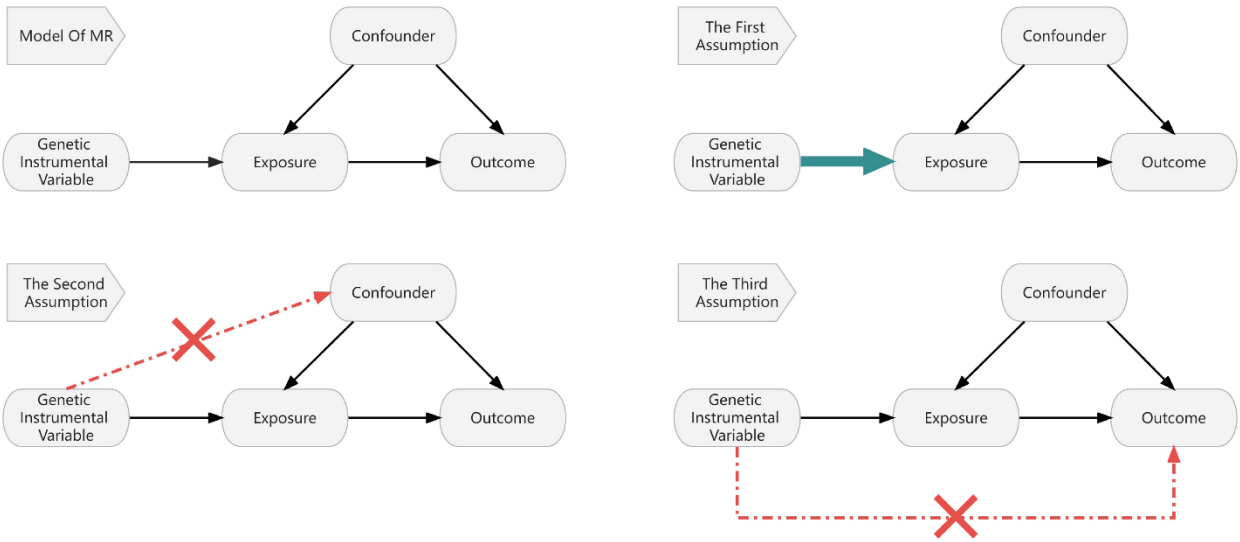

Figure 1. schematic diagram of MR and its three core assumptions.

2.2. RA GWAS summary statistics

Publicly available summary statistic estimates for the associations between genetic variants and risk of RA were obtained from a GWAS meta-analysis, including 14, 361 RA cases and 43, 923 controls from European [15]. All RA cases fulfilled the 1987 RA diagnosis criteria of the American College of Rheumatology or were diagnosed as RA by a professional rheumatologist [16]. Among all RA cases enrolled in this study, 88.1% were seropositive 9.3% were seronegative for anti-citrullinated peptide antibody or rheumatoid factor, and 2.6% had unknown autoantibody status.

2.3. ON GWAS summary statistics

The GWAS summary statistics for ON in individuals of European ancestry (218, 073 participants) based on the Finnish database were obtained from the IEU GWAS database, including 582 ON cases and 217, 491 controls. Both sexes in the statistical population.

2.4. Selection of IVs

We performed stringent filtering steps to control SNP quality. First, SNPs that were linked to the right exposure were chosen using genome-wide significance thresholds ($p < 1 \times 10^{-5}$). Second, SNPs that have a total linkage disequilibrium (LD, $R^2 \geq 0.001$ and 10 Mb). Third, to figure out the strength of genetic tools, we left out SNPs with F-statistics less than 10 [17]. Meanwhile, secondary phenotypes were searched for each SNP in order to exclude potential pleiotropic effects. We found SNPs associated with confounders (smoking, alcohol, body mass index (BMI)) in PhenoScanner V2 (http://phenoscanner.medschl.cam.ac.uk).

Herein, the formula is as follows: $F = \frac{R^2(n-k-1)}{(1-R^2)k}$, where n denotes the sample number of the chosen GWAS, k denotes the number of SNPs involved, and R^2 denotes the explained variance (cumulative) of the chosen SNPs during exposure. F>10 indicates a strong correlation between exposure and IVs, and the MR analysis results are independent of the weak-tool bias.

