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Potential therapeutic targets for Membranous Nephropathy: Muti-omics Mendelian randomization and colocalization analysis

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Objectives : The currently available medications for treating membranous nephropathy (MN) still have unsatisfactory efficacy in inhibiting disease recurrence, slowing down its progression, and even halting the development of end-stage renal disease. There is still a need to develop novel drugs targeting MN.
Methods : We utilized summary statistics of MN from the Kiryluk Lab and obtained plasma proteins from Zheng et al., Decode, and UKBioBank and gene data from eQTLgen and GTEX. We performed Mendelian randomization, SMR analysis, HEIDI test, Bayesian colocalization, phenotype scanning, external validation, mediation analysis, drug bank analysis, and protein-protein interaction network.
Results : The Mendelian randomization analysis uncovered 8 distinct proteins associated with MN after multiple corrections of the false discovery rate. Proteins associated with an increased risk of MN in plasma include ABO (Histo-Blood Group Abo System Transferase), VWF (Von Willebrand Factor) and CD209 (Cd209 Antigen), and proteins that have a protective effect on MN: HRG (Histidine-Rich Glycoprotein), CD27 (Cd27 Antigen), LRPPRC (Leucine-Rich Ppr Motif-Containing Protein, Mitochondrial), TIMP4 (Metalloproteinase Inhibitor 4) and MAP2K4 (Dual Specificity Mitogen-Activated Protein Kinase Kinase 4). ABO, HRG, and TIMP4 successfully passed the HEIDI test. None of these proteins exhibited a reverse causal relationship. Bayesian colocalization analysis provided evidence that all of them share variants with MN. In external validation, ABO, CD27, HRG, MAP2K4, TIMP4, and VWF showed significant mediation results. We identified type 1 diabetes, trunk fat, and asthma as having intermediate effects in these pathways. We discovered several genes that are causally related to MN.
Conclusions : Our comprehensive analysis suggests that these proteins hold potential as promising therapeutic targets for the treatment of MN, unveiling the pathways through which they exert their effects. Furthermore, we have identified several genes that exhibit causal relationships with MN.

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Exposure	Method	FDR	HEIDI	SMR	OR(95% CI)
ABO	Wald ratio	0.090	0.134	0.0008	1.12 (1.05 to 1.19)
CD209	Wald ratio	0.090	0.310	0.8121	1.19 (1.07 to 1.31)
CD27	Wald ratio	0.020			0.78 (0.68 to 0.90)
HRG	Wald ratio	0.020	0.091	0.0009	0.84 (0.76 to 0.93)
LRPPRC	Wald ratio	0.090			0.79 (0.69 to 0.91)
MAP2K4	Wald ratio	0.090			0.82 (0.72 to 0.92)
TIMP4	Wald ratio	0.090	0.916	0.0008	0.67 (0.53 to 0.84)
VWF	Wald ratio	0.020			1.41 (1.16 to 1.72)

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