Exploring causal correlations between inflammatory proteins and Bullous pemphigoid:bi-directional mendelian randomisation study

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Abstract

Bullous pemphigoid (BP), the most common autoimmune bullous disease, typically presents with generalized crops of tense, pruritic cutaneous blisters and mostly affects the elderly, Here, we aimed to figure out the interplay between peripheral inflammatory proteins and BP. Based on publicly available genetic data, bidirectional Mendelian randomization (MR) analysis was performed to determine the causal association between 91 inflammatory proteins and BP. The inverse-variance weighted (IVW) method was used as the primary MR method to estimate causal effects, while MR-Egger, weighted mode methods, weighted median, and simple mode were performed to explore the causal association. The leave-one-out (LOO) analysis, MR pleiotropy residual sum, and Cochran's Qtest were used to exclude possible horizontal pleiotropic outliers and verify the robustness, heterogeneity, and horizontal pleiotropy of the results. The results indicated that 2 inflammatory proteins associated with the risk of BP were identified, These are Macrophage Inflammatory Protein 1a (MIP-1a) [IVW OR = 1.69, 95% CI = 1.00-2.84, p = 0.048] with a total of 6 SNPs and Leukemia Inhibitory Factor Receptor (LIFR) [IVW OR = 1.34, 95% CI = 0.24-0.93, p = 0.029] with 3 SNPs. In addition, Fractalkine levels [IVW OR = 0.99, 95% CI = 0.98-1.00, p=0.033] was suggested to be the consequences of BP,Sensitivity analysis further excluded the influence of heterogeneity and horizontal pleiotropy. This study suggested that MIP-1a and LIFR were positively associated with the risk of BP, while the LIFR was negatively associated with the risk of BP ,besides,the Fractalkine levels is more likely to be involved in BP development downstream,which furthers our understanding of immune cells in the pathogenesis of BPand contributes to the study of accurate treatment.

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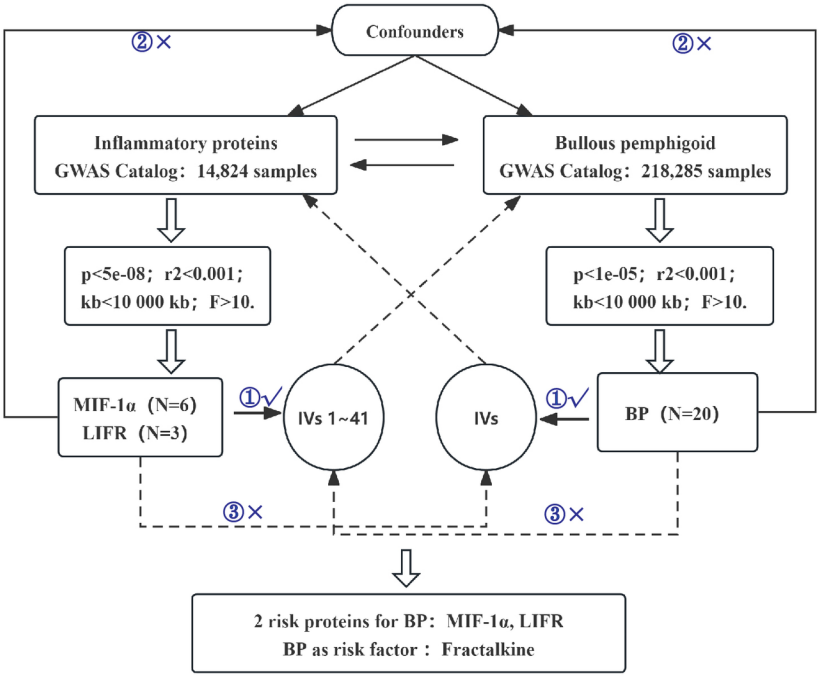

BP	method	nSNP	Beta	se	OR(95 %CI)	*P*value
BP as outcome	**Leukemia inhibitory factor receptor levels**					
	Inverse variance weighted	3	-0.753	0.345	0.47（0.24-0.93）	0.029
	MR Egger	3	-0.379	0.719	0.68（0.17-2.80）	0.691
	Simple mode	3	-0.746	0.499	0.47（0.18-1.26）	0.273
	Weighted mode	3	-0.689	0.399	0.50（0.23-1.10）	0.226
	Weighted median	3	-0.712	0.351	0.49（0.25-0.98）	0.043
	Macrophage inflammatory protein 1a levels					
	Inverse variance weighted	6	0.524	0.265	1.69（1.00-2.84）	0.048
	MR Egger	6	0.387	0.485	1.47（0.57-3.81）	0.470
	Simple mode	6	0.980	0.609	2.66（0.81-8.79）	0.169
	Weighted mode	6	0.453	0.290	1.57（0.89-2.78）	0.179
	Weighted median	6	0.441	0.291	1.55（0.88-2.75）	0.130
BP as exposure	**Fractalkine levels**					
	Inverse variance weighted	20	-0.009	0.004	0.99（0.98-1.00）	0.033
	MR Egger	20	-0.007	0.006	0.99（0.98-1.01）	0.272
	Simple mode	20	-0.015	0.01	0.98（0.97-1.00）	0.148
	Weighted mode	20	-0.016	0.008	0.98（0.97-1.00）	0.070
	Weighted median	20	-0.015	0.006	0.99（0.97-1.00）	0.010