2.5. Statistical analyses

All statistical analyses were conducted using R software (version 4.3.1). For each set of IVs, we harmonized exposure and outcome data to ensure the effect sizes for each GWAS were aligned to the same alleles. After finding SNPs for exposure and outcome, our study used a range of methods for sensitivity analyses. First, the heterogeneity of the different SNP estimates was assessed by Cochran's Q test. If $P > 0.05$, there was no heterogeneity. Second, MR-Egger Intercept analysis was used to investigate the horizontal pleiotropy of IVs [18]. In the MR-Egger test, the mean of the horizontal pleiotropy effect was estimated based on the intercept across SNPs, and if $P < 0.05$, the Inverse-variance Weighted (IVW) estimates might be biased. Third, the leave-one-out analyses were used to validate the results that could be produced by individual SNPs. The leave-one-out analyses showed how the causal effect of IVW was produced when each variable was removed from the analyses in order to assess whether the observed causality depended on any individual SNP because if IVW changes drastically, this means that one variant contributes more than the others.

After that, we used three methods for MR analysis. IVW dominated the MR analysis [14]. It has the highest statistical power because of its underlying assumption that all SNPs are valid SNPs. Meanwhile, MR-Egger and Weighted Median (WM) were used to clarify causality [17]. Different assumptions about the validity of SNPs were made using each method. Assuming that at least half of the SNPs were valid, Weighted Median was performed, which had the second highest statistical power after IVW ($p>0.05$ proved that IVW results were reliable when performing MR-Egger intercept); assuming that all SNPs were invalid SNPs, MR-Egger was performed, and MR-Egger was used because it corrected for levels of pleiotropy, albeit with lower statistical power [19, 20]. Finally, the MR-PRESSO test was performed to detect outliers with possible polyvalence [21]. Once outliers were detected, we removed them and repeated the MR analysis.

3. Result

3.1. Forward MR analysis: causal effect of ON on RA

We identified 8 eligible SNPs associated with RA ($P < 1 \times 10^{-5}$) as IVs. None of these SNPs showed an association with confounding factors such as smoking, alcohol, or BMI in PhenoScanner V2. Details of IVs can be accessed in Additional file 1.

Utilizing the IVW method, we found that ON was significantly associated with an increased risk of RA. Having genetic predisposition to ON was associated with a 5.6% higher risk of developing RA (odds ratio (OR) = 1.056, 95% confidence interval (CI): 1.003-1.104, p = 0.039). The MR estimates of different methods were presented in Table 1 and Figure 2, 3A.

Assessment of heterogeneity using the Cochran's Q test revealed no significant heterogeneity among the SNPs (Q = 3.173, p = 0.787, Figure 3B). Furthermore, leave-one-out sensitivity analysis did not identify any outliers, indicating that the MR results were not driven by any individual SNP (Figure 3C). The MR-Egger intercept test showed no evidence of directional pleiotropy (intercept of 0.028, p = 0.091). Additionally, the MR-PRESSO test did not detect any outliers.

In summary, the main MR analyses using the inverse variance weighted method and sensitivity analyses indicating that the genetically predicted ON was causally associated with RA.

3.2. Reverse MR analysis: causal effect of RA on ON

In our reverse MR analysis, we investigated whether RA as an exposure factor had a causal effect on ON. We identified 84 eligible SNPs for this analysis, all with F-statistic values exceeding 10, indicating sufficient strength as IVs. Details of IVs can be accessed in Additional file 2.

Using the IVW method, we found no evidence of a causal link between RA and ON (Table 1) (Figure 2, 4A). The estimated OR was 0.937, with a 95% CI of 0.830-1.058, and a p-value of 0.293. These results suggest that RA is not causally associated with the risk of developing ON.

Furthermore, our analysis did not uncover significant evidence of pleiotropy (intercept of 0.028, p = 0.091) or heterogeneity(Cochran's Q = 100.438, p = 0.081) for the IVs(Figure 4B-C).

Based on previous research, we have listed the STROBE-MR checklist of MR studies to ensure the integrity of our processes in Additional file 3[22, 23].

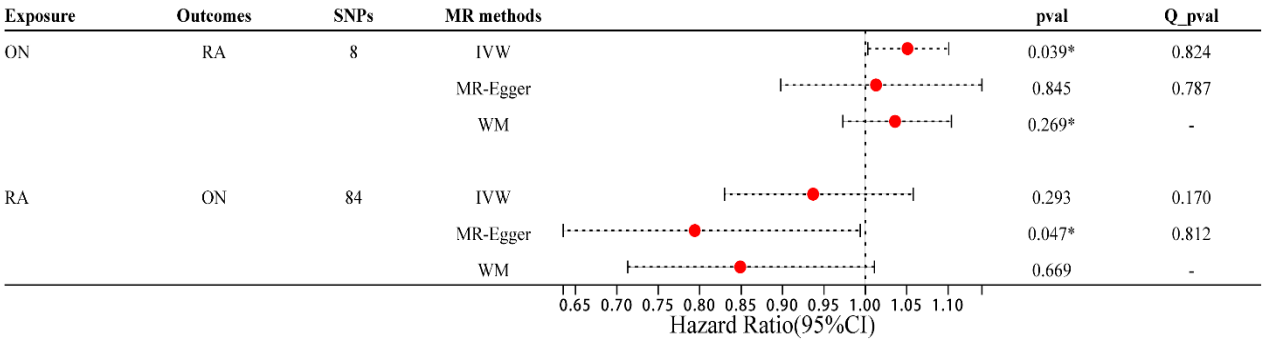

Figure 2. Forest plot of MR results of association between ON and risk of RA by IVW, MR Egger, and weighted median.

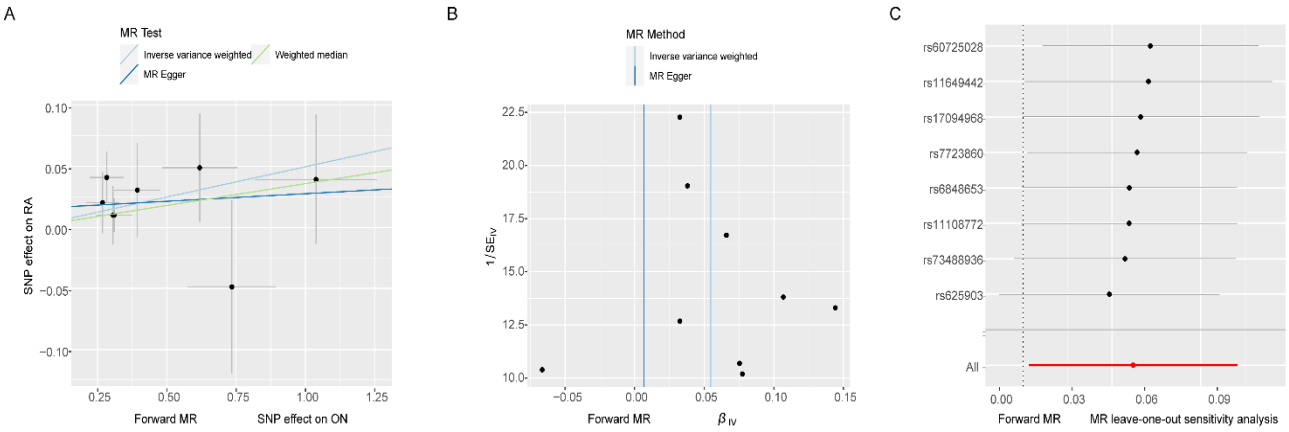

Figure 3. The result of forward MR. A: The scatter plots for MR analyze the causal effect between ON and RA using the conventional IVW, MR-Egger, and Weighted median. B: IVW and MR-Egger regression slopes were used to explore asymmetry as a sign of pleiotropy of the effect between ON and RA, with the vertical line in the middle indicating the sum of different effect sizes. C: Leave-one-out analysis was used to determine whether any single SNP drove the causal association of ON on RA, which repeated the IVW analysis by discarding each exposure-related SNP.

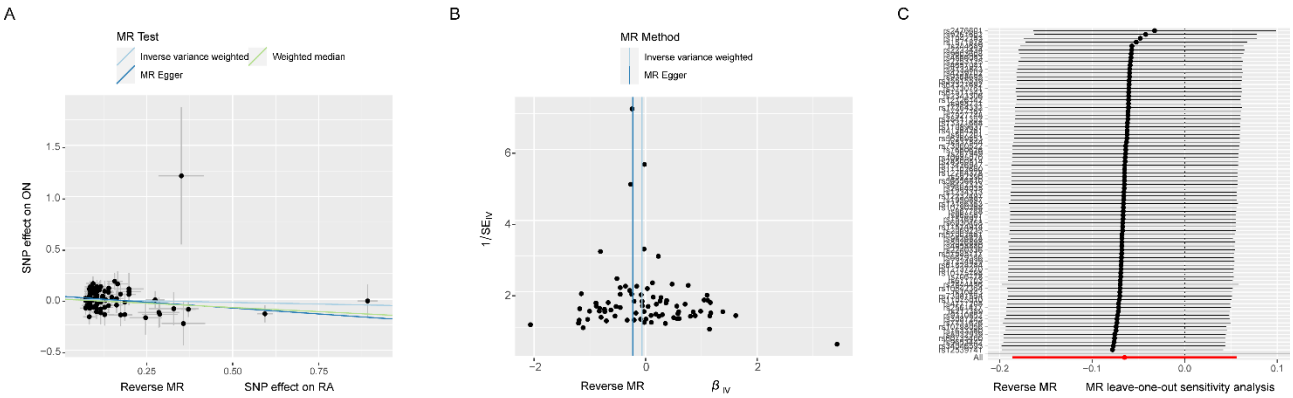

Figure 4. The result of reverse MR. A: The scatter plots for MR analyze the causal effect between RA and ON using the conventional IVW, MR-Egger, and Weighted median. B: IVW and MR-Egger regression slopes were used to explore asymmetry as a sign of pleiotropy of the effect between RA and ON, with the vertical line in the middle indicating the sum of different effect sizes. C: Leave-one-out analysis was used to determine whether any single SNP drove the causal association of RA on ON, which repeated the IVW analysis by discarding each exposure-related SNP.

Table 1. The causal effect between RA and ON and the sensitivity analysis.

Exposure	Outcomes	SNPs	MR methods	OR	95%CI	pval	Q_pval
ON	RA	8	IVW	1.051	(1.003,1.104)	0.039*	0.824
			MR-Egger	1.012	(0.898,1.141)	0.845	0.787
			WM	1.036	(0.977,1.099)	0.232	-
RA	ON	84	IVW	0.937	(0.830,1.058)	0.293	0.059
			MR-Egger	0.794	(0.635,0.994)	0.047	0.081
			WM	0.849	(0.715,1.008)	0.062	-

4. Discussion

The association between RA and ON has been the subject of several studies, but no study has definitively established a causal relationship. This study is the first to employ a two-sample MR approach based on GWAS summary statistics to explore the bidirectional causal relationship between RA and ON. Surprisingly, the findings suggest that the occurrence of ON is associated with an increased risk of developing RA.

RA is known to be a systemic disease, but its involvement in the brain and eyes is not well understood. While RA is rarely the direct cause of ON, the influence of RA on ON should not be disregarded [24]. Epidemiology suggests that ON is an immune-mediated disease [25]. However, the association between ON and autoimmune diseases is still unclear. It has been observed that patients with ON have a higher cumulative incidence of autoimmune diseases compared to those without ON, particularly in young or female individuals [10]. Therefore, ON may serve as an early sign or risk factor for autoimmune diseases and subsequent systemic involvement.

There is epidemiologic support for an increased prevalence of ON in patients with RA. Previous studies have also demonstrated that while RA is a chronic and incurable disease, most patients can achieve significant control and improvement with current treatments. However, long-term use of these drugs, even at recommended doses, carries a potential risk of serious adverse events, including

those affecting the eyes. Additionally, optic neuromyelitis optica (NMO), a neurological disorder characterized by recurrent episodes of ON, has been associated with an increasing number of autoimmune disorders in up to 20-30% of NMO patients [26]. The contradiction between our findings and epidemiologic results may be explained by the fact that these autoimmune disorders may present with symptoms before or after the onset of NMO, often long after the NMO diagnosis, leading to misattributed symptoms to NMO itself, its residual effects, or drug side effects.

Strengths of this study include: the use of objective ON measures rather than self-reported measures; the ability of MR to provide more convincing results than observational studies; and the ability of MR to provide an opportunity to examine associations between exposures and outcomes, which can minimize the potential for confounding and reverse causation bias [22]. By leveraging the random assignment of alleles to offspring, MR analyses can generate more robust evidence.

However, this study also has limitations. The MR analyses primarily focused on European populations to minimize racial mixing and population stratification bias. The generalizability of the results to other populations with different genetic backgrounds is uncertain, and reliable datasets on non-European or mixed populations are needed. Additionally, the genetic associations of biomarkers are based on relatively small GWAS, which may limit the statistical power of the analysis.

5. Conclusion

Bidirectional two-sample MR analyses support a causal relationship between genetic susceptibility to ON and RA, but not between genetic susceptibility to RA and increased risk of ON. These findings provide new insights into the biological relationship between ON and RA, opening up new avenues for clinical investigation.

Acknowledgements

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